CARDIOVASCULAR FUNCTION DURING EXPERIMENTAL HYPERTHERMIA WITH SPECIFIC REFERENCE TO CIRCULATORY FAILURE

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AAN MY OUERS

To this circumſtance the oppreſſion on my breath muſt be partly imputed, the blood being forced into my lungs quicker than it could paſs through them; and hence it may very reaſonably be conjectured, that ſhould an heat of this kind ever be puſhed ſo far as to prove fatal, it will be found to have killed by an accumulation of blood in the lungs, or ſome other immediate effect of an accelerated circulation

Charles Blagden: "Further Experiments and Observations in an Heated Room"

Philos. Tran. R. Soc. Lond. 65, 484-494 (1775)

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I N T R O D U C T I O N

The physiological effects imposed by environmental heat is an event which most people experience during life. These effects may vary from the common slight discomfort to the extreme which is characterised by wide-spread tissue damage, often culminating in death. Heatstroke is the most serious heat disorder; indeed its known occurrence dates back to Biblical times: "And it came to pass when the sun did arise that God prepared a vehement east wind; and the sun beat down on the head of Jonah that he fainted and wished in himself to die....." (Jonah 4:8). In more recent times, the occurrence of heatstroke has been especially evident during the Middle-East campaigns of both world wars, in heat waves, and, in South Africa, in the gold-mining industry.

Despite the wealth of information which is currently available, both clinical and experimental, a critical review of the literature indicates that the pathogenesis of heatstroke has not been clarified adequately. The major problems can probably be ascribed to the fact that (a) heatstroke is characterised by a rapid onset so that little or no knowledge of the prodromal stage exists, (b) therapeutic measures may to some extent obscure relevant clinical signs, (c) the unpredictability of the affliction, and (d) variables such as age, sex, race, degree of acclimatisation and climate.

By virtue of the gold-mining industry (*vide supra*), the physiological responses to environmental heat exposure have

been the subject of intensive research in South Africa. In general, research has been conducted along the following lines:

(a) Measurements of physiological responses to subacute levels of heat stress and the prevention of heatstroke by artificial acclimatisation (acclimation) have been conducted by Professors Wyndham, Strydom and their co-workers of the Human Sciences Laboratory (currently the Industrial Hygiene Division) of the Chamber of Mines.

(b) Extensive clinical studies of heatstroke patients have been undertaken by Professor M.C. Kew and co-workers of the University of the Witwatersrand.

(c) The induction of heatstroke in animals and the subsequent assessment of tissue damage at cellular and biochemical level have been investigated by several workers, most notably Professor F.J. Burger, currently of the University of Durban-Westville.

Without distracting from the valuable contribution made in each instance, it is clear that the pathogenesis of heatstroke rests on extrapolation: subacute heat stress is extrapolated to events that initiate heatstroke, clinical findings are back-extrapolated to a probable origin and animal studies attempt to bridge the gap by extrapolation from animal to man.

From the preceding passages it therefore becomes clear that the researcher into the field of the physiology and pathology of environmental heat stress is faced with a formidable task

in that he deals with a mercurial and dangerous affliction which, by virtue of these self same properties, defies attempts at proper analysis and evaluation.

OBJECTIVES

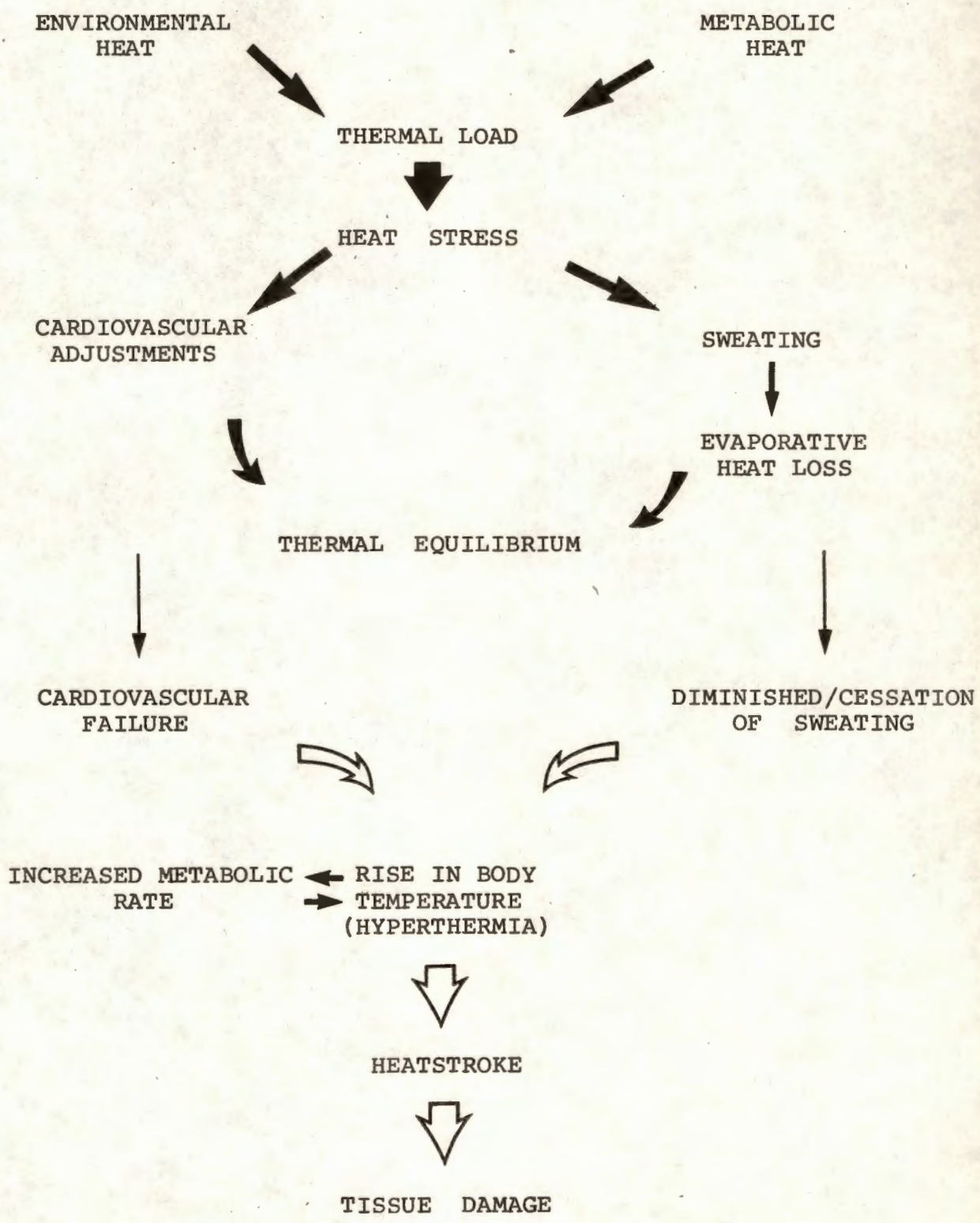
This thesis concerns cardiovascular responses to induced heat stress in animals. In order to state the objectives with clarity, a brief review of the pertinent aspects of thermal homeostasis during heat exposure, as well as the development of heatstroke, is warranted.

Figure 1 shows that thermal homeostasis is maintained by cardiovascular adjustments and evaporative heat loss through sweating. According to Belding (1967) the cardiovascular system represents the "first line of defence" although, quantitatively, the sweat mechanism is the more significant avenue of heat dissipation. Failure of either or both mechanisms may result in an increase in body temperature and the possible establishment of a vicious cycle, heatstroke.

The pathogenesis of heatstroke is largely unknown. Direct thermal damage is at least partly responsible (Shibolet *et al*, 1967; Sohar *et al*, 1968) but for the rest, the "multifactorial" hypothesis of Bělehrádek (1967), a view supported by Burger (1972), is probably the most plausible explanation to date. The crucial issue in the current context, however, does not concern cell damage as such but rather the events that occur

F I G U R E 1

GENERAL PHYSIOLOGICAL RESPONSES DURING THE MAINTENANCE AND FAILURE OF THERMAL HOMEOSTASIS



prior to cell damage, and which may lead to the establishment of a self-perpetuating heatstroke. These events are related to cardiovascular performance and sweating and in this respect impaired sweating is regarded as of paramount importance. According to Leithead and Lind (1964): "The major question which is unanswered (i.e., in the pathogenesis of heatstroke - Author) is whether cessation of sweating precedes or follows hyperpyrexia". Cardiovascular malfunction, as a major factor, is relegated to a position of secondary importance. Since the cardiovascular system is charged with (a) the transport of metabolic heat from the core to the periphery, (b) facilitating radiative heat loss by peripheral vasodilation, (c) the concurrent perfusion of all other vital centres, and, (d) effecting an adequate dermal perfusion rate, thereby maintaining the integrity of the sweat mechanism (Kuno, 1956), it is therefore somewhat surprising that "circulatory failure, either peripheral or cardiac in origin, is an occasional complication of heatstroke but by no means an invariable finding" (Minard and Copman, 1963).

The validity of the above statement is not questioned as such. However, in view of the thermoregulatory status accorded the cardiovascular system by Belding (1967), the possibility exists that a transient or inapparent cardiovascular insufficiency may well constitute the trigger mechanism of a self-perpetuating hyperthermia. Indeed, it is characteristic of a vicious cycle sequence of events that removal of the "trigger" (e.g.,

transient cardiovascular insufficiency) by no means breaks the cycle. Thus, the first objective concerns the relationship between various degrees of heat exposure and cardiovascular function and malfunction.

The second objective stems from observations that (a) a moderate elevation in body temperature enhances cardiac efficiency (Singh, 1963) and that (b) pronounced heatstroke is often associated with myocardial infarction (Malamud *et al*, 1946; Knochel *et al*, 1961) or, at least some sign of myocardial damage (Kew, 1969). It is reasonable to assume that between these extremes a transition stage is reached where myocardial function may become impaired. The second objective therefore concerns (a) the possible identification and analysis of such a transition in terms of parameters of contractility and cellular integrity, and (b) in the event of such an occurrence, the relationship thereof to the prevailing haemodynamic status.

The final objective is based on the conclusion that the mechanism of circulatory failure of acute hyperthermia has not been clarified adequately (O'Donnell and Clowes, 1972). According to Daily and Harrison (1948) the mechanism of failure is peripheral in origin while Gold (1960) postulates high-output cardiac failure as the primary event. Although Daily and Harrison's view represents the general consensus of opinion, there appears to be definite merit in Gold's hypothesis. The final objective therefore represents a fresh

attempt to shed light on these conflicting views and, in fact, is merely a definite restatement of the latter part of the second objective.

The general theme of this thesis is therefore an evaluation of cardiovascular function during acute, experimental heat stress. The experimental techniques and approaches, motivated and described in detail elsewhere, essentially comprise an evaluation of electrocardiographic, haemodynamic and sub-cellular parameters of cardiovascular function.

C H A P T E R 1

REVIEW OF THE LITERATURE

Since time immemorial man has been fascinated by the heart: it has served as a source of poetic inspiration, an object of religious rituals and, relatively recently, has become an object of scientific research. Undoubtedly, this preoccupation may be attributed mainly to the "automatic" pump action of the heart. In addition, from a physiological point of view, the functional integrity of the heart and vascular system represents a common denominator in the fundamental well-being not only of individual organs but also of the organism as a whole. Conversely, cardiovascular malfunction may well be of fundamental significance in the aetiology of apparently unrelated diseases. One of the objectives of this investigation is to evaluate the latter thesis with reference to the circulatory stress imposed by hyperthermia and consequently considerable emphasis will be placed on these aspects in this review of the literature.

This investigation is essentially a study of cardiovascular responses to heat stress with special reference to the heart. At the outset therefore, general aspects of thermal homeostasis are discussed in conjunction with the thermoregulatory function of the cardiovascular system, cardiovascular failure, hyperthermia and heatstroke as well as clinical and experimental findings.

1.1 HEAT STRESS AND HEATSTROKE: GENERAL ASPECTS

1.1.1 HISTORICAL ASPECTS

Man is equipped with a thermoregulatory system admirably suited to life in hot climates: He is in possession of a sweat mechanism which effects evaporative heat loss, a circulatory system well adapted to meet the demands of thermoregulation and a skin practically devoid of hair. Yet, despite these physical and physiological attributes, heatstroke is one of the oldest recorded afflictions known to man. Biblical references to fatalities caused by heatstroke are found in Jonah 4:8 and 2 Kings 4:18-20. The ancient Arabians termed the disease "siriasis" after the star Sirius which "follows the sun" during the hot summer months (Wilson, 1940). In 1743, eleven thousand people died in the streets of Peking from heatstroke (Levic, 1859). According to El Halawani (1964) heat illnesses accounted for over 800 deaths out of one and a quarter million pilgrims in the 1959-60 pilgrimages to Mecca. Haseeb and Fayiz (1958) reported the deaths of 187 out of 281 prisoners locked overnight in a ward intended for occupation by 16 soldiers in the town of Kosti, Sudan, 1956. Both world wars exerted their toll of heatstroke victims, especially in the Middle-East campaigns, while Alistair Mars, recounting his exploits during World War II, reported heatstroke in submarines operated in the Pacific Ocean.

The existence of a thermoregulatory system gradually dawned on man. One of the earliest references relates to Lining's observation in 1748 namely, that his body temperature remained constant while exposed to an environmental temperature of 50°C. Shortly afterwards, in 1768, Lind demonstrated the beneficial influence of acclimatisation to heat (Leithead and Lind, 1964).

In spite of the contributions of these early pioneers, heatstroke still remains an enigma. The fact that the incidence of heatstroke has been drastically reduced during the last few decades is perhaps a greater reflection of man's awareness of potential hazards and effective acclimatisation procedures in industry rather than of his understanding of the affliction. Heatstroke is regarded as one of the few true medical emergencies (Eichler *et al*, 1969) and if treatment is not instituted promptly, it carries a mortality rate of up to 80% (Kew, 1976). In summary, the words of Leithead and Lind (1964) accurately state the case:

> *"And with a body temperature of 40,6°C one patient walks into the clinic whereas another dies in convulsions and coma".*

1.1.2 *HEATSTROKE: PREDISPOSING FACTORS AND THE CLINICAL PICTURE*

Although this study is not directly concerned with heatstroke as such, it is deemed appropriate to present this section in order that the aims of the current project may be seen in greater perspective.

The characteristics of the human thermostat are such that while it regulates the body core temperature within extremely narrow limits, it will permit under certain circumstances (e.g. exercise) an elevation in body temperature which is not only physiological and normal, but also beneficial. However, a similar elevation in body temperature under different circumstances may be regarded as grossly abnormal since the elevated temperature is not consonant with the degree of physical effort expended. Under such circumstances, the condition is described as hyperthermia and while in general the thermoregulatory system remains fully operative, the condition potentially constitutes a grave danger in that it may trigger a self-perpetuating and self-destructive vicious cycle sequence of events, heatstroke.

Heatstroke has been defined as a disorder of thermoregulation characterised by a total absence of sweating, a self-perpetuating hyperthermia usually of 41,1^{o}C (106^{o}F) and higher, and severe disturbances of consciousness and brain function (Minard and Copman, 1963). A major objection to such a definition is the setting of an apparently arbitrary temperature (Leithead and Lind, 1964). In addition, sweat cessation is not always one of the cardinal signs of heatstroke since heatstroke may occur not only from failure of the thermoregulatory system but also from overloading of its capacity (Shibolet *et al*, 1967; Kew, 1976).

Predisposing factors include both environmental and physiological aspects. From an environmental point of view, the

best criterion appears to be the "wet-bulb temperature" which takes into account in a single measurement the effects of temperature, humidity and wind velocity (Eichler *et al*, 1969). According to Kew (1976)a wet-bulb temperature of 32°C represents the upper limit for moderate physical exertion irrespective of the degree of acclimitisation. Heat waves, or dramatic changes in weather, have a profound effect on the incidence of heatstroke (Ferguson and O'Brien, 1960; Kumar *et al*, 1964). For example, Leithead (1960) reported that during a sudden increase in humidity during the dry summers of Kuwait, seasonally-acclimatised road workers exhibited advanced signs of syncope. From a physiological point of view the incidence of heatstroke is high in unacclimatised individuals (Cook, 1955; Yaglou and Minard, 1957), children in the age group 0 - 10 years (Kumar *et al*, 1964) and in elderly people (Gold, 1960). Apart from these "high-risk" groups, a small fraction of the population appears to be heat intolerant, revealing no sign which might account for this inherent susceptibility to heat (Minard and Copman, 1963; Kew, 1976). Finally, it is not only the degree of hyperthermia which predisposes to the development of heatstroke but also the duration of heat exposure (Kew, 1968).

Heatstroke is usually characterised by widespread tissue damage. These findings, based on clinical and autopsy findings, are extremely well-documented e.g., cardiac damage (Metz, 1940; Malamud *et al*, 1946; Knochel *et al*, 1961; Kew, 1969; Kew *et al*, 1969; 1971), central nervous system disturbances (Malamud *et al*, 1946; Gore and Isaacson, 1949;

Ferguson and O'Brien 1960; Kew *et al*, 1967a; 1971), liver damage (Malamud *et al*, 1946; Herman and Sullivan, 1959; Kew, 1969; Kew *et al*, 1970b; 1971) and renal damage (Baxter and Teschan, 1958; Kew *et al*, 1967b; 1970a; 1971; Schrier *et al*, 1970). Although many tissues are damaged in heatstroke, the patient's outcome depends mainly on the degree of injury to the brain, kidney and liver (Kew *et al*, 1971), the latter two organs being damaged almost invariably in heatstroke.

The preceding passage serves to illustrate the extent of damage sustained during heatstroke. A comprehensive account naturally falls outside the scope of this study but reference will be made (elsewherein this review) to more specific details which are of greater relevance.

1.2 THE PHYSIOLOGY OF CARDIOVASCULAR FUNCTION DURING THERMAL STRESS

1.2.1 THERMOREGULATORY RESPONSES OF THE CARDIOVASCULAR SYSTEM DURING HEAT EXPOSURE

The cardiovascular system fulfils a prominent role during heat exposure: not only is it charged with the convective transport of metabolic heat from the core to the periphery, but also it enhances radiative heat loss to the surroundings by invoking peripheral vasodilation, thereby increasing the temperature gradient between the periphery and its environment (Leithead and Lind, 1964). By virtue of its high conductivity and specific heat, blood presents an ideal medium of heat transport (Robinson, 1963). Furthermore, the functional integrity of the sweat mechanism is partly maintained by an

adequate dermal perfusion rate (Kuno, 1956). It is therefore not surprising that Belding (1967) regards the cardiovascular system as the "first line of defence" to an elevation of body temperature.

The principal circulatory adjustments which occur during heat exposure are (a) peripheral vasodilation and (b) a compensatory vasoconstriction in other vascular beds, notably that of the splanchnic area (Robinson, 1963; Leithead and Lind, 1964; Rowell *et al*, 1965). The relative fall in the circulating blood volume that may ensue is not only compensated for by vasoconstriction but also by the withdrawal of fluid from extravascular spaces (Bass and Henschell, 1956), while augmented secretions of antidiuretic hormone (Hellman and Weiner, 1953) and aldosterone (Streeten *et al*, 1960) are implicated to a lesser extent. According to Robinson (1963), an increase in cardiac output also takes place but the advantage inherent in this adjustment is largely cancelled due to the inconsistency of this event. This finding appears to be substantiated in a different form by the observations of Rowell *et al* (1966), namely, that the added demands made on the circulatory system during heat dissipation are met by repartitioning the cardiac output rather than by increasing it. Potentially, however, these circulatory adaptations present a threat in so far that the cardiac reserve may be lowered to a critical level, an observation which explains the susceptibility of cardiac patients to hot environments as well as why such patients provide a particularly sensitive

index to thermal stress (Burch *et al*, 1961).

During acclimatisation to heat, the initial period is generally characterised by the presence of circulatory strain. The significant aspect is that circulatory strain is referable to an inadequate perfusion of non-skin areas (skeletal muscle, brain, etc) while an adequate circulation of the skin is effected (Wood and Bass, 1960). According to Bass and Henschell (1956) circulatory strain is alleviated during that stage of the acclimatisation process when splanchnic vasoconstriction exerts its beneficial effect and is manifested by decreases in rectal temperature and heart rate (Lind and Bass, 1963). The concept has therefore been extended that the major adaptation during acclimatisation to heat may be regarded as circulatory (Bass, 1963; Horvath and Howell, 1964).

Although it is generally accepted that the three major cardiovascular adaptations include (a) an increased maximal cardiac output, (b) a decreased peak heart rate and (c) an increased stroke volume (Rowell *et al*, 1966; Wyndham *et al*, 1968), it is doubtful whether a diminished splanchnic blood flow can compensate for the combined losses of plasma water into muscle, repartitioning of blood flow to muscle and skin and losses of extracellular fluid volume in the form of sweat (Knochel, 1974). The net effect is a sharp diminution of the effective arterial blood volume, an event considered to be physiologically deleterious.

From the preceding discussion emerges a point of particular significance, especially so in view of its relevance to this study, namely, that the thermoregulatory commitments of the cardiovascular system enjoy a priority status to the cost of other organs and systems. Further support for this view is based on the observation of Belding (1967) that the limiting factor to exercise in heat appears to be the fraction of the maximal cardiac output (approximately 40%) which is directed to the skin in contrast to exercise in a thermally neutral environment where the limiting factor appears to be the fraction directed to skeletal muscle (approximately 90%). Cardiovascular insufficiency during the initial stages of acclimitisation is therefore directly attributable to an inability to maintain an adequate perfusion of vital centres other than the skin (Bass, 1963). It is also clear that the keystone to man's ability to tolerate hard work in a hot environment is not only his capacity to increase, but also to sustain, cardiovascular performance (Knochel, 1974).

1.2.2 CARDIOVASCULAR STRAIN AND FAILURE DURING HEAT STRESS

Cardiovascular strain, as evidenced by tachycardia and arterial hypotension (Belding, 1967) is a consistent finding during heat exposure of the unacclimatised individual (Hill, 1920; Robinson and Gerking, 1947; Daily and Harrison, 1948; Webb, 1959; Gold, 1960; Minard and Copman, 1963; Folkow *et al*, 1965; Belding, 1967) and as such is regarded as the primary physiological strain (Hatch, 1963) as well as an indication of the

total physiological stress (Gold, 1961).

During acute heat stress, as mentioned previously, nearly 50% of the maximal cardiac output may eventually be shunted to the skin (Belding, 1967) before circulatory failure inevitably must occur. This failure is characterised by a sudden and drastic fall in the cardiac output (Asmussen, 1940; Ferguson and O'Brien, 1960; Gold, 1960; Williams *et al*, 1962; Folkow *et al*,1965). According to Minard and Copman (1963) circulatory failure is the more common consequence of intolerable heat stress and is seldom encountered in heatstroke proper. Bass (1963) regards circulatory collapse as a protective mechanism and explains this phenomenon as follows: "Figuratively, then, the body bows its head to the less dangerous foe - syncope - thus avoiding or at least postponing engagement with the more ominous enemy - heatstroke".

In contrast, the absence of gross cardiovascular malfunction in heatstroke is a finding which cannot be readily explained in view of the major contribution of the cardiovascular system in thermoregulation. For example, on the basis of systolic hypotension as a manifestation of cardiovascular insufficiency, only 19 to 27% of the fatal heatstroke cases reported by Ferris *et al* (1938), Malamud *et al* (1946) and Austin and Berry (1956), exhibited pressures of below 100 mm Hg prior to death. Although Kew (1969) found myocardial damage in the majority of heatstroke cases, "in no case was

the damage sufficiently severe for overt cardiac failure to develop". Yet, in the same publication, Kew expresses the opinion that the tissue injury associated with heatstroke may be caused, amongst others, by tissue anoxia secondary to the hypotension and circulatory collapse which may occur in the acute stage. Although direct thermal injury is at least partly responsible in tissue damage, it has been reported by Schrier *et al* (1970) that hypotension may precipitate acute oliguric renal failure. It remains but to point out that renal damage is invariably present in heatstroke (Kew *et al*, 1967b; Kew, 1969), although a direct "cause-effect" relationship remains speculative. In summary, it appears that cardiovascular insufficiency, in some form or another, is often encountered in heatstroke victims but it is not regarded as a primary factor in the pathogenesis of tissue damage.

1.2.3 THE MECHANISM OF CARDIOVASCULAR FAILURE

Attempts to elucidate the mechanism of cardiovascular failure of heat stress have been a subject of considerable controversy in the past. In 1948, Daily and Harrison posed the following question: "What are the mechanisms of circulatory collapse which complicates stroke? Is it cardiac or peripheral? Obviously, rational treatment must depend on an understanding of the type of failure present". According to Daily and Harrison (1948) the mechanism of circulatory failure may be regarded as peripheral although the cardiac reserve is lowered. These findings represent the general consensus of opinion.

In contrast, Gold (1960) states that "... the primary event in the circulatory collapse of heat pyrexia is high-output cardiac failure ..." It is patently clear that there exists a vast difference in views concerning the mechanism of failure and consequently a more detailed analysis of the respective results and interpretations is warranted.

Essentially, Daily and Harrison's view is based on the finding that venous pressure did not increase during induced hyperthermia. Circulatory failure was signified by a sudden, drastic fall in cardiac output and was ascribed to the abolishment of splanchnic vasoconstriction due to "the accumulation of acid metabolites" although the cardiac reserve was reduced. Gold's hypothesis of high-output cardiac failure stems from the observation that during heat stress venous pressure increased precipitously immediatly prior to the fall in cardiac output. These findings were explained as follows: "The greatly diminished peripheral resistance allows for an abundantly rapid venous return, which in turn increases the cardiac output. Assuming the left side of the heart cannot keep pace with the right, this increase in venous return results in an elevation of venous pressure ...", the sequel to this event being high-output cardiac failure. Gold, by citing Cecil and Loeb's Textbook of Medicine (8th edition, W.B. Saunders, Philadelphia) stresses the fact that in diseases characterised by a high cardiac output while the patient is at rest (e.g., anaemia, thyrotoxicosis, etc.) circulatory failure usually develops before the resting cardiac output falls and thus can mask an underlying cardiac failure.

These widely differing views must, however, be placed in proper perspective. Daily and Harrison experimented with mice, rats and dogs while Gold used human volunteers. Daily and Harrison subjected their animals to an environmental temperature of 45 - 50°C (humidity unknown) and Gold subjected his volunteers to temperatures varying from 54,4°C to 71,1°C at humidity levels of up to 26 mm Hg vapour pressure. Animals were allowed to achieve a rectal temperature of up to 43°C while human volunteers in Gold's study were removed from the heat chamber in obvious distress at rectal temperatures of just over 40°C. It is patently clear that the respective methods employed feature radical differences despite having a common aim. The consequent emergence of two widely differing views is therefore perhaps a logical outcome.

A more detailed analysis of Daily and Harrison's hypothesis (1948) reveals that their findings could not explain the clinical occurrence of pulmonary congestion which often manifests itself in heatstroke (Wilson, 1940; Logue and Hanson, 1946; Kumar, *et al*, 1964). Essentially, pulmonary congestion may result from any factor that displaces blood from the systemic to the pulmonary circulation (Rushmer, 1970), one such mechanism being systemic venous constriction. One therefore may assume the following sequence of events: left heart failure, pulmonary hypertension, right heart failure and ultimately, an elevated venous pressure. It appears, however, that there is ample evidence in the literature that pulmonary congestion in heatstroke is not always the result of cardiac

insufficiency and may occur prior to cardiac failure (Werkö, 1962). Wallace and Bushby (1944) observed an increase in venous pressure during therapeutic hyperthermia but regarded this event as compatible with an increased venous return and not as being indicative of congestive cardiac failure.

In contrast, Knochel *et al* (1961) observed an elevation in venous pressure, in agreement with the findings of Gold (1960), as well as pulmonary congestion associated with myocardial damage. Kumar *et al* (1964) reported a mortality figure of 47% in heatstroke of which 50% of deaths were ascribed to central vasomotor failure and the remainder to pulmonary oedema coupled to central vasomotor failure. While the vascular collapse could have been due to cardiac failure, none of these cases exhibited any signs of cardiac involvement. On the other hand, the fact that Daily and Harrison (1948) could not explain the clinical occurrence of pulmonary congestion in the light of their own experiments, need not be relevant at all. In support, reference is made to the findings of Ferris *et al* (1938) who reported the absence of congestive cardiac failure in 12 severe cases of heatstroke while, according to Schrire (1963), pulmonary congestion is the usual consequence of congestive cardiac failure. By implication, therefore, pulmonary congestion is not a constant finding in heatstroke and even when present, cannot be regarded as a manifestation of cardiac failure in view of the findings of Kumar *et al* (1964) (*vide supra*). This in turn suggests that

pulmonary congestion in heatstroke may result from some factor other than a circulatory abnormality, possibly from direct thermal effects *per se*.

An analysis of the arterio-venous oxygen differences ($A\text{-}V\text{-}O_2$) recorded in the respective studies of Daily and Harrison (1948), and Gold (1960), shows little agreement. In Gold's subjects, the $A\text{-}V\text{-}O_2$ decreased and this decrease was ascribed to an increase in the venous oxygen content. Although Gold did not seek to interpret this finding in detail, one assumes that it reflects a rapid dermal perfusion rate which is partly maintained by effective splanchnic vasoconstriction. If under these circumstances the circulation fails, it would be reasonable to ascribe it to cardiac failure and not to peripheral failure. In contrast, Daily and Harrison's measurements reveal an initial decrease in the $A\text{-}V\text{-}O_2$ which increases drastically in the terminal stages; the latter event being ascribed to a greater oxygen extraction following peripheral failure. Of significance is the fact that this sudden upsurge in the $A\text{-}V\text{-}O_2$ difference occurs prior to the fall in cardiac output thus reinforcing the concept of peripheral vascular collapse. In direct support Folkow *et al* (1965) stated that the critical decrease in venous return in heat syncope is the result of excessive peripheral vasodilation.

Although the hypothesis of peripheral failure propounded by Daily and Harrison (1948) represents the general consensus of opinion, there are definite indications of cardiac involvement in the mechanism of circulatory failure (Borden *et al*,

1945; Knochel *et al*, 1961). The cardiac reserve is depleted beyond doubt (Daily and Harrison, 1948; Kubicek *et al*, 1958) and although the magnitude of cardiac damage sustained in heatstroke appears to be insufficient to produce overt cardiac failure (Kew, 1969), it is not known whether, in the words of Gold (1960), a high-output cardiac failure may be the "triggering-mechanism of circulatory collapse".

In the light of the apparent existence of two contradictory theories concerning the mechanism of circulatory failure, the author recently deemed it necessary to reassess cardiovascular function during acute, experimental hyperthermia in rats (Kielblock, 1973). From the experimental findings it was clear that death could ultimately be ascribed to those factors which caused a fatal reduction in peripheral resistance. It did, however, appear that the fatal reduction in peripheral resistance was preceded by a high-output cardiac failure and thus, in the words of Gold (1960), becomes the "primary event" in circulatory failure of acute heat stress. This finding does not necessarily detract from the observations of Daily and Harrison (1948) in that a reduced cardiac reserve, as opposed to overt failure, merely represents a difference in degree of cardiac insufficiency.

The most likely explanation for the reduction in peripheral resistance probably is the abolishment of splanchnic vasoconstriction following tissue damage in this area,in conjunction with an already widely dilated skin capillary network. This

view is based on the findings of Burger *et al* (1970a) who demonstrated the extreme susceptibility of tissues of the splanchnic area to heat damage under identical experimental conditions as described in the author's paper (*vide supra*). Of significance in this context are the findings of Rowell *et al* (1968) who observed that during exercise in a hot environment (48,9°C DB, 25°C WB), unacclimatised young males exhibited a hepatic venous blood temperature of 41,6°C (107°F) while the core temperature was 40,0°C (104°F). In the final analysis, the findings reported above must to a certain extent remain inconclusive in view of the fact that once again, a different set of procedures and conditions was employed from those used by Daily and Harrison (1948) and by Gold (1960).

Finally, to emphasise the complexity of the problem, reference can be made to the treatment of hypotension incident to heat-stroke as prescribed by Knochel (1974). He suggests that although "the pronounced peripheral vasodilatation during hyperpyrexia will often respond to cooling alone .. large quantities of .. plasma expanders .. may overload the central circulation and produce acute pulmonary edema" and "if hypotension persists after cooling, appropriate agents used in therapy of cardiogenic shock should be administered since the patient may have myocardial damage from heat injury *per se* or lactic acidosis". In view of the preceding therapeutic measures advocated by Knochel (1974), it appears that Daily and Harrison's original question concerning the mechanism of circulatory collapse ("Is it cardiac or peripheral?") remains largely unanswered.

1.2.4 *CIRCULATORY FAILURE AS A PRIMARY FACTOR IN THE PATHOGENESIS OF HEATSTROKE*

A review of the literature reveals that circulatory failure, either cardiac or peripheral in origin, is not regarded as a primary factor in the pathogenesis of heatstroke (Minard and Copman, 1963). This view is supported by the extent of myocardial damage in the clinical reports of Kew (1969): " ... in no case was the (myocardial) damage sufficiently severe for overt cardiac failure to develop". Of particular relevance, however, is whether cardiovascular failure, either cardiac or peripheral in origin, overt or transient, could initiate a vicious cycle sequence of events culminating in tissue damage. With this end in mind, a brief discussion of the literature concerning the role of circulatory failure in the pathogenesis of heatstroke is warranted.

Minard and Copman (1963) state that circulatory failure is the more usual response to acute heat stress and is seldom encountered in heatstroke proper. Apart from the "protection" afforded by syncope (Bass, 1963), the underlying physiology as to why circulatory failure is involved in one set of conditions and not in another, remains obscure.

Gold (1960) demonstrated that the elevation in venous pressure following high-output cardiac failure was accompanied by cessation of sweating. He subsequently postulated that this elevation in venous pressure was ultimately responsible for the cessation of sweating characteristic of heatstroke.

According to Minard and Copman (1963) Gold observed "severe circulatory strain in a subject whose central thermoregulatory mechanisms, though under stress, were fully operative". Minard and Copman (1963) furthermore state that since there is clear evidence clinically that cessation of sweating occurs in the absence of circulatory failure, the mechanism of sweat cessation should be sought not in an elevation of venous pressure, as suggested by Gold, but elsewhere. This is in accord with the findings of Kuno (1956) who observed that ischaemia is the only circulatory change conducive to sweat cessation.

On the other hand, an elevation of venous pressure may not necessarily be indicative of an increase in flow rate. In fact, the contrary might apply in that the elevated venous pressure is the result of an inadequate capacity of the right heart to handle the prevailing venous return thereby enforcing a venous build-up of blood, a condition described as "backward failure" (Rushmer, 1970). Such circumstances may promote the functional equivalent of ischaemia in view of the stagnant state of blood and would be reflected by an increased A-V-O_2 as reported by Daily and Harrison (1948). In the light of current concepts the above considerations may well explain Gold's conclusion that sweat cessation is referable to an elevated venous pressure secondary to cardiac insufficiency.

A second point of criticism levelled against Gold is that the diminished sweating reported by him may be regarded as an example of "fatigue of sweating" and the picture of circulatory collapse akin to heat syncope (Leithead and Lind, 1964). Although the validity of this statement is not questioned as such, it must be pointed out that the mechanism of "fatigue of sweating" is largely unknown except that it is independent of water depletion (Leithead and Lind, 1964). In any event, the question of sweat cessation may in all probability be of no consequence: according to Shibolet *et al* (1967) sweat cessation is not always one of the cardinal signs of incipient heatstroke since heatstroke may result not only from failure of the thermoregulatory system but also from overloading of its capacity.

Finally, in support of cardiovascular malfunction as a pathogenic factor, reference can be made to the classic report on the autopsy findings in 125 fatal cases of heatstroke submitted by Malamud *et al* (1946) wherein they state: "Most of the lesions apart from those in the brain can be attributed to the anoxia and circulatory failure incident to shock".

1.3 MANIFESTATIONS OF HEAT STRESS

1.3.1 CLINICAL FINDINGS

Clinical findings in established cases of heatstroke, though often obscured by therapeutic measures, may to a certain

extent yield valuable information pertaining to the prodromal sequence of events which, characteristically, is seldom manifest. For this reason, such findings require further consideration in the context of this study.

1.3.1.1 ELECTROCARDIOGRAPHY AND SERUM ELECTROLYTES

Electrocardiographic evidence of myocardial damage appears to be a constant finding in heatstroke and reflects a wide range of abnormalities. The most common abnormality pertains to T-wave changes (Metz, 1940; Logue and Hanson, 1946; Malamud *et al*, 1946; Herman and Sullivan, 1959; Gold, 1960; Ferguson and O'Brien, 1960; Kew, 1969; Kew *et al*, 1969) which therefore indicates an abnormal repolarisation pattern. Prominent U-waves (Logue and Hanson, 1946), tachycardia and atrial fibrillation (Ferguson and O'Brien, 1960) and a high incidence of ST-segments abnormalities (Kew *et al*, 1969; Knochel, 1974) have also been observed.

Limited information is available regarding the EKG obtained during the prodromal period. Clagett (1944), in a series of fever therapy cases, concluded that the majority of changes was insignificant and probably due to the effect of tachycardia. In contrast, Gold (1960) observed inverted T-waves, ST-segment depression, ectopic foci and extra-systoles during experimentally induced hyperthermia. Whether the latter observations are significant or not, remains speculative.

In view of the variety of EKG-abnormalities reported, it appears difficult, if not impossible, to interpret these findings except to discern between "normal" and "abnormal". Although Kew (1969) established a good correlation between EKG-abnormalities and elevated LD-levels in serum, no relationship could be detected between the level of serum LD and the type of EKG-abnormality. Moreover, electrocardiographic changes could be referable not only to myocardial damage but to secondary factors such as electrolyte imbalance.

Serum electrolytes, especially potassium, are known to exhibit significant changes during various stages of heat stress, including heatstroke. In view of the potentially profound effect of variations of serum potassium levels on cardiovascular function, this aspect is briefly discussed below.

Mild exposure to heat with concomitant hyperventilation often results in hypokalaemia (Daily and Harrison, 1948; Iampietro, 1963). Performance of strenuous physical labour in heat is generally accompanied by hyperkalaemia (Kilburn, 1966; Spurr and Barlow, 1970) while in heatstroke proper both hypokalaemia (Knochel *et al*, 1961; Shibolet *et al*, 1967) and hyperkalaemia (Austin and Berry, 1956; Baxter and Teschan, 1958) have been observed. Hyperkalaemia also appears to be a consistent finding in experimental heat stress in animals (Barlow *et al*, 1956, Spurr and Barlow, 1959a, 1959b, 1970; Burger *et al*, 1970b; Kielblock, 1972).

According to Spurr and Barlow (1959b) the basic cause of hyperkalaemia is due to cellular damage and a subsequent efflux of potassium although epinephrine release may at least be partly responsible. The primary sources of potassium appear to be the liver, jejunum, connective tissue (Spurr and Barlow, 1970) and muscle (Kilburn, 1966).

Hyperkalaemia exhibits a characteristic electrocardiographic pattern (Burch and Winsor, 1960; Pryor and Blount, 1966) and depresses cardiac function in several ways (Herndon *et al*, 1955; Greenspan *et al*, 1965; Winsor, 1968). However, pronounced hyperkalaemia has been observed in the absence of any electrocardiographic sign thereof (Spurr and Barlow, 1959a; Kielblock, 1972), a phenomenon ascribed to an observed concomitant intracellular elevation of cardiac potassium content (Spurr and Barlow, 1959a), whereby the ratio of extra- to intracellular potassium remains unaltered.

Of greater significance perhaps is the potent vasodilatory effect of potassium (Kjellmer, 1965; Laurell and Pernow, 1966; Skinner and Powell, 1967). In severe heat stress, therefore, hyperkalaemia may well be implicated in circulatory failure along this avenue. On the other hand, hypokalaemia may have an equally disastrous effect: Knochel *et al* (1970) demonstrated a sharp fall in cardiac output in dogs during exercise.

Although many other changes in serum and tissue electrolytes have been reported in the literature, a detailed discussion thereof falls outside the scope of this review.

In summary it therefore appears that despite the extensive electrocardiographic evidence of myocardial damage reported in the literature, no clear patterns emerge. Moreover, in the presence of observed electrolyte imbalance, the interpretation of the EKG becomes an extremely hazardous affair.

1.3.1.2 *SERUM ENZYME LEVELS*

The diagnosis of heatstroke, which is readily based on certain clinical findings as well as a knowledge of the prevailing environmental conditions, is often complicated during the presentation of atypical symptoms. Although elevated serum enzyme levels in heatstroke have been reported by many researchers and clinicians, the significance thereof has apparently been largely underrated. Relatively recently, however, Kew *et al*, (1967a) proposed the use of serum enzyme estimations to enable a more accurate diagnosis of the affliction. Subsequent findings have amply substantiated this approach not only from a diagnostic point of view but also in establishing the severity and extent of tissue damage as well as the general prognosis (Kew *et al*, 1967a; Kew *et al*, 1971).

A review of the literature indicates that an elevation of serum enzyme levels is a consistent finding in heatstroke

(Herman and Sullivan, 1959; Shibolet *et al*, 1962; Wyndham *et al* 1974; Kew *et al*, 1967a; Kew 1969; Kew *et al*, 1969; Kew *et al*, 1971). Of especial prognostic significance is the elevation of AST in that it is regarded as an indicator of the severity of tissue damage (Kew *et al*, 1967a; Kew *et al*, 1971) while an elevation in CK in cerebrospinal fluid may provide a good index of neurological damage (Kew *et al*, 1967a.) Furthermore, ALT and LD levels are almost invariably increased in heatstroke (Kew *et al*, 1971) and the former enzyme also in artificially induced fever (Gupta *et al*, 1963). An analysis of the isoenzyme pattern of LD reveals a significant increase in the LD_1 -fraction in 69% of cases (Kew, 1969), a finding which is in agreement with the observations of others (Gore and Isaacson, 1949; Shibolet *et al*, 1967). Although cardiac damage was definitely sustained in the cases reported by Kew (1969) and Kew *et al*, (1971), the damage was insufficient to produce overt cardiac failure. An elevation in serum CK, accompanied by electrocardiographic evidence of myocardial damage, strongly suggests a cardiac origin, although skeletal muscle may also be the source thereof (Kew *et al*, 1967a).

A final consideration concerns the elevation of serum enzyme levels during exercise where a physiological increase in core temperature takes place (Garbus *et al*, 1964; Schrier *et al*, 1970). In this context, the observations of Rowell *et al*, (1968) in untrained young men exercising in a hot atmosphere (WB = 25°C), are highly significant: " ... temperature of hepatic venous blood rose as high as 41,6°C (107°F) while

simultaneous core temperature was 40,0°C (104°F)". These findings are in agreement with those reported by Gilat *et al*, (1963) who recorded rectal temperatures of 42°C (107,6°F) in physically conditioned men performing strenous work. It is therefore logical to assume that exercise induced hyperthermia could well lead to tissue damage.

Limited data are available concerning serum enzyme estimations in experimentally-induced hyperthermia in animals, although elevated LD-isoenzyme levels of myocardial origin have been reported after exercise in untrained rats (Garbus *et al*, 1964); Papadopoulos *et al*, 1967). These elevations correlated with evidence of cardiac damage on the basis of histological examinations.

1.3.1.3 CARDIOVASCULAR FUNCTION

According to Knochel (1974) "the most critical determinant of man's defence against environmental heat resides in the integrity of his cardiovascular system ..." It therefore follows in the first instance that any form of cardiovascular disease could jeopardise survival, a deduction readily substantiated by the adverse effects of environmental heat on patients with congestive heart failure (Burch, 1946; Burch and Hyman, 1957; Ansari and Burch, 1969). In 100 selected cases reported by Austin and Berry (1956), 84% of patients had some form of cardiovascular disease while Levine (1969) reported 25 fatal cases of hyperpyrexia of which 72% exhibited arteriosclerotic heart disease.

While the above references pertain to elderly people and invalids, fatal heatstroke can occur in perfectly healthy, highly acclimatised and physically conditioned individuals when heat dissipation is exceeded by endogenous heat production (e.g. sustained strenous physical labour in heat). Whereas cardiovascular involvement is patently clear in the former group, it is less evident as a primary factor in the latter although by no means irrelevant. To illustrate the extent of cardiovascular involvement in the latter group, extracts of a number of case reports are given.

CASE 1.[1] *A 20-year old football player was admitted to hospital after having collapsed during practice. His rectal temperature exceeded 42,2°C (108°F), the pulse rate was 160 beats per minute and his blood pressure 80/0 mm Hg. One hour later, after having received only 800 ml of fluid intravenously, he showed signs of frank pulmonary oedema. After 18 hours the EKG showed ST-T changes compatible with acute posterior myocardial ischaemia. He died approximately 36 hours after admission.*

CASE 2.[1] *A 21-year old Vietnam veteran was admitted to hospital because of insomnia, agitation and confusion. Approximately one week later heatstroke developed. His rectal temperature was 43,3°C (110°F) his pulse 140 beats per minute and his blood pressure 60/40 mm Hg. Despite cooling, his blood pressure did not respond. He died 3 days after the onset of heatstroke.*

CASE 3.[2] *A 19-year old man collapsed at the end of a strenuous 10-km run. Upon admission to hospital, his temperature was 40°C (104°F), his pulse 140 and the blood pressure 70/40 mm Hg. After fluid therapy, the blood pressure rose to 120/80 mm Hg while a pulse rate of 144 beats per minute was recorded. The patient remained in stupor. On the third day the blood pressure suddenly dropped to 0. There was no response to epinephrine nor to hydrocortisone. He died shortly afterwards.*

CASE 4.[2] *A 19-year old man was admitted to hospital after a strenuous march, exhibiting typical signs of heatstroke. The rectal temperature was 41,6°C (106,8°F) and hypotension, subsequently partly alleviated by norepinephrine, was present. He died 64 hours after admission.*

CASE 5.[2] *A 20-year old man was admitted to hospital after a 15-km march. His rectal temperature was 42,5°C (108,5°F) and hypotension was present which did not respond to intravenously administered norepinephrine. He died 48 hours after admission.*

Case reports by Knochel (1974)[1], Shibolet *et al* (1962)[2], and Herman and Sullivan (1959)[3].

CASE 6.[3] *A 23-year old man undergoing military service became unconscious a short while after leaving practice on the rifle range. On admission his rectal temperature was 42,2°C (108°F), pulse 180 and blood pressure 120/80 mm Hg. During the examination his blood pressure fell to 76/0 mm Hg. Ice packs and intravenous fluid administration had a beneficial effect. He was eventually discharged with no serious after-effects.*

A striking feature in the above cases is the presence of circulatory shock on admission (Cases 1 - 5) or soon thereafter (Case 6). In all instances (except Cases 2 and 6) strenuous physical exercise preceded collapse while therapeutic measures met with little success in most of the cases (1, 2, 4 and 5). The important question which arises is whether circulatory failure could have initiated the onset of heatstroke or whether it merely is the result thereof. Case 1 not only strongly supports the former speculation but also suggests cardiac failure as a primary factor in the observed circulatory collapse.

The presentation of these case reports, and the emphasis placed on circulatory collapse, are by no means intended to give the impression of being representative of heatstroke cases. For example, in a number of cases reported by Ferguson and O'Brien (1960) the blood pressure on admission was generally normal (130/80) or even hypertensive (180/70). The major difference between the latter and those cited in this review is that Ferguson and O'Brien's cases were elderly individuals living

sedentary lives and who were exposed to increases in environmental heat. It would, however, appear that in certain situations circulatory instability is a prominent feature which may well play a major part in the pathogenesis of heatstroke.

1.3.2 EXPERIMENTAL FINDINGS

It is generally accepted that heat *per se* is at least partly responsible for cellular damage and as such must play a significant part in the pathogenesis of heatstroke. According to Michaeli (1969) "the aetiology of heatstroke is variable, but the pathogenesis is similar in all cases. It is the widespread cellular damage due to heat which is the base of the process". While the validity of this statement is recognised in the current study, this thesis concerns the role of a specific system (the cardiovascular system) in general and a specific organ (the heart) in particular. However, in so far that the basic mechanism of tissue damage is referable to cellular and subcellular malfunction, an aspect which is an integral part of this study, the following review is presented.

The most sensitive indicator of heat damage appears to be the reduction in the *in vitro* oxygen uptake (Q_{O_2}) of tissues (Burger and Engelbrecht, 1967). Using this criterion, Burger *et al* (1970a) concluded that liver, spleen, small intestine and skeletal muscle were the most heat sensitive of those tissues investigated. It is interesting to note that with

the exception of skeletal muscle, these tissues are perfused by the splanchnic circulation which may account for their particular susceptibility to heat damage "during the period of diminished splanchnic flow" described by Daily and Harrison (1948). Of further significance is the fact that whereas these findings were based on the reduction in Q_{O_2} after 10 minutes of exposure to a core temperature of 42,5°C, exposure for 20 minutes to the same temperature did not significantly lower the Q_{O_2} of cardiac muscle. In another series of experiments (Burger and Engelbrecht, 1966; 1967) an analysis of the results obtained from a wide variety of tissues indicates a relatively high degree of heat sensitivity of cardiac muscle in comparison with others. It must be pointed out that in the latter series (Burger and Engelbrecht, 1966; 1967) tissues were incubated while subjected to heat whereas in the former (Burger *et al*, 1970a) the intact animal was subjected to heat and only thereafter the tissues removed and incubated. Whereas the former series represents a more "physiological" situation, an interesting conclusion may be reached, namely, that while cardiac tissue is essentially heat senstive (similar to skeletal muscle), the *in vivo* state of affairs affords protection to cardiac tissue by some mechanism (circulatory?) which does not extend to skeletal muscle. As far as the apparent discrepancy between the *in vivo* and *in vitro* situations (*vide supra*) is concerned, Burger (1972) established that the heat sensitivity of tissues *in vivo* differed from the heat sensitivity *in vitro*.

In the above context, the findings of Opie *et al*, (1965) are noteworthy. Isolated perfused rat hearts were subjected to supranormal temperatures and while "unaltered mechanical performance ... at high temperatures" was observed, evidence of biochemical damage (fall in myocardial ATP content and an increased LD output, creatine output and ammonia production) became evident at a perfusate temperature of 41°C. The biochemical derangement appears to be in conflict with the maintenance of mechanical performance. According to the authors, the observed biochemical changes are likely to be caused by the direct effect of hyperthermia on myocardial cellular metabolism. *In vivo*, heat exposure is accompanied, initially at least, by a hyperkinetic circulation. In so far that this condition was not simulated in the isolated perfused heart system, the extent of biochemical derangement observed in these experiments could well be responsible for overt cardiac failure *in vivo*.

Of further significance are the findings of Burger *et al* (1970b) who were able to demonstrate an acute lactic acidosis in the blood of hyperthermic animals. According to Wildenthal *et al*, (1968) lactic acidosis exerts a direct negative inotropic effect on the left ventricle and reduces ventricular responsiveness to exogenous catecholamines. By implication therefore, theoretically at least, cardiac function *in vivo* will not only be burdened by a hyperkinetic circulation but will also be depressed by secondary factors such as acidosis during heat exposure.

In the current study it is intended to largely duplicate the experimental procedures of Burger and his co-workers with regard to (a) the choice of experimental animals, (b) the level of hyperthermia and (c) the approximate duration thereof. The foregoing review is therefore particularly relevant to the current study.

1.4 THE EXPERIMENTAL MODEL

The current study employs an animal model and in so far that rats do not sweat, it may be argued that this feature precludes the extrapolation of animal data to man. In point of fact, according to Bynum *et al* (1977), the absence of a sweat mechanism in most laboratory animals has constituted a serious obstacle in the development of animal models in the past, the major objection being related to the fact that sweat cessation was regarded as one of the cardinal signs of heatstroke. This has since been questioned in view of the observation that heatstroke may occur in the presence of profuse sweating (Shibolet *et al*, 1967; Eichler *et al*, 1969), an observation which has paved the way to the development of animal models.

The choice of the laboratory rat as experimental model in the current study is motivated in the next chapter (Section 2.1) and the validity of the model is discussed in the final chapter (Section 5.2). It remains to point out that the laboratory rat has recently been extensively employed in similar studies (Hubbard *et al*, 1976; 1977; 1978).

1.5 SUMMARY

The cardiovascular system is regarded as the "first line of defence" to an elevation in body temperature, and cardiovascular adaptations as the major event during acclimatisation to heat. Although cardiovascular strain is a consistent finding during heat exposure of unacclimatised individuals, circulatory failure is not regarded as a primary factor in the pathogenesis of tissue damage in heatstroke. Certain findings do, however, support a contrary view. In this respect it would appear that exercise-induced heatstroke manifests profound circulatory instability which may constitute the cause/result of the initiation of heatstroke. In contrast, heatstroke of environmental origin *per se*, exhibits little cardiovascular involvement.

The mechanism of circulatory failure during heat exposure is explained by conflicting theories. Electrocardiographic and serum enzyme analyses consistently reflect some form of myocardial damage but the magnitude of damage is not regarded as sufficient to cause circulatory failure. In addition, cardiac tissue, inherently susceptible to heat damage *in vitro*, appears to be heat resistant *in vivo*, although serious biochemical derangements have been demonstrated.

C H A P T E R II

MATERIALS AND METHODS

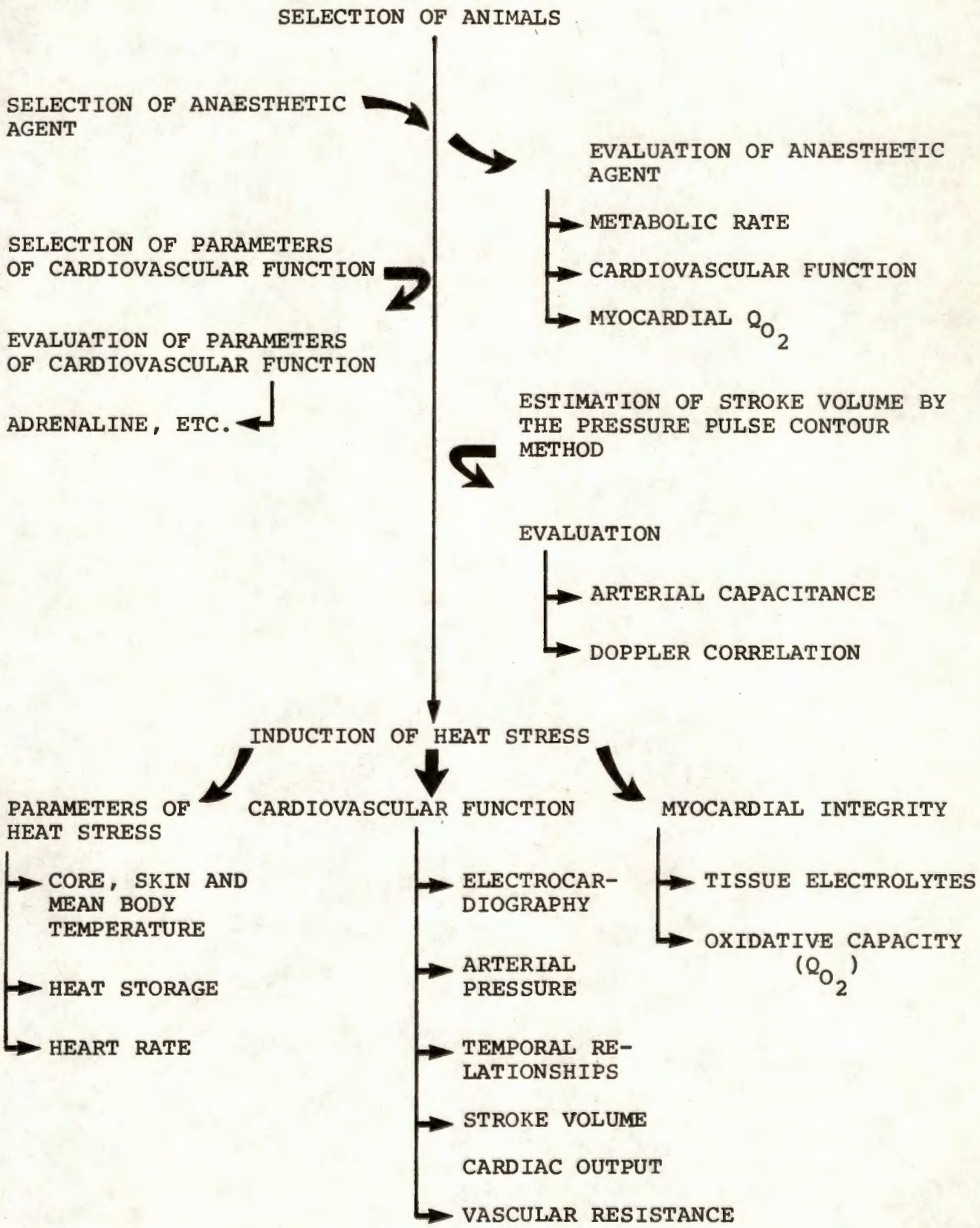
The objectives of this study have been detailed at the outset and the relevant background presented in the literature survey. In its widest sense, these objectives concern an evaluation of cardiac performance during conditions of stress. For this purpose, certain techniques and procedures were adopted and in as much as this was deemed highly relevant, the selection of these techniques and procedures is motivated in this chapter where applicable. The experimental protocol is summarised schematically in Figure 2.1.

2.1 EXPERIMENTAL ANIMALS

Male albino rats (*Rattus norvegicus*) of 250 - 300 g were exclusively used in all experiments. This body mass corresponds to an age of about 3 months and the rats may therefore be classed as young, healthy adults. On the basis of the findings of Kumar *et al* (1964) and Gold (1960), which demonstrate the heat intolerance of the young and the aged respectively, this stage of development is likely to represent a maximal natural tolerance to heat in the animals.

All animals were bred and raised in a constant environment room (temperature : 20^{o}C; relative humidity : 65%). The rat pellet diet (Epol) was supplemented twice-weekly with raw vegetables and skimmed milk. These procedures were adopted

FIGURE 2.1 *EXPERIMENTAL PROTOCOL*



to ensure uniform growth and metabolic rates and to eliminate seasonal acclimatisation. For practical purposes, the animals were regarded as unacclimatised. All animals were fasted for 24 hours prior to an experiment; water being available *ad libitum*.

The choice of the albino rat as experimental animal is based on several factors not the least of which is, as was pointed out above, the relative ease with which variables such as age, mass, metabolic rate and state of acclimatisation may be controlled. The second consideration stems from the observation that the rat, with a large body surface area to mass ratio, experiences a greater degree of physiological stress at a given environmental heat load than do larger animals (Schmidt-Nielsen, 1964). This means that the time factor in these experiments is reduced considerably and that the influence of various experimental interventions *per se* e.g., anaesthesia, catheterization, etc., is not as profound as in longer experiments. Thirdly, in much research of this nature rats have been used extensively. Examples are *in vitro* and *in vivo* tissue damage assessments (Burger and Fuhrman, 1964 a and b; Burger and Engelbrecht, 1966, 1967 and Burger *et al*, 1970 a and b), heat tolerance studies (Baker and Horvath, 1964), cardiovascular function during heat stress (Daily and Harrison, 1948; Opie *et al*, 1965) and comprehensive biochemical analyses (Burger, 1972). The obvious advantage of the wide usage of rats is that the interpretation of newer findings is greatly facilitated.

There are, however, certain disadvantages attached to the use of rats as experimental animals in studies of this nature. These pertain largely to the limited number of measurements which may be recorded simultaneously in small animals. Also, due to their small size, blood and tissue analyses are restricted to a relatively small number and consequently a large number of animals may have to be used to derive statistically meaningful data. Probably the only formidable obstacle, however, concerns attempts to extrapolate such data to man. Despite these problems, it was nevertheless concluded that the use of rats, especially in view of the amount of research already published, is justified, and that the advantages clearly outweigh the disadvantages.

2.2 *ANAESTHESIA*

2.2.1 *CHOICE OF ANAESTHETIC AGENT*

For the purpose of the current investigation sodium pentobarbitone anaesthesia ("Sagatal", Maybaker, S.A.) appeared to be the most suitable anaesthetic agent. The ultra short-acting thiobarbiturates, due to the toxic effect of the sulphur atom, and the phenobarbiturates, due to their long lasting effects (Sharpless, 1966), were both deemed unsuitable, while the indiscriminate use of ether causes marked bradycardia (Kisch, 1953). The extensive usage of sodium pentobarbitone in similar experiments was regarded as a further recommendation.

2.2.2. *DOSAGE AND ADMINISTRATION*

In compliance with the Helsinki Declaration regarding the proper use, care and treatment of experimental animals, and by virtue of surgical intervention (carotid catheterization), all animals were anaesthetised by an intraperitoneal injection of sodium pentobarbitone. The dosage was 40 mg/kg body mass. The stock anaesthetic (60 mg/ml) was diluted with a solution of 0,85% sodium chloride to give a final concentration of 10 mg/ml.

2.2.3 *EVALUATION OF SODIUM PENTOBARBITONE*

Sodium pentobarbitone anaesthesia exhibits a demonstrable suppression of cardiovascular function which is manifested in decreases in heart rate, cardiac output, mean arterial pressure and total peripheral resistance (Sharpless, 1966; Pretorius *et al*, 1966; Kielblock 1972). According to Rieke and Everett (1957), pentobarbitone anaesthesia also causes a redistribution of blood in rats so that increases in blood volume occur in the splanchnic organs, the skin and genitalia while decreases occur in the central nervous system, bone and skeletal and cardiac muscle.

While the effects of sodium pentobarbitone anaesthesia described above are widely held to be negligible in normothermic animals, the effects of this drug during thermal stress have not been adequately described. According to Setnicar and and Temelcou (1961) the induction of hypothermia during

anaesthesia results in a decrease in the rate of catabolism of the drug. Whether the opposite occurs during hyperthermia, is not known. However, an increase in ammonia production, over and above the increase observed in unanaesthetised animals, has been reported during experimental hyperthermia (Burger and Fuhrman 1964b) and although the potentially cytotoxic ammonia may aggravate the condition of hyperthermia, cytotoxic elevations (8 - 12µg/ml of blood) were not encountered as a result of the induction of hyperthermia.

In so far as the primary site of action of sodium pentobarbitone is the central nervous system (Whitehead and Virtue, 1965), it was reasonable to assume that central thermoregulation would be impaired during anaesthesia, and that this impairment, while possibly exhibiting negligible effects in normothermic animals, could result in profound intolerance to thermal stress.

The implication of impaired thermoregulation due to anaesthesia, in investigations concerning thermoregulation, is that so-called control animals may be rendered grossly abnormal, to such an extent, in fact, that the experimental model becomes meaningless in a physiological sense. It was therefore deemed necessary to delineate the effects of pentobarbitone anaesthesia on the integrity of thermoregulation, not only in normothermic animals but also in animals subjected to heat. In order to gain more insight, these preliminary studies were extended to include the stress of cold so that the full spectrum of thermal stress could be evaluated in the anaesthetised animals.

Selected animals were divided into two main categories viz., unanaesthetised and anaesthetised. Each category was then subdivided into three subgroups, namely, hyperthermia, normothermia and hypothermia. The groups were then subjected to environmental temperatures of 45, 20 and 5^{o}C, respectively, for a period of 30 minutes i.e., the approximate minimum duration of anaesthesia during normothermic conditions. During this period, the heart rate and core and skin temperatures were monitored every 5 minutes. These measurements are described in details under appropriate headings elsewhere in this chapter.

At the end of this period, metabolic rate was assessed on the basis of oxygen consumption, the principle of the method being the relationship between metabolic rate and oxygen consumption.

The apparatus (Palmer) consists of an airtight chamber containing a soda-lime carbon dioxide absorbent and a small fan to circulate air within the chamber. An inlet is the means by which oxygen is introduced into the chamber. The outlet is connected to a water manometer.

The animal was placed within the chamber and, with a second outlet open to atmospheric air, allowed to become accustomed to its new surroundings. The chamber was then sealed off from the atmosphere after which 20 ml of oxygen was injected into the chamber by means of a pre-filled syringe, the initial level of the water column being noted immediately after the introduction of oxygen. The difference between

this level and that recorded when the chamber was open to the atmosphere, was regarded as the equivalent of 20 ml of oxygen.

After 5 minutes, the volume of oxygen consumed was calculated from the proportionality between the vertical deflection in the level of fluid in the manometer and 20 ml of oxygen. This volume was then converted to oxygen consumption in litres per hour under conditions of standard temperature and pressure. Assuming an RQ of 0,91 (Zarrow *et al*, 1964) the energy expenditure was calculated at a caloric equivalent of 4,93C per litre of oxygen consumed (20,64 kJ/l of O_2) and, using the formula of Engelbrecht (1964) for body surface area (A):

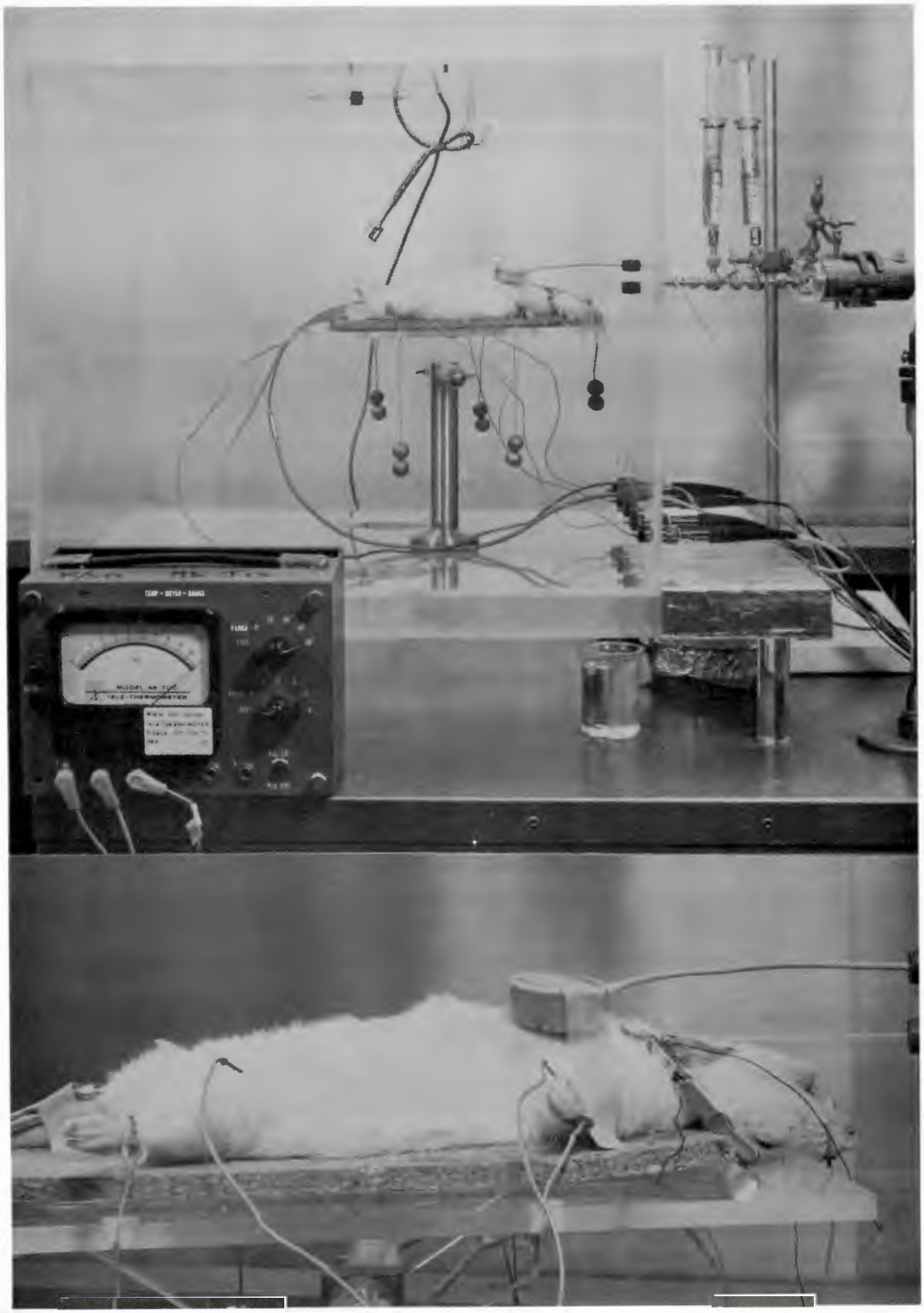
$$A = (m^{0,666} \times 11,36)/10^4$$

where A is given in m^2 and m in g body mass, metabolic rate was finally expressed in $C/m^2/h$.

2.3 *INDUCTION OF HEAT STRESS*

Heat stress was induced in a cabinet of special design (Figure 2.2). The cabinet was constructed of "Perspex" and consisted of a base and a lid of which one of its four sides had been omitted and, instead, attached to the base. This side served as a terminal board through which the EKG electrodes, the PCG cable, carotid catheter and the core and skin temperature thermistors were led to the interior of the cabinet. The lid was placed on the base in special slots which ensured a

FIGURE 2.2: *THE INDUCTION OF HEAT STRESS (ABOVE) AND MEASUREMENTS OF THE EKG, PCG AND ARTERIAL (CAROTID) PRESSURE (BELOW)*



reasonably airtight seal. An outlet valve was fitted into the roof of the lid. Heat was generated by a standard, high-capacity "Shandon" drying oven and ducted into the cabinet via its base. Using the oven thermostat for coarse settings, the temperature within the cabinet could be controlled to within ± 0,1°C of the desired value by manipulation of the outlet valve. No measurable temperature gradients could be detected within the cabinet. The relative humidity varied between 10 and 15% within the cabinet.

Anaesthetised experimental animals were placed on a special platform in the supine position. Following carotid catheterisation, the EKG leads, the PCG microphone and the temperature probes were positioned and the lid replaced. The desired cabinet temperature could be re-established within less than one minute.

The major advantage afforded by this design, in contrast to the water-bath method of induction of heat stress, is the relatively large amount of data which may be recorded concurrently. Secondly, in so far as the various leads do not have to be relocated between obtaining control and experimental recordings, as would have been necessary for the water-bath method, a direct and more meaningful comparison could be made between base-line and experimental data. It was estimated that the heat load induced by this method, at an air temperature of 45°C, is approximately 30% less than that induced by the water-bath method where the animal was partially submerged at a water temperature of 42°C.

2.4 *MEASUREMENTS OF CARDIOVASCULAR FUNCTION*

2.4.1 *BASIC RECORDINGS AND INSTRUMENTATION*

The basic recordings comprised the electrocardiogram (EKG), the phonocardiogram (PCG) and arterial (carotid) pressure. All the basic data were relayed to an Elema-Schönander "Mingograf 81" 8-channel polygraph.

This recorder is equipped with, amongst others, six EKG-amplifiers, a phonocardiogram pre-amplifier (EMT 21) and an electromanometer (EMT 31). The "Mingograph 81" employs a recording system with ink-jet galvanometers providing recordings in rectilinear co-ordinates. The principle is that writing fluid is jetted directly onto writing paper at a pressure of about 25 atmospheres.

Due to the low inertia of the writing system, high fidelity recordings are obtained. The frequency response of the combined galvanometer and final amplifier is practically linear from d-c to 500 Hz and some 10% down at 700 Hz.

The final amplifiers were calibrated to give a 2 cm deflection per 1mV-impulse for EKG and PCG recordings while pressure was calibrated against a mercury manometer so as to give a 3,3 cm deflection per 100 mm Hg. These calibrations, as well as the recording speed of 250 mm per second, were rechecked regularly.

2.4.1.1 *ELECTROCARDIOGRAPHY*

The EKG was recorded from sub-cutaneous needle electrodes placed in the axillae and the lower abdomen, immediately medial to the anterior superior iliac spine (Figure 2.2).

For electrocardiographic analyses, a programme was selected to give leads I, II, III, aVR, aVL and aVF.

2.4.1.2 *PHONOCARDIOGRAPHY*

The heart sounds were picked up by means of a piezo-electrical microphone (Elema-Schönander EMT 25C) placed in the mid-sternal area (Figure 2.2). The full spectrum of heart sounds was subsequently subjected to electronic filtering (EMT 21) which allowed the registration of 6 PCG's having the following characteristics -

PCG-CHANNEL NO	FREQUENCY (Hz) OPTIMUM	RANGE
1	12	0 - 200
2	150	12 - 600
3	200	50 - 800
4	500	150 - 1200
5	700	300 - 1200
6	400	12 - 1000

For analytical purposes other than pure electrocardiography, a programme was selected to include EKG lead II (channel 1) as monitor, PCG leads 2 - 6 (channels 2 - 6), while channels 7 and 8 were allocated to pressure recordings. The advantage

of recording as many as 5 PCG's was noted in a previous study (Kielblock, 1972) where, it was found that, during drastic alterations in cardiovascular function, greater reliance may be placed on channels other than those used routinely for analytical purposes.

2.4.1.3 BLOOD PRESSURE

Blood pressure was measured directly by catheterization of the left common carotid artery (Figure 2.3). The catheter ("Intramedic" PE 50) was heparinized prior to being placed in position by way of an incision in the carotid wall. About 0,2 ml of saline was injected into the general circulation via the carotid catheter to ensure that no air bubbles were lodged in the system, thereby causing a "damped" pressure recording.

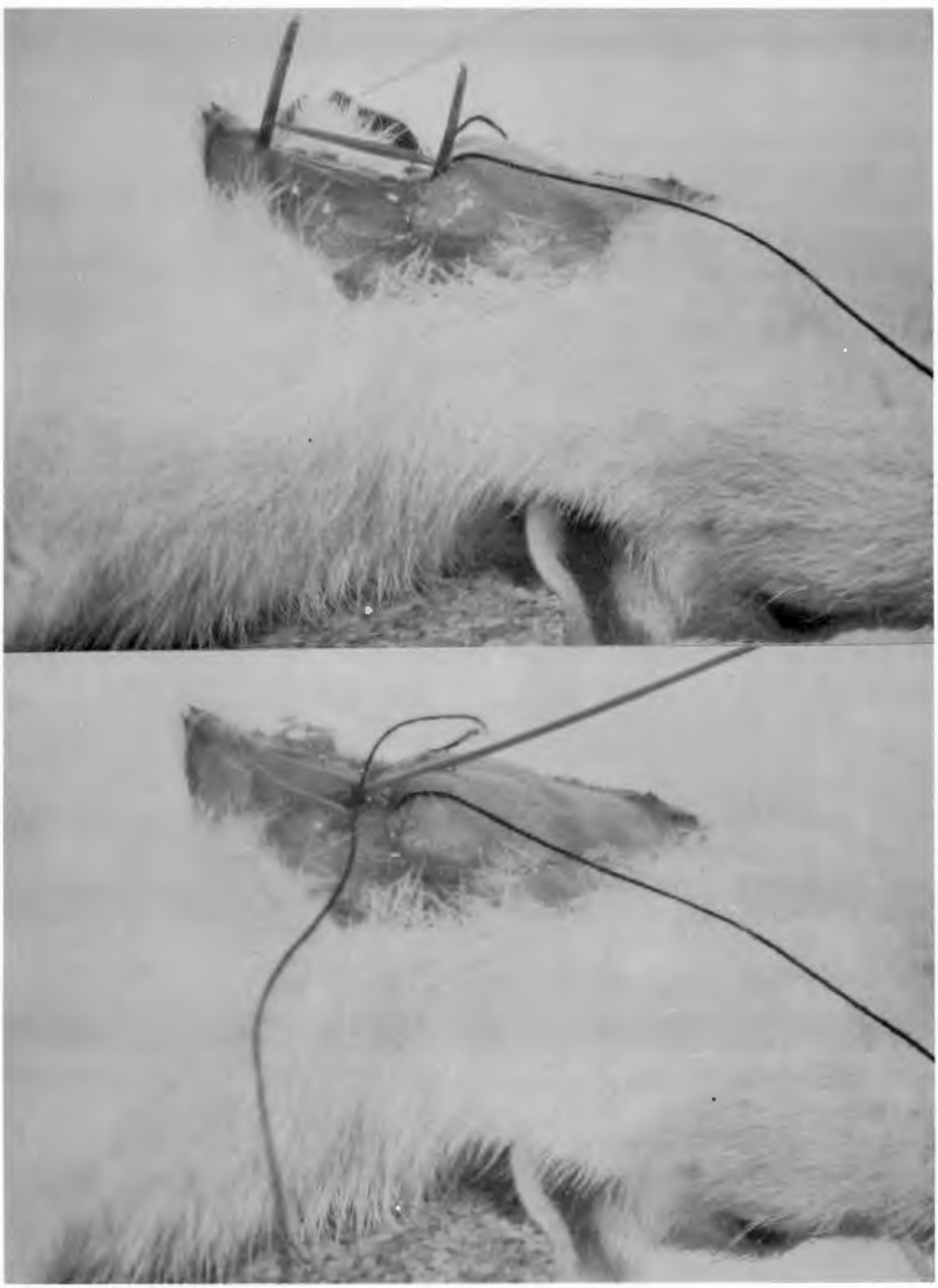
The pressure transducer (EMT 34) was calibrated against a mercury manometer at the start of all experiments. The volume displacement of the transducer constituted 0,09 mm^3/ 100 mm Hg.

2.4.2 ANALYTICAL PROCEDURES

All measurements were the mean of 5 consecutive heart beats at any given point during an experiment. All basic measurements were made in mm and by using appropriate correction factors, converted into the appropriate units. For analytical purposes a recording speed of 250 mm per second was chosen. The EKG and pressure calibrations were set to 1mV = 2 cm and

FIGURE 2.3: CAROTID CATHETERIZATION

The exposed artery (above) is hemisected prior to insertion of the catheter (below). For demonstration purposes, blood was drawn into the catheter.



100 mm Hg = 3,3 cm, respectively, in all cases. The basic measurements were obtained by using an electronic digitizer, the raw information thus obtained being relayed to a programmed Wang computer.

2.4.2.1 EKG-INTERVAL MEASUREMENTS

In order to assess rhythm and the integrity of cardiac conductivity, certain temporal relationships were determined. Atrio-ventricular continuity was evaluated in terms of the PQ-time (by convention, PR), ventricular repolarization by the QT-time, which, according to Rushmer (1970), is probably the only electrocardiographic indication of possible metabolic disturbances. To allow for rate, QT_c was also determined and expressed in conventional units (seconds):

$$QT_c = QT \; / \; \sqrt{RR}$$

The upper limit in humans is reported as 0,425 seconds. Finally, the RR'-interval was used in calculating heart rate.

2.4.2.2 EKG-AMPLITUDE MEASUREMENTS

Although the P- and T-wave amplitudes were checked in all the standard leads, they were not analysed except where gross changes became noticeable.

The majority of electrocardiographic data derived was from analyses of the QRS-complex of the standard leads. Firstly

the direction and magnitude of the mean frontal QRS vector were determined according to conventional methods based on Einthoven's equilateral triangle. The second consideration is based on the direct proportionality between heart size and the QRS-complex as reported by Manoach (1971), and left ventricular function and the sum of the R-wave amplitudes in selected leads as reported by Gottwik *et al* (1978).

2.4.2.3 PRESSURE PULSE CONTOUR ANALYSES

(a) From the directly recorded pressure pulse, the basic measurements comprised arterial (carotid) systolic and diastolic pressures while pulse pressure and mean arterial pressure could readily be calculated. The latter was computed as functional mean arterial pressure (mean perfusion pressure) as distinct from arithmetic mean pressure. Systolic pressure serves as an index of ventricular contraction, diastolic pressure as an index of peripheral resistance while mean arterial pressure reflects the general competence of the vasomotor system (Valbonna, 1974). The various components of the pressure pulse were, however, also subjected to further analysis (*vide infra*).

According to Rushmer (1970) the most sensitive indicators of cardiac performance are the rates of change of cardiovascular responses which, amongst others, include the rate of change of pressure (dP/dt). In this context, the rate of rise of central arterial pressure is regarded as an important

criterion of ventricular performance and capability, i.e., cardiac contractility. However, in order to obtain meaningful information concerning cardiac contractility, it would appear that dP/dt should be measured so as to yield a maximum rate of change in pressure i.e., during early systole (Noble *et al* 1966a; Schlant, 1978a; Hurst and Schlant, 1978), a measure little affected by heart rate changes (Noble *et al*, 1966b). Furthermore, it is evident that dP/dt should also be evaluated in terms of peak systolic pressure. For example, during enhanced sympathetic discharge, the rate of pressure rise is increased to a greater extent than the absolute peak pressure elevation (Rushmer, 1970). The measurement, and subsequent evaluation of dP/dt is therefore in accordance with these views.

A second consideration concerns total peripheral resistance. After closure of the aortic valves, the rate of pressure decline is determined by the end-systolic pressure, the flow rate through the peripheral resistances and the diastolic interval, the minimal diastolic pressure being determined primarily by total peripheral resistance and heart rate (Rushmer, 1970). The use of diastolic pressure *per se*, as a measure of peripheral resistance, should therefore not proceed without due caution.

(b) Stroke Volume

Further analysis of the pressure pulse contour stems from the observation that the arterial pressure pulse contour is physically related to the stroke volume output and, theoret-

ically at least, provides the means for estimating cardiac output from beat to beat (Guyton, 1963). "The pulse contour method has one very important potential advantage. It permits computation of the stroke volume of individual cycles, even though its accuracy may be limited" (Rushmer, 1970). The advantage afforded by this method was particularly relevant to the current experimental model wherein many and varied stroke volume changes were anticipated. In this respect the use of the Fick-principle method or indicator- and thermo-dilution techniques were deemed impractical and undesirable for continuous monitoring.

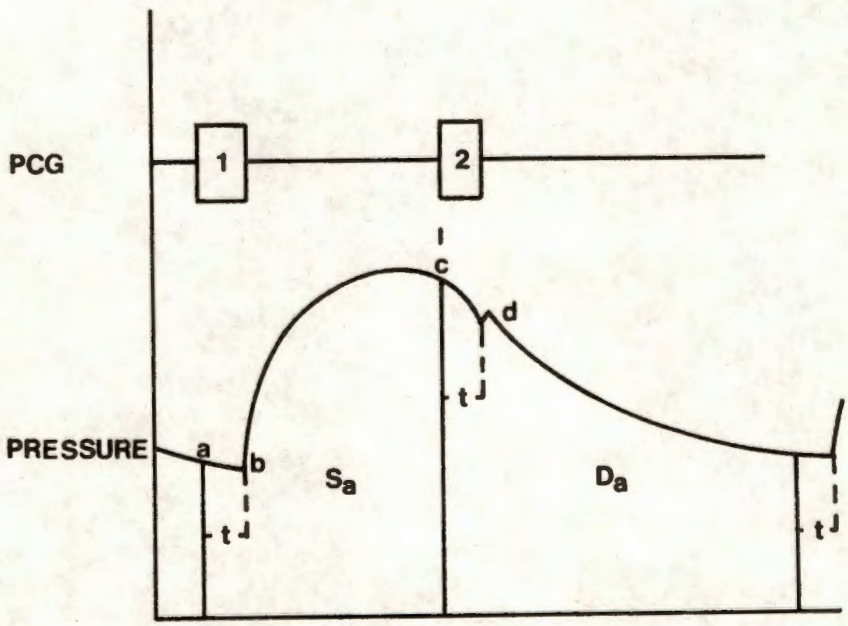
The method employed is based on the method of Warner and his associates (Warner *et al*, 1953; Warner, 1954; Warner, 1966) as described by Guyton (1963). In essence, the method relates the area of the pressure pulse to stroke volume. Compared with the Fick-principle method, the indirect method exhibits an error of only ±9% (Guyton, 1963).

The Warner formula for stroke volume (SV),

$$SV = c(\overline{P}_{cd} - \overline{P}_{ab})(1+S_a/D_a)$$

features only one unknown factor which cannot be derived from the pressure pulse, i.e., c, the capacitance of the arterial tree (the other symbols are explained in Figure 2.4). In the present study, arterial capacitance was estimated by rapid exsanguination via the aorta at a site just proximal to its

FIGURE 2.4 *ESTIMATION OF STROKE VOLUME FROM THE ARTERIAL PRESSURE PULSE ACCORDING TO THE WARNER METHOD*



S_a: Systolic drainage area

D_a: Diastolic drainage area

t : Transmission time

The Warner formula for stroke volume (SV) is:

$$SV = c(\overline{P}_{cd} - \overline{P}_{ab})(1 + S_a/D_a)$$

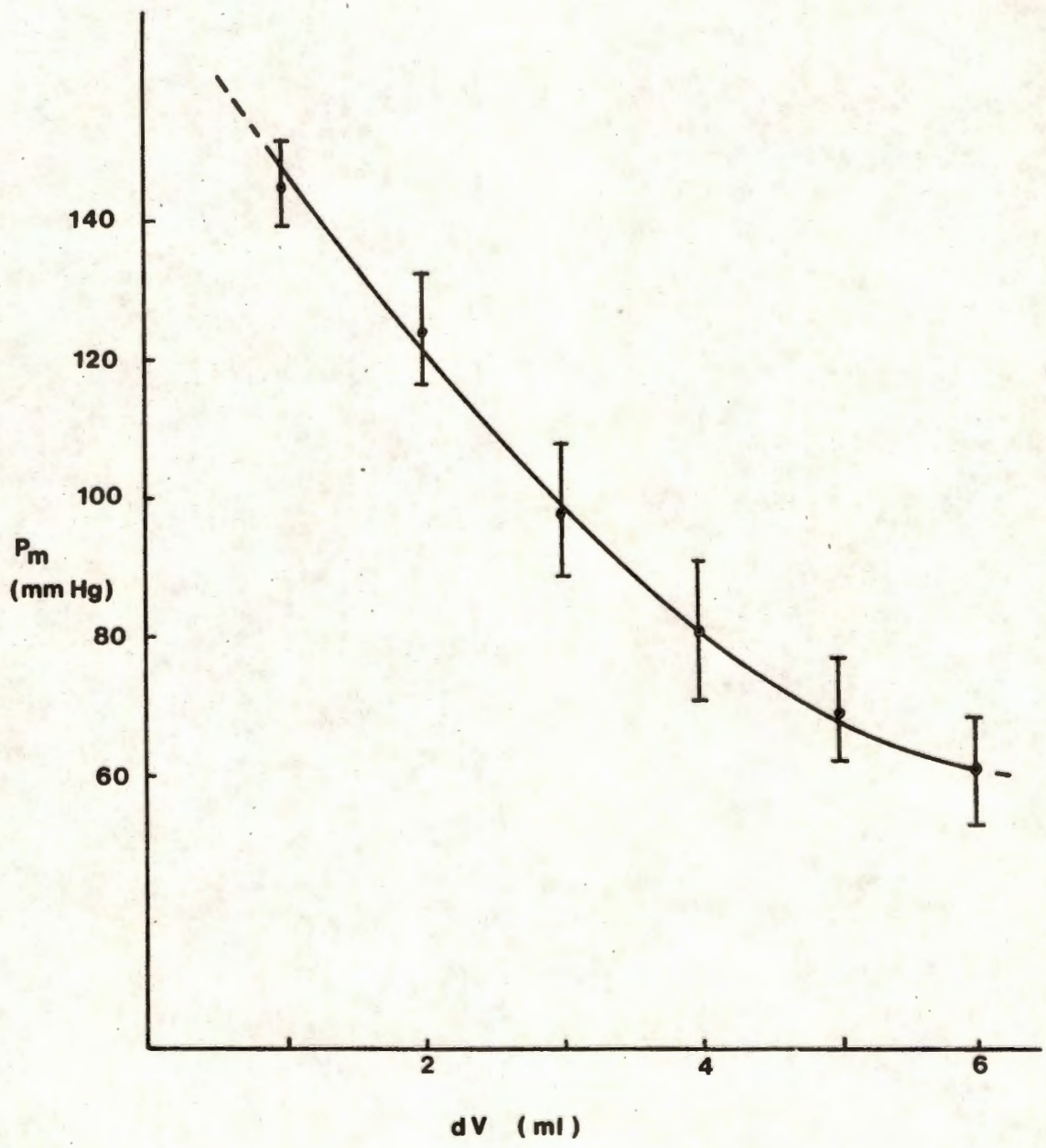
In the present study diastolic pressure was substituted for $\overline{P}_{ab}$ (See text).

FIGURE 2.5 *ARTERIAL CAPACITANCE*

Means ± SD (5 experiments)

P_m: Mean arterial pressure

dV: Volume exsanguinated



bifurcation while simultaneously monitoring arterial pressure. This procedure is based on the conclusions of Guyton *et al* (1956), namely that "the large arteries are probably responsible for most of the characteristics of the pressure-volume curves" and that "total capacitance of the small arteries calculates to be insignificant in comparison with total capacitance of the large arteries".

Arterial capacitance was determined in 5 animals having a mean mass of 278±7,5g (Mean ± SD). The change in volume (dV) per unit change in mean arterial pressure (dP), is presented in Figure 2.5. An analysis of the capacitance curve confirms the fundamental principle that for a given value for dP, the corresponding value for dV initially becomes smaller as the mean pressure increases, but that eventually a linear relationship tends to develop. In the present investigation, the latter event seems to apply above diastolic pressures of about 120 to 130 mm Hg, in other words dV becomes directly proportional to dP.

The relationship between dV and dP constitutes capacitance:

$$c = dV/dP$$

Rearrangement of the above equation shows that

$$dV = c.dP$$

and, in as much as dP is represented in the Warner formula as $(\overline{P}_{cd} - \overline{P}_{ab})$, the latter formula may be abbreviated to

$SV = dV(1+S_a/D_a)$

In the present study the difference between P_a and P_b was experimentally found to be negligible, and the term P_{ab} was consequently ignored in favour of substitution of diastolic pressure. In contrast, since the difference between P_c (systolic pressure, denoted P_s in the current study) and P_d (end-systolic pressure, denoted P_{es} in the current study) was not only significant, but also subject to considerable variation, P_{cd} was retained in all calculations. From a practical point of view, dV was determined from Table 2.1 and not from the capacitance curve itself. The latter table is simply a convenient reference which allows dV to be read off directly.

The indirect method of stroke volume estimation was then related to the ultrasonic Doppler-based systolic velocity integral. The method employed was based on that of Colocousis *et al* (1977) wherein stroke volume was determined over a wide range of cardiac output variations (sequential exsanguination and fluid infusions) and correlated with the thermodilution method, the correlation being reported as r = 0,95±0,04SD's . In the latter study (Colocousis *et al*, 1977), the area of the aortic blood velocity integral was related to stroke volume. For the purpose of the current investigation it was concluded that this technique would serve as a reliable index of the validity of the Warner method.

In the present investigation, blood flow was measured in the exposed right common carotid artery by means of the Doppler

TABLE 2.1 *PRESSURE-VOLUME RELATIONSHIPS IN THE ARTERIAL SYSTEMIC TREE*

From the pressure-volume curve of the arterial systemic tree the volume change (dV in $ml \times 10^{-1}$) per unit change in pressure (dP in mm Hg) was obtained from the equation for capacitance (c):

$$c = dV/dP$$

The table below only lists relevant data within the operating pressure range. The "pulse pressure" is related to a specific volume change at given diastolic pressures.

Diastolic pressure	Mean of systolic and end-systolic pressure											
	10	15	20	25	30	35	40	45	50	55	60	65
80	7	9	12	14	16	18	20	21	23	25	26	27
85	6	8	10	12	14	16	17	19	21	22	23	24
90	5	7	9	11	13	14	16	18	19	20	21	22
95	5	7	9	10	12	13	14	15	16	17	18	19
100	4	6	8	9	11	12	13	14	15	16	17	18
105	4	6	7	9	10	11	12	13	14	15	16	17
110	4	6	7	8	9	10	11	12	13	14	15	16
115	3	5	7	8	9	10	11	12	13	14	15	16
120	3	5	7	8	9	10	11	12	13	14	15	16
125	3	5	6	7	8	9	10	11	12	13	14	15
130	3	5	6	7	8	9	10	11	12	13	14	15
135	2	3	4	5	6	7	8	9	10	11	12	13
140	2	3	4	5	6	7	8	9	10	11	12	13
etc.	(dV remains linearly related to pulse pressure)											

technique ("Directional Doppler", Model 806-C, Parks Electronics, Oregon), the probe positioned on the artery at a recommended angle of 45° to the flow origin. Arterial pressure was simultaneously recorded from the left common carotid. Variations in flow were induced by mild exsanguination and norepinephrine (4µg in 0,2 ml of 0,85% saline, i.a.). The results obtained are presented in Table 2.2 and three representative recordings in Figure 2.6.

An analysis of the results in Table 2.2 indicates that the Warner formula yields stroke volume values that are in good correlation with flow rate (r=0,831±0,089 SD). Of particular interest is the observation that Reference 1 (mild exsanguination)exhibits a "pulse pressure" of 18 mm Hg which, at a diastolic pressure of 100 mm Hg, corresponds to a volume change (dV) of 8 units. In contrast, Reference 7 exhibits a 200% increase in pulse pressure which only elicits a 57% increase in dV. Placed in perspective, Reference 7 exhibits a mere 7,6% increase in stroke volume. These findings are in accordance with generally accepted principles and it was therefore concluded that despite the limitations of the method, pressure pulse contour analyses provide a simple yet reliable method of estimating stroke volume on a semiquantitative basis. The potential of the method merits an in-depth investigation.

2.4.2.4 SYSTOLIC TIME INTERVALS

Systolic time interval measurements are parameters of cardiac function i.e., the contractile state of the left ventricular

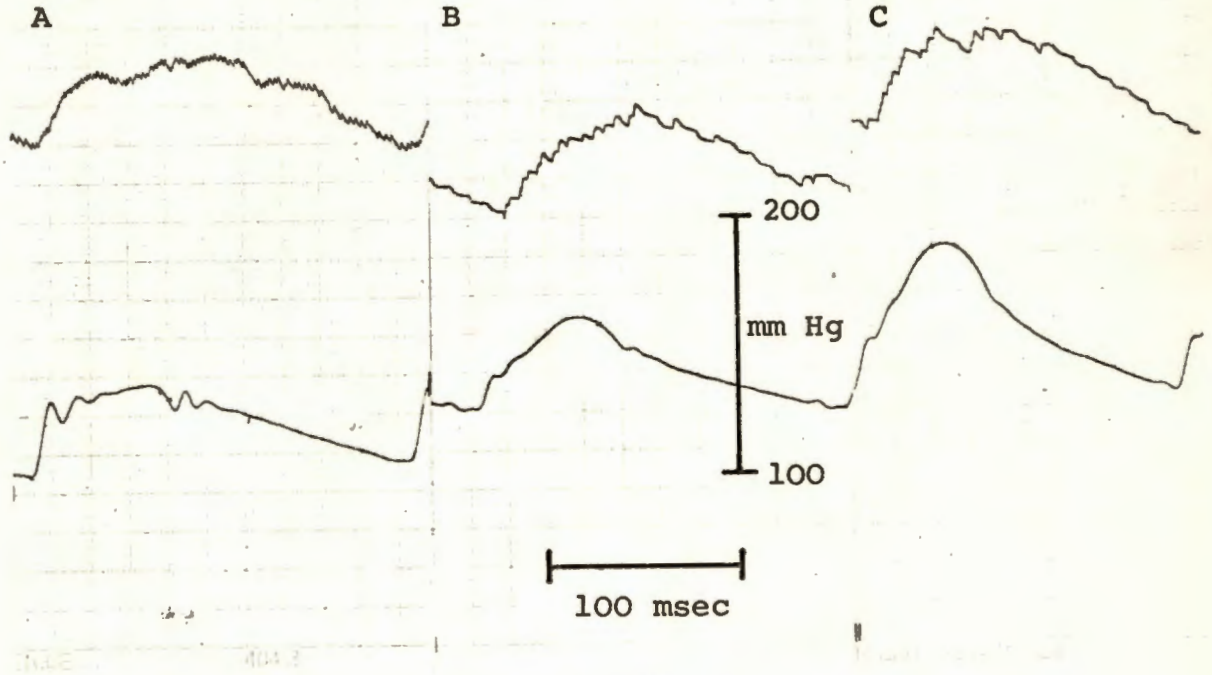
TABLE 2.2 *ESTIMATION OF STROKE VOLUME USING THE PRESSURE PULSE CONTOUR METHOD & THE ULTRASONIC DOPPLER-BASED FLOW RATE*

Reference No.	Pressure P_d	Pressure $(\overline{P}_s-\overline{P}_{es})$	dV	Pulse Area S_a	Pulse Area D_a	Pulse Area S_a/D_a	Stroke Volume Warner	Stroke Volume Doppler
1	100	18	8	44	57	0,77	14,16	447
2	160	24	5	91	106	0,86	9,30	302
3	160	27	6	99	112	0,88	11,28	287
4	178	42	8	133	133	1,00	16,00	379
5	190	33	7	113	122	0,93	13,51	360
6	190	36	7	135	122	1,11	14,77	410
7	193	54	11	218	175	1,25	24,75	481

NOTES:

1. Values are the means of 5 experiments.
2. Categories: Mild exsanguination - Reference 1
   Control - Reference 2 and 3
   Hypertension (Norepinephrine) - Reference 4 - 7
3. Pressure in mm Hg.
4. dV in ml $\times 10^{-1}$
5. Pulse areas in mm^2.
6. Doppler flow volume proportional to area in mm^2.
7. Coefficient of correlation between stroke volume estimations: $r = + 0,831 \pm 0,089 SD$

FIGURE 2.6 *THE RELATIONSHIP BETWEEN THE DOPPLER-BASED FLOW RATE AND THE PRESSURE PULSE DURING (A) MILD EXSANGUINATION, (B) CONTROL LEVELS AND (C) NORADRENALINE INFUSION*



Tracings of right carotid blood flow (upper) while simultaneously monitoring left carotid pressure (lower).

The area under the flow curve, the systolic velocity integral is in direct proportion to stroke volume exhibiting a correlation coefficient of r = +0,831 with the Warner method of estimating stroke volume from the pressure pulse contour.

According to Colocousis *et al* (1977)*, area rather than peak velocity is a more reliable indicator of stroke volume when using the Doppler technique.

* Circulation 56 : 914 - 917

myocardium (Ahmed *et al*, 1972) and as such yields a simplified semiquantitative measure of circulatory impairment in abnormal cardiac function (Weissler *et al*, 1969). These measurements, in conjunction with others pertaining to the cardiac cycle, are schematically presented in Figure 2.7.

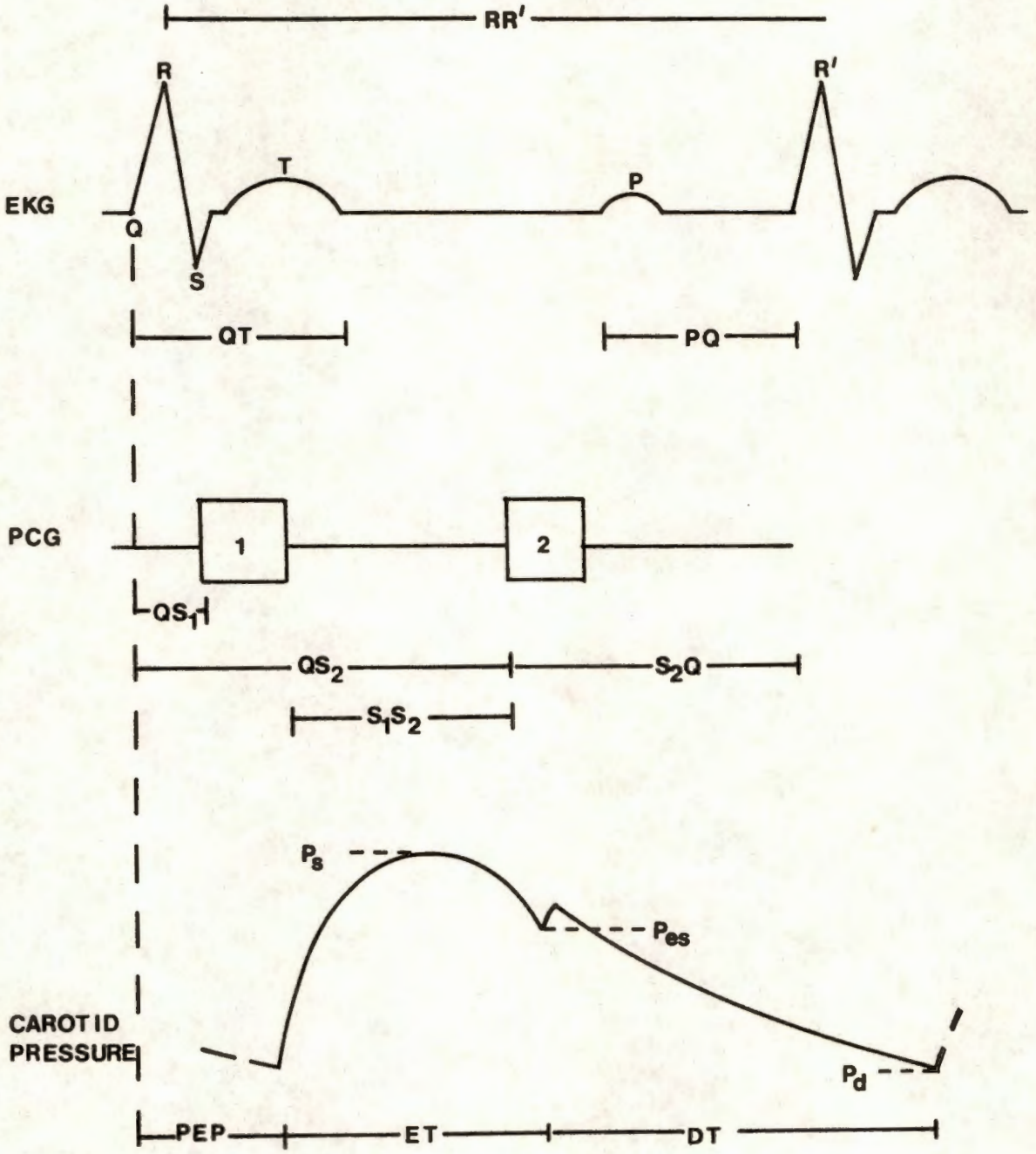
For the analysis of any given cardiac cycle, the electrocardiographic Q-wave served as reference point. The two basic measurements comprised (a) total electromechanical systole i.e., from Q to the onset of the second heart sound (QS_2) and (b) ejection time (ET) i.e., from the onset of the rise of the pressure pulse to the nadir of the incisura on the descending limb. From these, the pre-ejection period (PEP) could be determined:

$$PEP = QS_2 - ET$$

PEP is that fraction of the QS_2 which precedes left ventricular ejection (PEP cannot be directly read off in view of the time lag which occurs for the pulse to travel from the left ventricle to the carotid). The procedure to estimate PEP indirectly is in accordance with the method of Harris (1974) and also in agreement with the method of Weissler *et al* (1968; 1969) where systolic time intervals were obtained from the carotid pulse, EKG and the PCG.

In view of the anticipated changes in heart rate, the influence of the latter on these intervals had to be considered.

FIGURE 2.7 *TEMPORAL MEASUREMENTS WITHIN THE CARDIAC CYCLE*



According to Harris (1974) QS_2 and ET vary inversely with heart rate while heart rate *per se* does not influence PEP. The latter phenomenon is explained by the fact that an increase in heart rate elicits a decrease in PEP through an abbreviation of all intervals of the cardiac cycle but which is countered by the aortic diastolic (increase) and left ventricular end-diastolic (decrease) pressure gradient. This gradient increases with heart rate, a view also subscribed to by Blumberger and Meiners (1965) and Harley *et al* (1969).

In view of the foregoing, PEP was not corrected for heart rate. However, ET was corrected for heart rate according to the method of Pigott *et al* (1971):

$$ET_c = ET / \sqrt{RR}$$

where ET_c is the corrected ET and RR the cardiac cycle.

The PEP/ET ratio was used as an index of the contractile state of the heart since it has been shown to increase in cardiac failure (Weissler *et al*, 1969; Ahmed *et al*, 1972) and to decrease in exercise (Pigott *et al*, 1971). According to Blumberger and Meiners (1965), the inverse relationship i.e., ET/PEP (referred to as the "haemodynamic ratio") is proportional to stroke volume.

2.4.2.5 *HEART RATE*

Although heart rate measurements *per se* are of obvious importance in evaluating the circulatory status at any given instant, it was also considered important to relate heart rate to various other measurements.

The reduction of the various intervals of the cardiac cycle during cardioacceleration is accomplished by (a) a moderate reduction in the duration of systole and (b) a significantly greater reduction in the diastolic filling interval (Rushmer, 1970). In other words, a physiological elevation in heart rate should exhibit an increase in the duration of systole relative to heart rate, or an increase in the systole/diastole ratio. For this purpose, the QS_2/S_2Q ratio (electromechanical systole/electromechanical diastole) was determined.

The second relationship is based on cardiac responses to exercise, as envisaged by Rushmer (1970) in terms of the Frank-Starling mechanism. During exercise, cardiac output is increased by two mechanisms. Firstly, an increased stroke volume occurs in response to an increase in venous return which, in turn, is facilitated by the pumping action of the contracting muscles. Secondly, the fall in arterial pressure as a result of regional vasodilation, elicits cardioacceleration via the pressure receptor pathway. It would also appear that the degree of cardioacceleration would depend on the degree of compensatory vasoconstriction, an event which would be manifested in terms of mean arterial pressure (Valbonna, 1974)

as well as the level of exertion. Thus, within physiological levels of exertion, although the systolic arterial pressure is characteristically elevated, mean arterial pressure remains essentially unchanged. "If a drop in arterial pressure occurs at all, it is so transient at the beginning of exertion that it cannot be consistently demonstrated in man or experimental animals" (Rushmer, 1970). It was therefore deemed important to relate heart rate to mean arterial pressure as an index of cardiovascular strain, a view not without precedent (Belding, 1967).

2.4.3 EVALUATION OF ANALYTICAL PROCEDURES

Although the assessment of cardiovascular function was largely based on accepted methods and techniques, it was nevertheless deemed important to re-evaluate some of these procedures within the current context. The method of evaluation was based on the approach of other investigators (Piemme *et al*, 1966; Rademeyer, 1969), whereby, through the infusion of selected drugs, certain desired circulatory changes could be induced. These changes pertain mainly to cardiac contractility, stroke volume and total vascular resistance.

The drugs selected, the respective dosages and effects are summarised in Table 2.3. In some instances the precise physiological dosage for rats could not be ascertained and consequently the human dosage per kg, was scaled down to an estimated animal dosage. The desired amount was

infused intra-arterially in 0,2 ml of 0,85% of NaCl in order to minimise volume effects on the circulation. The mean changes were then determined, each animal acting as its own control.

Myocardial contractility was evaluated in terms of two basic parameters, namely (a) the maximum rate of change in carotid pressure at the onset of systole (dP/dt_{max}) and (b) the ratio of the pre-ejection period to ejection time (PEP/ET). The use of dP/dt_{max} is based on the view of Noble *et al* (1966a), Hurst and Schlant (1978) and Schlant (1978a) and in so far as this measure is little affected by heart rate (Noble *et al*, 1966b), no correction was made for rate. However, in similar studies, dP/dt was expressed in terms of left ventricular end-diastolic pressure in an attempt to correct the influence of pre- and afterload on contractility (Mirvis *et al*, 1978; Schmidt and Hoppe, 1978). Although these researchers could not demonstrate marked differences between the corrected and uncorrected forms, it was nevertheless decided to employ the same principle in this evaluation by the use of the equation below:

$$dP/dt_c = (dP/dt_{max}) / \sqrt{P_d}$$

where the square root of diastolic pressure is used in conformation with standard procedures employed for correction.

The ratio PEP/ET is also regarded as a sensitive measure of myocardial contractility and, in contrast to dP/dt, has been

extensively evaluated by means of the carotid pulse tracing (Weissler *et al*, 1969; Pigott *et al*, 1971; Ahmed *et al*, 1972; Harris, 1974). This measure also correlates well with the angiographically (Garrard *et al*, 1970) and Tc - 99m albumin measured ejection fraction (Qureshi *et al*, 1978).

According to Harris (1974), PEP is not dependant on heart rate and may thus be left uncorrected. ET, however, does require correction. In the present study, ET was corrected in accordance with the method of Pigott *et al* (1971) and Cohn (1978):

$$ET_c = ET / \sqrt{RR}$$

With reference to propranolol infusion (Table 2.3) the corrected version (ET_c) appears to confer greater sensitivity on PEP/ET (as PEP/ET_c) as a measure of contractility than the uncorrected form.

Vascular resistance to blood flow is in actual fact calculated by analogy to Ohm's law:

Resistance (R) = Pressure (P) / Flow (F)

which, according to Fransch (1978), refers to the mean pressure differential across the vascular bed divided by blood flow or cardiac output (Q). On the assumption that the mean pressure gradient would be given by the mean arterial pressure (P_m) minus the so-called critical flow pressure of 20 mm Hg (Schlant,

TABLE 2.3 EVALUATION OF PARAMETERS OF CARDIOVASCULAR FUNCTION

Feature investigated	Parameter employed	Control level (mean)	Change Observed (%) A	N	P	I	R
Heart Rate	-	332	-4*	-21	-30	+2	+23
Cardiac Contractility	dP/dt_{max}	2,55	+121	+28	-20	+26	+177
	dP/dt_c	0,25	+116	+12	-26	+57	+319
	PEP/ET	0,52	-17	-36	-10*	-10	-28
	PEP/ET_c	7,10	-16	-29	+7	-12	-34
Stroke Volume	Pulse Contour	1,11	+56	+28*	-13	+25	+62
Vascular Resistance	P_d	131	+5*	+21	+15	-35	-54
	$(P_m-20)/Q$	0,334	-8	+26	+63	-47	-63
Dosage	- µg/0,2 ml		20	4	200	0,2	50

Notes:

1. The drugs employed are, respectively, adrenaline, noradrenaline, propranolol, isoproterenol and regitin.
2. The asterisks (*) denote changes opposite to the postulated responses according to Charlier (1971), Laurence (1973) and Goldberg and Hsieh (1978).
3. The changes observed represent the means of two experiments in each case and therefore merely reflect tendencies.
4. The units employed are in accord with those pertaining to this study.
5. PEP/ET is inversely related to contractility.

1978a), stroke volume being determined by the Warner method (2.4.2.3), the above equation may be modified as follows:

$$R = (P_m - 20) / Q$$

Using this equation (simplified to P/Q in Table 2.3) the calculated total peripheral resistance, in arbitrary units, is in each instance in exact agreement with the postulated response. Conversion into cgs units does not add to the intrinsic significance of these measurements (Fransch, 1978) and was consequently omitted.

There is general consensus that in the absence of other measures, diastolic pressure is a fair reflection of total peripheral resistance (R). With the exception of adrenaline infusion, this surmise could be verified experimentally. In the case of adrenaline it is likely that the unexpected responses (diastolic pressure and heart rate) represent the outcome of homeostatic compensation. The underlying principle is that the minimum diastolic pressure is determined not only by peripheral resistance, but also by heart rate (Rushmer, 1970). It is therefore concluded that while diastolic pressure is an insensitive measure of actual changes in peripheral resistance, it nevertheless seems a fair reflection of the effective peripheral resistance.

Despite the cursory nature of this investigation it was nevertheless concluded that the use of these parameters of cardiovascular function is also applicable to the laboratory rat, and hence fully justifiable in this study.

2.5 *MEASUREMENTS OF HEAT STRESS*

The assessment of physiological heat stress was limited to measurements of body temperature and the derivation of certain indices. These aspects are described below.

2.5.1 *BASIC MEASUREMENTS AND INSTRUMENTATION*

All temperature measurements were performed by means of an electrical thermometer which has the decided advantage over its mercury counterpart of having remote read-out capabilities (Figure 2.2).

Two basic measurements were performed. Core temperature (T_c) was measured after introducing a YSI (Yellow Springs Instruments) "302" rectal probe to a depth of about 7 cm into the colon by way of the rectal orifice. The recording site was at the left colic flexure and consequently represents deep or core temperature as opposed to rectal temperature. Skin temperature (T_s) was measured on the anterior surface of the base of the tail with a YSI "409" skin temperature probe. The probe, wrapped in cotton wool, was held in position with adhesive plaster, the latter procedure simultaneously holding the rectal probe in position.

Both probes consist of a thermistor temperature sensing element connected to a telephone jack by means of a shielded lead wire. The probes plug into the thermometer unit (YSI "Thermistemp Tele-thermometer" Model 46-TUC) and temperature readings were

directly obtained in degrees centigrade by way of a Wheatstone bridge. The accuracy of the system, according to manufacturer's specification, is ±1% of the scale which spans 11°C. Several operating ranges may be selected, namely, 0-11, 10-21, 20-31, 30-41 and 40-51°C. These operating ranges greatly facilitated the simultaneous measurement of various and varying temperatures on the same instrument i.e., T_c, T_s and using probe "405", air temperature. The entire system was regularly checked against a certified mercury thermometer.

2.5.2 ASSESSMENT OF HEAT STRESS

The assessment of heat stress was primarily based on the heat storage index of Burton (1935) where mean body temperature (T_m) is related to core (T_c) and skin (T_s) temperatures:

$$T_m = 0{,}67\ T_c + 0{,}33\ T_s \text{ in } {}^{\circ}C$$

Since the specific heat of the body tissues (collectively) is 0,83 C/kg/°C, body heat storage (S) may be calculated as follows:

$$S = 0{,}83\ m.T_m \text{ in C}$$

where m is body mass in kg. From the formula for body surface area (A) for rats (Section 2.2.3) heat storage may now be expressed in terms of unit surface area (C/m^2):

$$S = 0{,}83\ m.T_m/A$$

and from the rate of rise of T_m, S may finally be expressed in terms of $C/m^2/h$.

In as much as the accuracy of T_m depends not only on the number of T_s measurements, but also on the particular weighting factors, body heat storage is more appropriately designated an index rather than the absolute value that it implies (Minard and Copman, 1963). The use of the term "index" is therefore also applicable to this study.

2.6 *BIOCHEMICAL PARAMETERS OF MYOCARDIAL INTEGRITY AND FUNCTION AT CELLULAR LEVEL*

The objectives of this study, as have been stated before, concern the evaluation of cardiovascular performance during acute, experimental hyperthermia, with specific reference to cardiac function. While much may be gleaned from measurements of gross cardiovascular responses, it is critical that such findings be correlated with events occurring at cellular and subcellular level. With this objective in mind, two approaches were adopted. It was decided to measure firstly, the intracellular myocardial potassium and sodium levels and, secondly, myocardial cellular oxygen consumption.

2.6.1 *MYOCARDIAL POTASSIUM AND SODIUM LEVELS*

The choice of this approach was based on the sensitivity of the intracellular K^+/Na^+ ratio as an indicator of the advent myocardial infarction, or conversely, the reversibility of trauma (McVie, 1970; Cherry and Meiners, 1971). The under-

lying principle concerns the particular distribution of K^+ and Na^+ across the cell membrane, a distribution which is maintained by the so-called "Na^+ -pump" mechanism. On cell death, these ions follow the dictates of the existing diffusion gradients and soon the levels of these ions approach those of the extracellular fluid. Since the numerator and the denominator in the ratio change in the opposite sense, the K^+/Na^+ ratio of infarcted cells falls. According to McVie (1970), this method is therefore highly applicable in the detection of the early infarct.

2.6.1.1. BASIC METHODOLOGY AND INSTRUMENTATION

K^+ and Na^+ were determined by flame spectrophotometry (Wootten, 1964) with a Carl Zeiss Model PMQ II spectrophotometer, the light source of which was replaced by a burner and atomizer attachment. An oxyacetylene flame was used throughout, the gas flow being regulated at 100 mm WS acetylene and 0,3 kg/cm^2 oxygen.

Stock solutions of NaCl and KCl were prepared by dissolving 58,5 g NaCl and 74,6 g KCl in double distilled water, respectively, the final solutions being made up to 1 litre so as to yield concentrations of 1000 mEq/l in each instance. The salts were analytical grade reagents and were dried in an oven for 3 hours prior to use.

Standard solutions were prepared in accordance with the recommendation of Tietz (1970) whereby Na^+ is added to the K^+ standards in a concentration comparable with that anticipated

in the fluid under investigation. This addition compensates for the slight enhancement by Na^+ in the measurement of K^+. The procedure was reversed for the Na^+ standards. The preparation of the standard solutions is given in Table 2.4.

The final standards were then used to obtain the relationship between concentration and transmittance. In each instance, double distilled water was used as a blank. The effective transmittance of each standard was obtained by subtracting the registered deflection of the blank from that of the standard. The transmittance of the standards was obtained by setting the apparatus to 100% transmission using the highest standard, this setting then being used to determine the transmittance of the lower standards.

For Na^+, a wavelength of 590 nm and a slit width of 0,01 mm was used and for K^+, a wavelength of 769 nm and a slit width of 0,15 mm. The accuracy of the respective wavelengths was tested by contaminating known and identical standards with, in the case of Na^+, low and high K^+ standards, and in the case of K^+, low and high Na^+ standards. Since the respective transmittances were unaltered by contamination, it was concluded that the wavelengths of choice were absolutely specific in each instance.

The standard curve for Na^+ exhibited a linear relationship between transmission and concentration above a concentration level 0,2 mEq/l, the slope of the curve corresponding to a

TABLE 2.4 COMPOSITION OF STANDARD SOLUTIONS

SODIUM

Stock Na^+-ml	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Stock K^+ -ml	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Water -ml	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76
Na^+conc.-mEq/l	0	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150

POTASSIUM

Stock K^+ -ml	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Stock Na^+-ml	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Water -ml	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79
K^+conc.-mEq/l	0	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150

In each instance, the above standards were then diluted (1 in 100) to give the following final concentrations:

Na^+-mEq/l	0	0,1	0,2	0,3	0,4	0,5	0,6	0,7	0,8	0,9	1,0	1,1	1,2	1,3	1,4	1,5
K^+ -mEq/l	0	0,1	0,2	0,3	0,4	0,5	0,6	0,7	0,8	0,9	1,0	1,1	1,2	1,3	1,4	1,5

transmittance of 56,2 units per unit concentration. In the case of K^+, a linear relationship was also established between transmission and concentration, the curve originating from the "O" point of both axes. The slope of the curve corresponded to a transmittance of 66,7 units per unit concentration.

2.6.1.2 DETERMINATION OF MYOCARDIAL K^+ AND Na^+

The method employed was a modification of the method of McVie (1970). Excised rat hearts were trimmed in order to remove the pericardium and all connective tissue including the large coronary vessels. The hearts were washed in double distilled water and blotted to remove all traces of excess water and blood. Two rat hearts were then pooled and chopped into small pieces. The mass was accurately determined to the nearest 1g, and double distilled water added to give a mass-to-volume ratio of exactly 1 in 20. The heart tissue was subsequently homogenized in a Waring blender.

In contrast to the method of McVie (1970), which subsequently employed a glass homogenizer, 10 ml of 0,75 N HNO_3 was added to the homogenate for every 1,0 g of heart tissue, the exact volume being determined by the mass. The tubes were then sealed and digestion allowed to proceed for approximately 18 hours whereafter the solution was boiled for 3 hours to facilitate further digestion.

In the final instance, the cell debris was spun down at 1000 r.p.m. for 10 minutes and K^+ and Na^+ determined in a 1 in 5 dilution of the supernatant, the final level in each instance

being expressed in terms of the mass of the tissue from which it had originated.

2.6.1.3 *EXPERIMENTAL GROUPS*

The basic approach was to subject experimental animals to varying times of exposure to heat. In as much as it was deemed important to perform survival studies in this instance, the choice of a specific maximum duration of exposure was based on the animal's ability to survive heat exposure by at least 48 hours. In the light of certain preliminary findings, an exposure time of 50 minutes (maximum) was selected. In addition, other groups were subjected to exposure times of 20, 30 and 40 minutes respectively in order to obtain findings of a more intermediate nature. In two of these groups, the myocardial K^+ and Na^+ levels were determined (a) immediately after termination of heat stress, (b) 24 and (c) 48 hours after termination of heat stress. The latter groups (30 and 50 minute exposure times, respectively) were selected on the basis of findings obtained immediately on termination of heat stress (See Chapter 4: Results).

2.6.2 *MYOCARDIAL OXYGEN CONSUMPTION*

In the context of interrelating haemodynamic parameters of cardiovascular performance and metabolic parameters of cardiac function, it was considered important to evaluate the overall "metabolic status" of the heart with specific reference to the ventricles. According to Burger and Fuhrman (1964a and b) and Burger (1972), the most sensitive criterion of cell

injury is reflected by a decreased myocardial cellular oxygen uptake (Q_{O_2}). Although this measure cannot pinpoint the actual site of dysfunction when the Q_{O_2} falls, it serves as an indicator of the integrity of the oxidative machinery of the cell. In the current study the measurement of Q_{O_2} was employed accordingly i.e., to quantitate the extent of dysfunction (if any) with reference to the prevailing haemodynamic status.

2.6.2.1 GENERAL PRINCIPLES OF THE METHOD

Myocardial oxygen consumption was determined by a manometric technique using the Warburg apparatus. In all instances, the basic methodology was in strict accordance with the methods described by Umbreit *et al* (1964).

The manometric technique of estimating the exchange of gases is based on the principle that at constant temperature and a constant volume of space, changes in the gas volume within that space will be reflected by changes in pressure within the system. In order, therefore, to calculate changes in gas volumes, it is necessary to know the volume of the reaction flask, the volume of the reaction medium in the flask, the temperature of operation and the density of the fluid in the manometer used to achieve constant volume. Providing that the measurement only involves one gas, the amount of gas exchanged may be calculated. In this particular investigation oxygen was consumed, evolved carbon dioxide being absorbed.

2.7.2.2. *THE WARBURG APPARATUS*

The Warburg apparatus employed in this study was of standard design. A total of 7 manometers were used simultaneously, each manometer being matched to a specific reaction flask (Carl Zeiss NS 14,5) with a side-arm gas vent. During actual estimations of Q_{O_2}, the flasks were suspended in a constant temperature water bath which incorporated a shaking mechanism (B.Braun) to provide agitation of the contents of the reaction medium and to facilitate gas exchange.

(a) Reaction flasks, manometers and calibration procedures

The objective was to calibrate the system so that oxygen consumption could be calculated from observed pressure differences i.e., the volume of oxygen consumed is equal to the pressure evolved multiplied by an appropriate constant. This constant, the so-called flask constant (k), in its finally derived form, is given by the following equation:

$$k = |V_g(273/T)+V_f.\alpha|/P_o$$

where V_g is the volume of the gas phase in the flask and its connecting tubes down to the reference point on the closed arm of the manometer, T the temperature of operation in ^oA, V_f the volume of fluid in the flask, α the Bunsen coefficient for oxygen and P_o the standard pressure (760 mm Hg) in terms of the manometer fluid. The composition of this fluid (Brodie) results in a final density of 1,033 so that P_o in

terms of Brodie's fluid, is given by the following equation:

P_o = 760 × 13,60 / 1,033

= 10 000 mm

The term 13,60 represents the density of Hg.

All experiments were performed at 42,0°C. The choice of 42°C is motivated in Section 4.3. For the specific reaction medium, the Bunsen coefficient for the solubility of oxygen was 0,0224. The volume of the reaction medium was 3,0 ml while the centre well of the reaction flask contained 0,2 ml of 10% KOH as carbon dioxide absorbent. The total fluid volume (V_f) in the flask was, therefore, 3,2 ml (3200 µl).

In order to compensate for environmental pressure and temperature fluctuations, one of the manometers was used as a thermobarometer. The total volume of fluid placed in the reaction flask was identical to that used in the experimental flasks i.e., 3,2 ml. For this purpose, reaction medium was used. Corrections were made in the following manner: If the pressure in the thermobarometer rises (increased water temperature or decreased atmospheric pressure), the rise in the thermobarometer reading is added to that of the experimental manometers; a fall in the thermobarometer reading being subtracted. This procedure only applies when experimental manometers reflect a decrease in pressure i.e., as in this case, due to oxygen being consumed.

(b) Preparation of equipment and basic procedures

Immediately prior to the actual estimation of Q_{O_2}, the attachment joints of the manometer, the three-way stopcock and the sidearm stopper on the reaction flasks were carefully greased with silicon paste. Air bubbles in the manometer fluid columns were eliminated by alternately raising and lowering the fluid levels.

The reaction flasks were packed in ice and 3,0 ml of suspension medium added to each flask, an additional 0,2 ml being added to the thermobarometer. Tissue slices of recorded mass were then transferred to the chilled flasks whereupon 0,2 ml of 10% KOH was carefully pipetted into the centre well of each flask. The rim of the centre well was lightly greased with petroleum jelly to prevent the efflux of KOH into the reaction medium during the shaking process. Whatman 44 filter paper squares (2 × 2 cm) were made into rolls and inserted into the centre well thus increasing the area of absorption for evolved carbon dioxide.

All the manometers were subsequently gassed simultaneously with 100% oxygen for a period of not less than 7 minutes. At the end of this period the air vent was sealed with the side-arm stopper, complete sealing off of the reaction flask being effected by way of the manometer stopcock. The flasks were then transferred to the waterbath and attached to the shaker mechanism which, at a rate of 100 oscillations per minute through a 3-cm arc, promoted rapid gas exchanges

between the fluid and gas phases within the reaction flask. Since the temperature of operation induced a rapid expansion of gas within the reaction flasks, this pressure build-up had to be released through the air vent by means of the sidearm stopper until thermal equilibration between the flask contents and the waterbath had been achieved. This period of equilibration lasted approximately 15 minutes.

At the end of the period of equilibration, a reference point was selected on the closed arm of the manometer, usually at the 150 or 250 mm mark. Prior to any reading, the fluid level in the closed arm was adjusted to this mark in conformation to the principle of constant volume. Readings were taken at 10-minute intervals over a period of 60 minutes, the pressure difference in the two arms being recorded in mm and corrected by means of the thermobarometer. The readings were taken to the nearest mm or 0,5 mm.

2.6.2.3 INCUBATION MEDIUM

The incubation (reaction) medium was based on the original media of Webb *et al* (1949) and Krebs (1950) and used in its current form according to the modification proposed by Burger (1972). All solutions were prepared by using only "AR" graded reagents (Merck) and double distilled water. The exact composition of the final medium is given in Table 2.5.

2.6.2.4 PREPARATION OF TISSUES

Hearts from decapitated animals were rapidly excised and chilled in the incubation medium at a temperature of approximately 5°C. The hearts were then transferred to Petri dishes packed in ice and placed on filter paper soaked in chilled incubation medium. After removal of all connective tissue, the aorta, other large vessels and the atria, the ventricles were sliced into sections of approximately 0,5 mm using a Stadie-Riggs microtome. The first slice was always discarded.

The tissue slices were then lightly blotted and rapidly weighed on a torsion balance (White Electrical Instrument Co). Approximately 100 mg of tissue was then placed into each reaction flask, the flask number and corresponding tissue mass being carefully recorded.

In most experiments, a control, an anaesthetised control and an experimental animal were used simultaneously, each animal being represented in duplicate in the respective reaction flasks. The animals destined for anaesthetised controls and for heat exposure (experimental) were anaesthetised at the same time and, depending on the exposure time, sacrificed at the same time, the normal control included.

TABLE 2.5 *COMPOSITION OF INCUBATION MEDIUM*

Component	Stock Concentration mM	Volume of Stock ml
NaCl	112,54	95
KCl	4,74	4
$CaCl_2$	2,54	3
$MgSO_4.7H_2O$	1,18	1
Na-pyruvate	4,92	4
Na-fumarate	5,38	7
Na-L-glutamate	4,92	4
Glucose	11,54	5
Phosphate buffer*	5,38	7

* 0,1M $Na_2HPO_4.12H_2O$: 100 ml

0,1M $Na\ H_2PO_4.2H_2O$: 25 ml

pH = 7,4

2.6.2.5 *CALCULATION OF Q_{O_2}*

After each 10-minute interval, the thermobarometer corrected pressure difference in mm Brodie's fluid was multiplied by the flask constant to obtain oxygen consumption in micro-liters (µl). This value was subsequently expressed in terms of mg wet weight of tissue per hour:

$$Q_{O_2} = \mu l\ O_2 \ /\ mg\ /\ hour$$

2.7 *STATISTICAL METHODS*

Statistical analyses of the results were performed by analyses of variance and polynomial regression. The specific method will be referred to where applicable while further details of the method will be described in an appropriate appendix.

C H A P T E R III

THE INFLUENCE OF PENTOBARBITONE ANAESTHESIA ON THERMOREGULATION AND CARDIOVASCULAR FUNCTION

3.1 RESULTS

The influence of pentobarbitone anaesthesia on thermoregulation was investigated by measurements of heart rate, metabolic rate, mean body temperature and body heat storage during various conditions of thermal stress. In each instance, unanaesthetised animals were used as controls. Since blood pressure could not be measured in unanaesthetised animals, this aspect will be considered as a separate entity. The influence of anaesthesia on myocardial oxygen consumption (Q_{O_2}) was investigated independently.

In this investigation, 6 groups of animals were used, each group consisting of 7 animals. With the obvious exception of group NU (*vide infra*: normothermic, unanaesthetised), all groups were investigated at 5-minute intervals over a period of 30 minutes, i.e., the approximate duration of anaesthesia. Metabolic rate was only measured at the end of this period. The groups were respectively subjected to the following combinations of thermal stress and anaesthesia and designated accordingly:

Group designation	Environment ^{o}C	Anaesthesia
NU	±20*	NO
NA	±20*	YES
HU	45	NO
HA	45	YES
CU	5	NO
CA	5	YES

* room temperature.

The influence of the above environmental conditions on metabolic rate, in conjunction with anaesthesia, is given in Table 3.1.1 and summarised below:

	N	H	C
U	23,78	15,23	19,83
A	15,43	11,46	21,07
U-A	8,35	3,77	- 1,24

A statistical analysis of this table (Appendix 1) indicates a significant reduction in metabolic rate in anaesthetised normothermic animals at a level of significance of 1%. A similarly significant reduction in metabolic rate was observed in unanaesthetised animals exposed to heat but the slight reduction exhibited by cold exposed animals, both

TABLE 3.1 METABOLIC RATE & BODY HEAT STORAGE IN THERMAL STRESS

3.1.1

Group	Mass(g)		Metabolic rate($C/h/m^2$)		
n=7	Mean	Range	Mean	SD	Range
NU	272	252-310	23,78	2,59	21-28
NA	285	258-312	15,43	1,72	13-18
HU	283	250-312	15,23	1,83	12-18
HA	282	230-312	11,46	2,43	8-15
CU	279	252-299	19,83	2,83	15-23
CA	257	220-290	21,07	2,17	17-23

N: ±20°C H: 45°C C: 5°C U: Unanaesthetised
A: Anaesthetised.

3.1.2

Group	Mean body temperature (°C) - ^1T_m				^2E
n=7	0 minutes(x)	SD	0+30 minutes(y)	SD	
NU	32,04	0,58	32,04	0,58	100
NA	32,04	0,58	30,50	1,31	95
HU	32,04	0,58	39,33	0,47	77
HA	32,04	0,58	41,46	0,81	71
CU	32,04	0,58	27,92	0,74	87
CA	32,04	0,58	22,96	0,92	72

$^1T_m = (0,67 \times T_c) + (0,33 \times T_s)$ $\quad ^2E = \left[x - (\sqrt{(x-y)^2})/x\right] .100$

3.1.3

Group	Body area	Body heat storage(C/m^2)-S		ΔS
n=7	(m^2)	0 minutes	0+30 minutes	($C/h/m^2$)
NU	0,0475	152,3	152,3	0
NA	0,0490	152,3	147,2	-10,2
HU	0,0488	152,3	189,3	+74,0
HA	0,0487	152,3	199,3	+94,0
CU	0,0483	152,3	133,9	-36,8
CA	0,0458	152,3	106,9	-90,8

anaesthetised and unanaesthetised, was not regarded as significant.

The combined effects of both heat and anaesthesia are manifested in group HA. Using group HU as a reference, metabolic rate was found to be significantly reduced at a level of significance of 5%. However, the reduction in metabolic rate due to anaesthesia in normothermic animals was significantly greater than the reduction due to anaesthesia in hyperthermic animals. Conversely, the effect of anaesthesia in terms of metabolic rate, is reduced in a relative sense during hyperthermia.

The overall outcome of the various experimental interventions on thermoregulation is presented in Tables 3.1.2 and 3.1.3 and Figures 3.1 and 3.2. It is evident that groups HU, HA and CA were incapable of maintaining thermal equilibrium in terms of both mean body temperature and body heat storage. In contrast, using the respective means ±3 standard deviations (to include 99,73% of the population), it is also apparent that thermal equilibrium was not significantly affected in groups NA and CU. Furthermore, while the effect of anaesthesia is generally seen to impair thermoregulation, this is only significantly so during cold exposure i.e., in group CU. Within the precise context of this study, mean body temperature and body heat storage were not significantly altered by the use of sodium pentobarbitone anaesthesia during heat stress.

FIGURE 3.1 BODY TEMPERATURE CHANGES DURING COLD EXPOSURE (5°C)

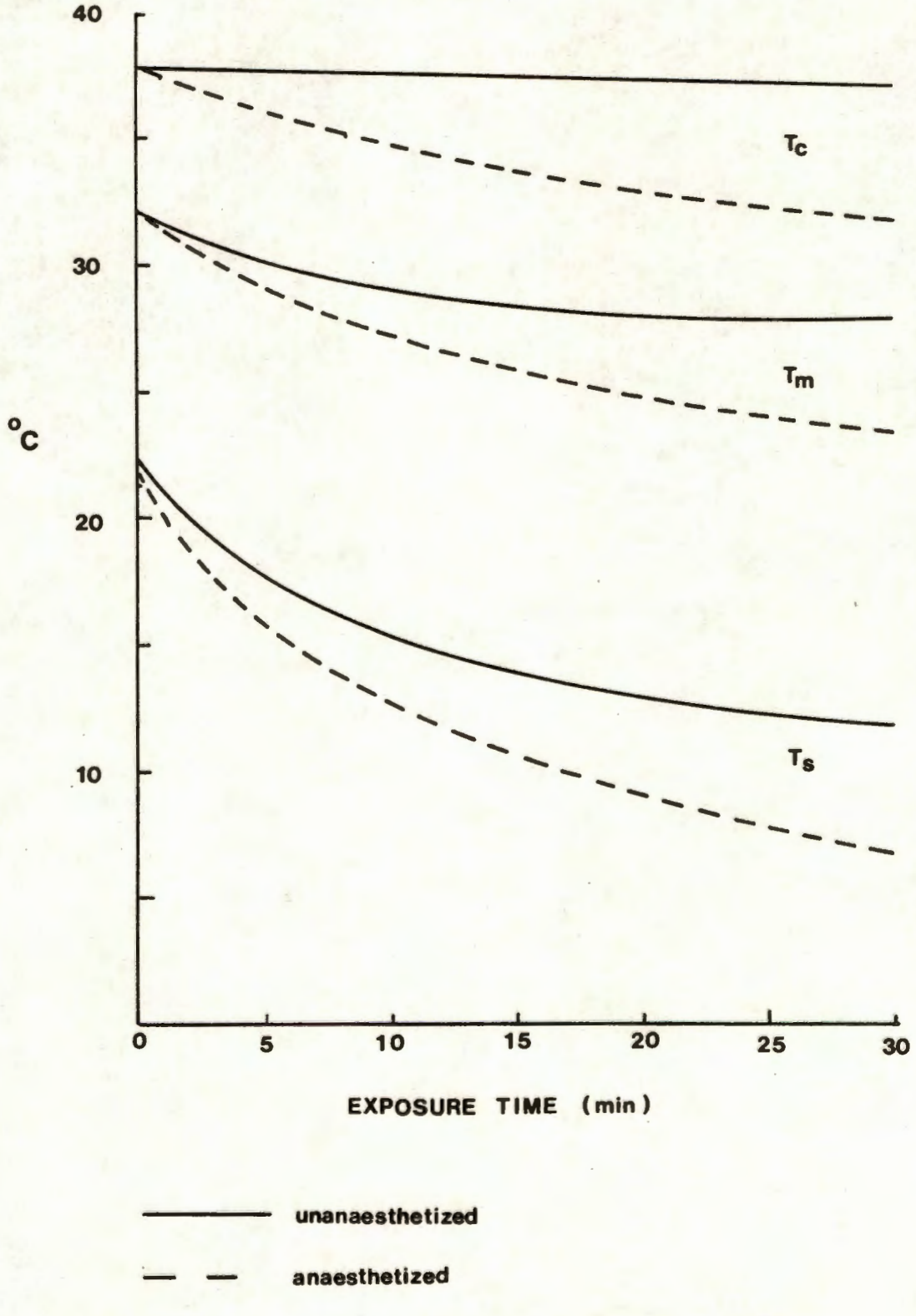


FIGURE 3.2 BODY TEMPERATURE CHANGES DURING HEAT EXPOSURE (45°C)

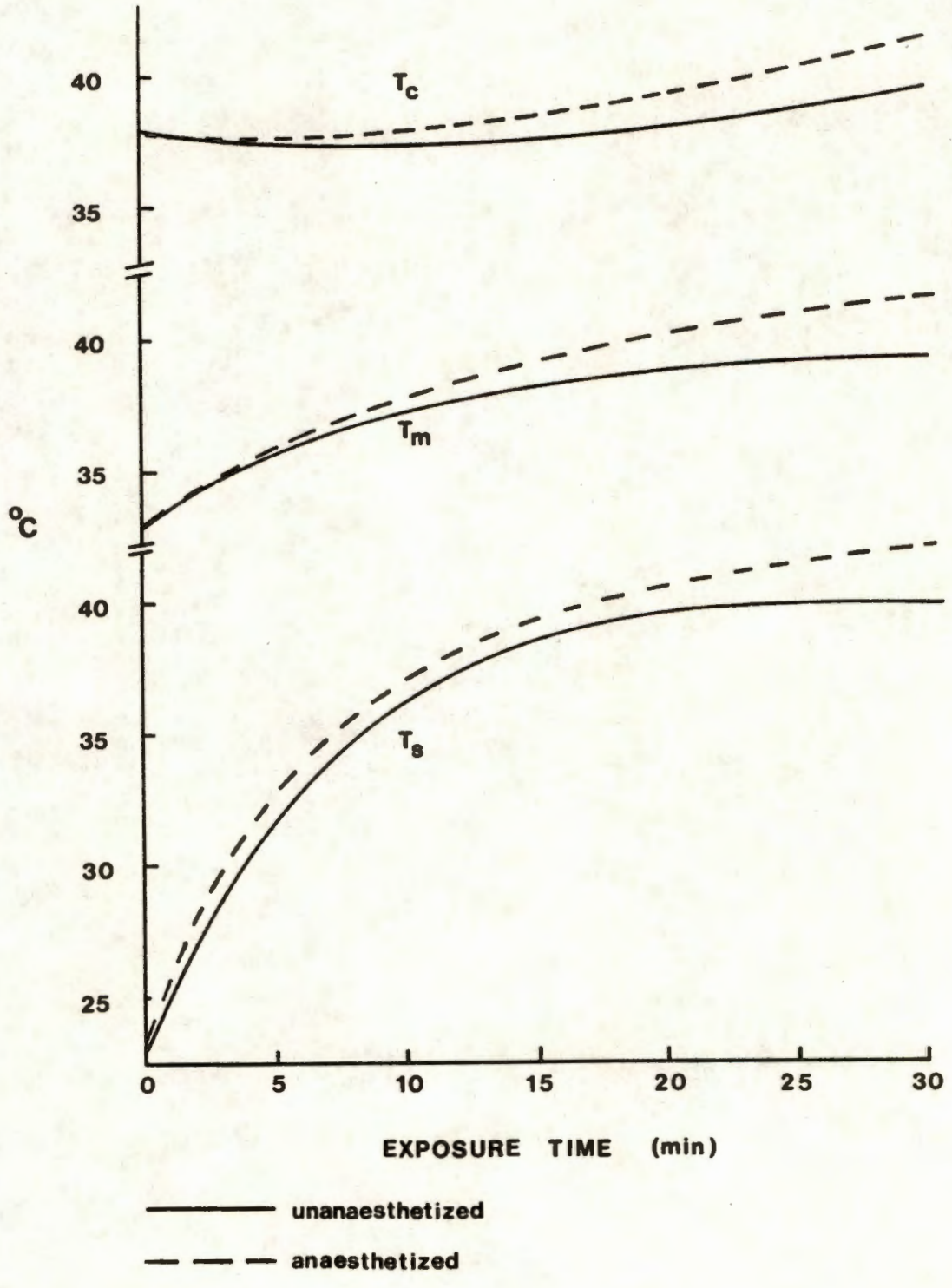
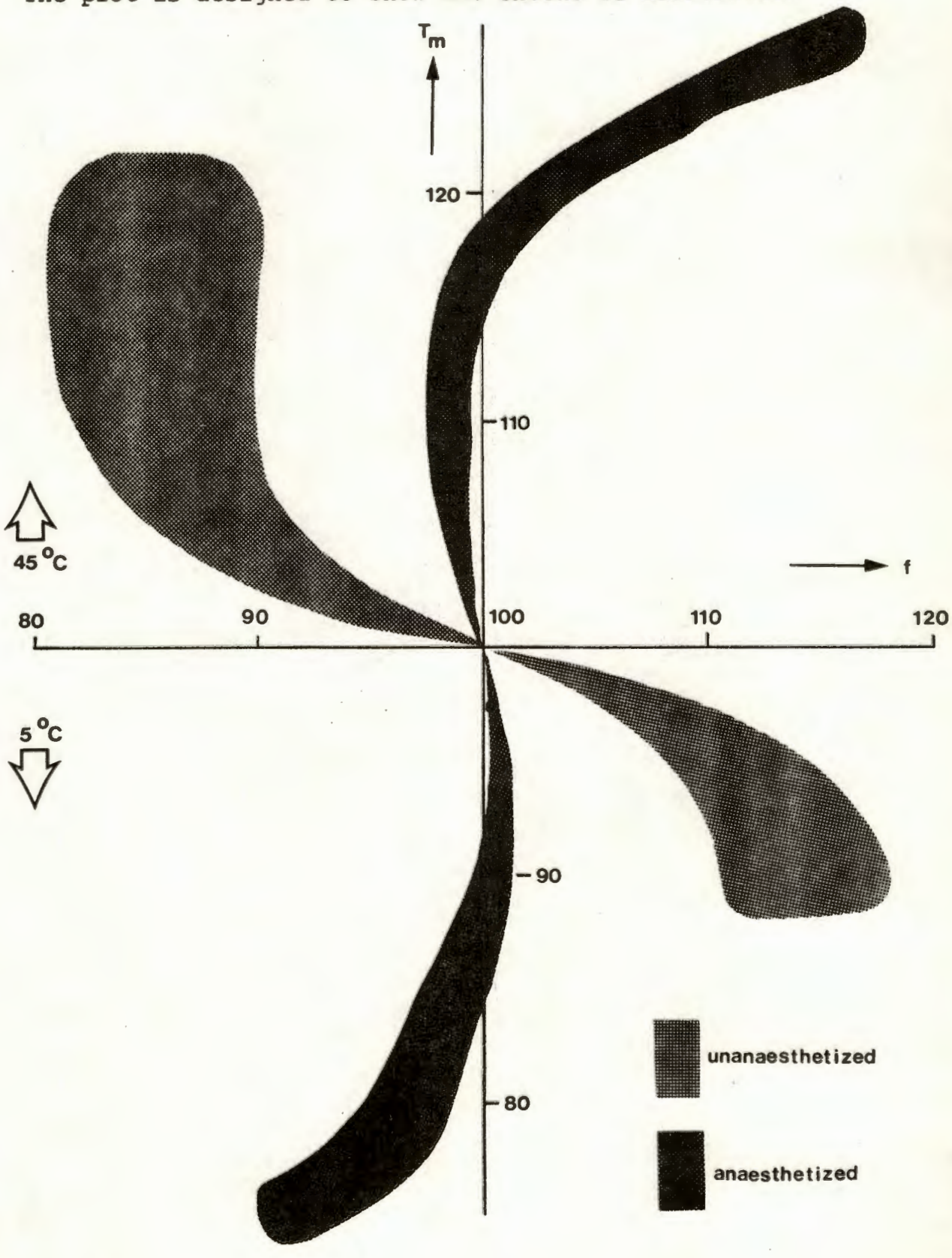


FIGURE 3.3 *THE RELATIONSHIP BETWEEN HEART RATE AND MEAN BODY TEMPERATURE DURING THERMAL STRESS*

The plot is designed to show the extent of oscillation



The relationship between mean body temperature and heart rate for groups HU, HA, CU and CA is shown in Figure 3.3. The intersect of the axes for mean body temperature and heart rate represents the respective means for group NU, each mean being equated to a numerical value of 100. All changes observed were accordingly converted. From Figure 3.3 it is evident that the relationship between mean body temperature and heart rate for the various groups is strikingly different in each case. Thus, unanaesthetised animals, with a relatively greater efficiency of thermoregulation, exhibit decreased heart rates in heat and increased heart rates in cold. Virtually opposite responses occur in the anaesthetised animals. Furthermore, whereas the relationship between mean body temperature and heart rate is represented throughout by a near smooth curve in anaesthetised animals, the terminal stages of this relationship, in unanaesthetised animals, are characterised by pronounced oscillatory patterns. An attempt was made in Figure 3.3 to emphasise these features. This oscillatory pattern was not the consequence of a wide range of individual values since all these animals exhibited this pattern individually.

An attempt was also made to establish the influence of anaesthesia on various parameters of cardiovascular function during the course of anaesthesia at room temperature conditions. The value of this analysis is extremely limited since, for obvious reasons, control data could not be obtained for unanaesthetised animals. The picture which emerged is one of general

depression of cardiovascular function. Heart rate was decreased by about 10% while the 7% fall in mean arterial pressure was related more to a fall in systolic pressure (9%) than to a fall in diastolic pressure (5%). None of these findings represented significant changes and, therefore, they merely reflect a general tendency.

In the final instance, the influence of pentobarbitone anaesthesia on oxygen consumption of left ventricle tissue slices was investigated. This measurement is the so-called Q_{O_2} and is expressed in microlitres of oxygen consumed per mg of tissue per hour. The basic method is described in detail in the previous chapter. The influence of anaesthesia was measured immediately after the onset of anaesthesia and subsequently after intervals of 40 and 85 minutes, respectively. The choice of an interval of 40 minutes is based on the observation that the duration of anaesthesia generally does not effectively exceed 30 to 35 minutes. The remaining time interval represents an interval where the obvious signs of anaesthesia have worn off.

The results of this investigation are given in Table 3.2 and graphically presented in Figure 3.4. Statistical analysis of the data was performed by analysis of variance, the details of which appear in Appendix 2. A summary of the data is given below:

TABLE 3.2 *THE INFLUENCE OF Na-PENTOBARBITONE ANAESTHESIA ON MYOCARDIAL OXYGEN CONSUMPTION (Q_{O_2})*

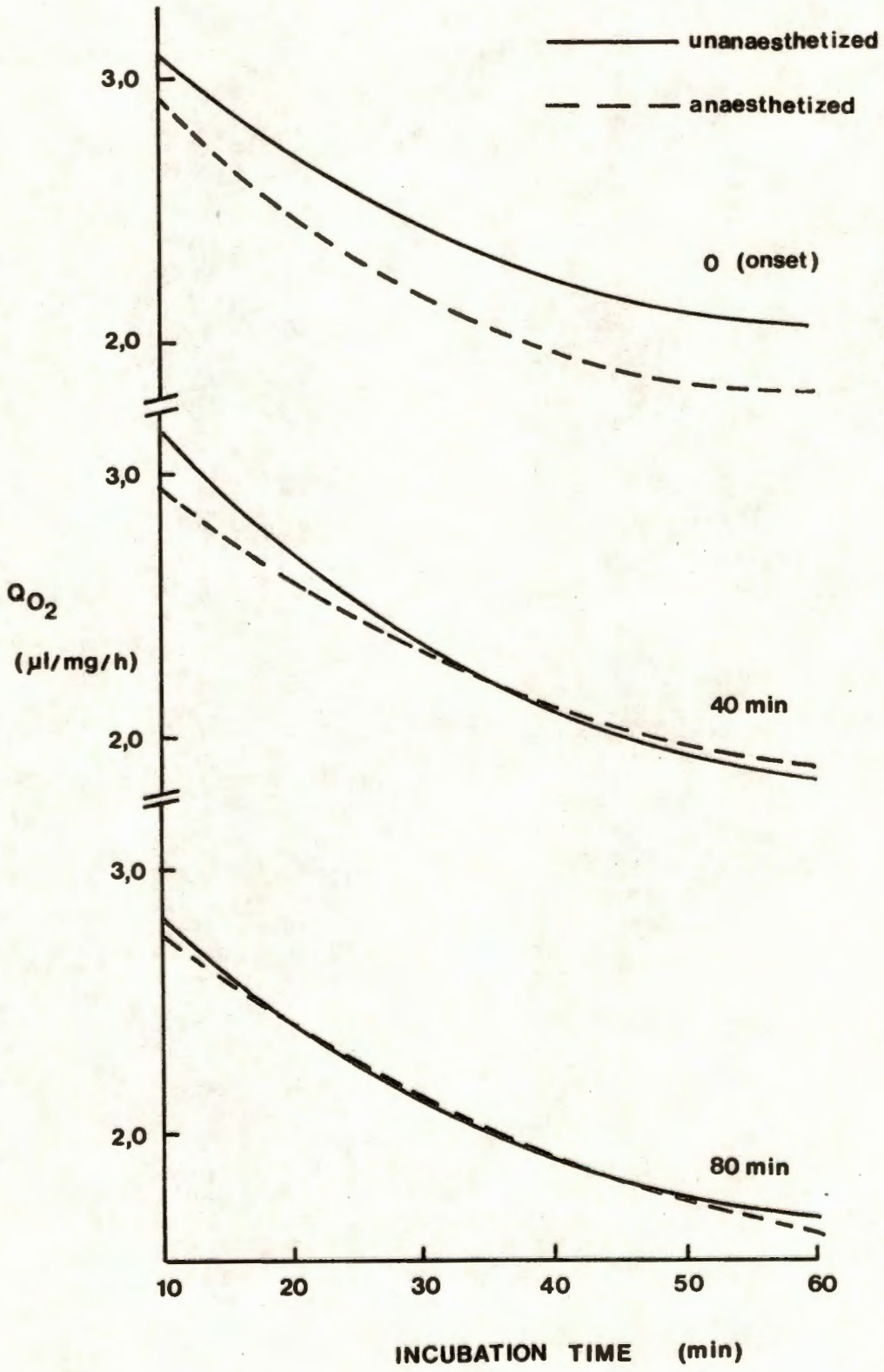
Duration of	Group*		Q_{O_2} (µl/mg/h) Incubation time (min) 10	20	30	40	50	60
0	C_1	Mean	3,062	2,671	2,512	1,896	2,120	2,069
(onset)	(n=15)	SD	0,374	0,184	0,260	0,465	0,263	0,285
		SEM	0,118	0,058	0,082	0,147	0,083	0,090
	C_2	Mean	2,856	2,451	2,162	1,908	1,865	1,802
	(n=15)	SD	0,473	0,315	0,326	0,379	0,336	0,334
		SEM	0,15	0,1	0,103	0,12	0,106	0,106
0+40	C_1	Mean	3,114	2,785	2,220	2,057	1,886	1,836
	(n=10)	SD	0,664	0,382	0,354	0,418	0,418	0,308
		SEM	0,21	0,121	0,112	0,132	0,132	0,907
	C_2	Mean	2,835	2,640	2,222	2,121	1,951	1,855
	(n=10)	SD	0,354	0,305	0,270	0,289	0,353	0,249
		SEM	0,112	0,096	0,085	0,091	0,112	0,079
0+85	C_1	Mean	2,821	2,289	1,931	1,896	1,799	1,711
	(n=20)	SD	0,690	0,555	0,483	0,365	0,382	0,359
		SEM	0,154	0,124	0,108	0,082	0,085	0,080
	C_2	Mean	2,726	2,274	1,979	1,933	1,761	1,705
	(n=20)	SD	0,642	0,632	0,496	0,441	0,392	0,321
		SEM	0,144	0,141	0,111	0,099	0,088	0,072

*C_1: unanaesthetised control

C_2: anaesthetised animal

Note: After 40 minutes the animals are strictly speaking no longer anaesthetised.

FIGURE 3.4 *THE INFLUENCE OF ANAESTHESIA ON MYOCARDIAL OXYGEN CONSUMPTION* (Q_{O_2})



Time interval	Q_{O_2} (mean) C_1* (µl/mg/h)	C_2*	% change from C_1 to C_2
0	2,492	2,174	- 12,76
0+40	2,316	2,271	- 1,94
0+85	2,075	2,063	- 0,58

* C_1: unanaesthetised control

C_2: anaesthetised animals.

An analysis of variance indicates that over the period of incubation, Q_{O_2} changes significantly. This is evident in Figure 3.4 and is largely referable to a relatively sharp initial decline prior to attaining steady-state conditions. Furthermore, the difference between C_1 and C_2 over the period of incubation does not change significantly, i.e. statistically the Q_{O_2} curves lie parallel to one another for all levels of anaesthesia.

The most important finding pertains to the observation that immediately after the onset of anaesthesia, the Q_{O_2} is significantly lower than its unanaesthetised control but 40 minutes after, and subsequently, there is no statistically significant difference between the two groups.

SUMMARY:

(a) The effect of anaesthesia on metabolic rate depended on the environmental temperature on the basis of a statistical evaluation.

(b) The reduction in metabolic rate due to anaesthesia observed in hyperthermic animals was significantly less than the reduction in metabolic rate due to anaesthesia observed in normothermic animals.

(c) Anaesthesia generally appeared to reduce the efficiency of thermoregulation but this reduction, while highly significant during hypothermic conditions, was not regarded as significant during hyperthermia nor at room temperature.

(d) The relationship between mean body temperature and heart rate was significantly altered by anaesthesia during both hyper-and hypothermia.

(e) During anaesthesia, normothermic animals exhibited slight decreases in heart rate and mean arterial pressure. These changes were not regarded as significant.

(f) Immediately after the onset of anaesthesia, a significant decrease in $\dot{Q}_{O_2}$ is evident. This decrease, is, however, abolished after 40 minutes so that no significant difference exists between the control animal and the anaesthetised animal.

3.2 *DISCUSSION*

One of the characteristics of mammalian thermoregulation is that of continuous proportional control (CPC). Essentially, this means that the physiological effector action is proportional in magnitude to the thermal load error that tends to

displace body temperature from its set point. Consequently, this concept accounts for the great stability of physiological temperature control during moderate exposures to heat and to cold (Hardy and Hammel, 1963). It is therefore not surprising that impairment of centrally mediated mechanisms of thermoregulation depresses CPC, resulting in a widening of the so-called "dead-zone" of thermoregulation, as was demonstrated in hypothalectomized and anaesthetised dogs (Keller and Hare, 1932). Thus, within the context of a study concerning mammalian thermoregulation and where the experimental techniques employed necessitated the use of an anaesthetic agent, the findings of Keller and Hare (1932) and Hardy and Hammel (1963) become highly relevant. For this reason the influence of pentobarbitone anaesthesia on thermoregulation was investigated over a wider spectrum of thermal stress than just heat.

Under normothermic conditions, the normal metabolic rate of adult rats of 28 C/h/m^2 (Zarrow *et al*, 1964) is reduced by about 50% following the induction of moderate pentobarbitone anaesthesia (Sellers and You, 1950), an event which is accompanied and characterised by a slightly hypokinetic circulation (Drill, 1958; Pretorius *et al*, 1966, Sharpless, 1966; Rademeyer, 1969). These findings were re-affirmed in the present study: metabolic rate was reduced from a normal value of about 24 C/h/m^2 by 35% while a hypokinetic circulation was reflected in slight, albeit definitive reductions in heart rate and mean arterial pressure. The latter findings are in complete agreement with those described by Sharpless (1966).

Despite the significant reduction in metabolic rate observed at room temperature (±20°C), the overall efficiency of thermoregulation was not significantly impaired by anaesthesia, mean body temperature and body heat storage being only slightly reduced. Since adjustments in metabolic rate are regarded as one of the major effector mechanisms of thermoregulation (chemical thermoregulation), it follows that in this context, the brunt of thermoregulatory activity must fall on the other major effector mechanism, namely, vasomotor adjustments, i.e., physical thermoregulation. In the complete absence of any apparent compensatory vasomotor adjustments, it is clear that the mechanisms involved in the maintenance of normothermia must reside at different levels.

According to Rieke and Everett (1957) a redistribution of the blood volumes of several vascular beds occurs during pentobarbitone anaesthesia in rats so that significant increases in blood volume were found in the organs of the splanchnic circulation, the kidney, the reproductive organs and the skin; decreases being recorded in the heart, skeletal muscle and bone. In as much as it may be argued that an increase in the skin blood volume would enhance heat dissipation, and consequently tend to lower the mean body temperature, it is equally likely that an increase in blood volume of the splanchnic organs would exert a beneficial influence by counteracting heat loss. This argument finds support in the current observation in that the slight reduction in mean body temperature may be ascribed, to a greater extent, to a lowering of skin temperature than to a lowering of core temperature. A tenta-

tive hypothesis may therefore be forwarded, namely, that under normothermic conditions the slight reduction in the efficiency of thermoregulation due to pentobarbitone anaesthesia represents the outcome between severe suppression of chemical thermoregulation and intact physical compensation. The slight reduction in the efficiency of thermoregulation is nevertheless in complete accord with the concept of a "widening of the dead-zone of physiological temperature control".

During cold exposure, however, the above hypothesis no longer seems to hold true: In both anaesthetised and unanaesthetised animals the respective metabolic rates fall within normal, unanaesthetised limits. In the case of the anaesthetised animals it would appear likely that the "dead-zone" had been exceeded in agreement with the findings of Keller and Hare (1932). Yet, despite the relatively high metabolic rate, significant decreases in mean temperature and body heat storage occurred in the anaesthetised animals. On the basis of findings of increased skin blood volumes (Rieke and Everett, 1957) and the abolishment of dermal vasocontriction (Whitehead and Virtue, 1965) during pentobarbitone anaesthesia, the inability to resist hypothermia seems referable to inadequate vasomotor adjustments rather than to a metabolic factor. While behavioural responses cannot be ignored, it is significant that unanaesthetised animals were able to maintain mean body temperature within the lower limits of normal and at virtually the same metabolic rate as normothermic controls.

The greater efficiency of thermoregulation of unanaesthetised animals in cold was also associated with a marked increase in heart rate. According to Sjöstrand (1976), such a response i.e., an increased heart rate, is the result of an increase of the central blood volume (volume of blood in the large veins and heart) so that the outflow of blood flow to the systemic circulation is augmented, thus preventing overload of the lesser circulation. The increased cardiac output then shifts the balance between the filtration and resorption of water at the capillaries towards a net increase in filtration. A fall in central volume would elicit an opposite sequence of events.

Since the central blood volume is on a level with the total blood volume, an elevated central blood volume could conceivably result from peripheral vasoconstriction, which occurs as an initial response to cold exposure (Horvath and Howell, 1964). This relative increase in blood volume, having been transferred to the central reservoir, could then explain the observed cardioacceleration in unanaesthetised animals subjected to cold. Similarly, the sustained decrease in heart rate observed in anaesthetised animals during cold exposure, may result from a fall in central blood volume due to an anaesthesia induced dermal vasodilation (Rieke and Everett, 1957; Whitehead and Virtue, 1965).

During heat exposure, the difference in the efficiency of thermoregulation between anaesthetised and unanaesthetised

animals was not significant, the latter group exhibiting a slightly lower terminal mean body temperature. According to Setnicar and Temelcou (1961), hypothermic conditions prolong the duration of anaesthesia due to a decreased catabolism of the barbiturate. Under these conditions the toxicity of the drug was also increased. In the absence of any direct evidence, it may be speculated that the negligible difference in the efficiency of thermoregulation observed between anaesthetised and unanaesthetised animals in heat may be related to an increased rate of drug catabolism at supranormal temperatures.

However, in both groups significant reductions in metabolic rate (over normothermic controls) were observed during heat exposure. Clearly, such reductions constitute a considerable physiological benefit in so far as heat gain from an environmental source is not compounded by a simultaneous heat gain from a metabolic origin. The reduction in metabolic rate constitutes an adjustment of chemical thermoregulation which is a normal response in rats suddenly exposed to hot environments (Gelineo, 1964) and during estivation (Schmidt-Nielsen, 1964). As in cold exposure, it therefore appears likely that chemical thermoregulation is not suppressed by pentobarbitone anaesthesia during heat exposure.

Considering the relationship between mean body temperature and heart rate, it was apparent that unanaesthetised animals maintained a decreased, albeit oscillatory, heart rate response

pattern. In terms of the concepts of Sjöstrand (1976) (*vide supra*), such a response would occur in response to a fall in central blood volume, the underlying mechanism being referable to a relative fall in total blood volume in response to rapid and efficient dermal vasodilation.

In contrast, anaesthetised animals exhibited an increase in heart rate, a response which may be traced back to an inability to effect adequate dermal vasodilation. In further support of this conclusion is the observation that despite the added advantage afforded by a lower metabolic rate, anaesthetised animals are, if anything, less efficient in resisting hyperthermia than unanaesthetised animals. By implication, at least, it would appear that the slightly lower efficiency of thermoregulation of anaesthetised animals exposed to heat resides in an inadequacy of vasomotor control to elicit effective dermal vasodilation.

With reference to the heart specifically, the significant reduction in Q_{O_2} immediately after the onset of anaesthesia indicates that the resulting hypokinetic circulation may be partly referable to a suppression of the intracellular oxidative capacity. While there is general consensus that cardiac contractility is decreased by barbiturates, the actual site of dysfunction remains largely obscure. On the basis of the findings of Morris and King (1962) it appears that the point of inactivation may in fact be on or near the flavoproteins in the respiratory chain. Speculatively, such an event could directly lead to diminished contractility. The

diminished contractility could however, also result from a redistribution of intracellular calcium due to sodium pentobarbitone (Nayler and Szeto, 1972), but the link between suppressed oxidative capacity and intracellular calcium redistribution remains uncertain in this context. However, despite the initial suppression of oxygen utilization, it is patently clear that after 40 minutes, this suppression is completely abolished and the normal oxidative capacity is reinstated.

In terms of the experimental observations of this investigation, and in terms of the relevant literature, the following conclusions were made:

(a) The effects of anaesthesia under normothermic conditions differ significantly from the effects exerted during thermal stress.

(b) Under normothermic conditions, pentobarbitone anaesthesia depresses chemical thermoregulation but not physical thermoregulation.

(c) During thermal stress, central vasomotor control appears to be unresponsive to the demands of thermoregulation as a result of pentobarbitone anaesthesia. Chemical thermoregulation is not, however, significantly affected.

(d) During heat stress, the reduction of effective vasomotor control, as a result of anaesthesia, is likely to constitute an additional burden on cardiac function, especially during the initial stages of anaesthesia.

(e) During hyperthermia, the use of pentobarbitone anaesthesia does not significantly alter the overall efficiency of thermoregulation and, from this point of view, its use in experiments of this nature seems fully justifiable.

(f) Pentobarbitone anaesthesia suppresses the overall oxidative capacity of myocardial tissue but only during the initial stages of anaesthesia.

C H A P T E R IV

RESULTS

The main objective of this study concerns an evaluation of cardiovascular function during acute, experimental hyperthermia with specific reference to events which may potentiate circulatory failure. Within the latter context, the emphasis falls on the integrity of cardiac function as motivated at the outset (See: Introduction). The fundamental approach, therefore, was to relate certain subcellular parameters of cardiac integrity (myocardial oxidative capacity and electrolyte balance) to the prevailing haemodynamic status at successive stages of progressive hyperthermia.

The presentation of the results of this study is largely based on the various experimental techniques employed and, therefore, comprises 4 major sections viz., body temperature changes (4.1), cardiovascular function in general (4.2), myocardial oxidative capacity (4.3) and myocardial electrolyte balance (4.4). In each instance, reference will be made to the statistical methods employed, the details of which are presented as an appendix to the study. Finally, an integrated view of the cardiovascular function is presented by way of a review of the results (4.5).

All animals were exposed to an environmental temperature of 45^{o}C. No attempt was made to alter humidity from the prevailing atmospheric level. On the basis of meteorological

data, it appears that in general relative humidity fluctuated between approximately 60 and 70%, while concurrent measurements within the cabinet exhibited reductions to between 10 and 15%.

4.1 MEASUREMENTS OF BODY TEMPERATURE

The basic measurements comprised core (T_c) and skin temperature (T_s), respectively. These measurements were then used to determine mean body temperature (T_m) and body heat storage (S). The details of these measurements and calculations appear in Chapter 2.

Body temperatures were measured at 10-minute intervals during the entire period of heat exposure which lasted until circulatory failure occurred. These findings, summarised in Table 4.1, were then subjected to an analysis of variance (Appendix 3) in order to establish the level of significance between the means for a particular measurement over the period of heat exposure. In all of the above cases, the differences between the means for any particular measurement over time were found to be highly significant at the 0,5% level of significance. Consequently each measurement was then subjected to a polynomial regression analysis to establish the true nature of the changes between the means. For this purpose, all the data collected to establish a particular mean, not only the means *per se*, were employed. The results of this analysis indicate that (a) T_c conforms to a linear relationship, (b) T_m and S conform to a second-order curve

TABLE 4.1 BODY TEMPERATURE CHANGES DURING HEAT STRESS

Measurement (°C)		Exposure Time (min) 0	10	20	30	40	50	60	70	80
T_c	Mean	37,2	37,3	37,9	38,8	39,6	40,3	40,9	41,5	41,9
	SD	0,42	0,39	0,49	0,59	0,53	0,53	0,54	0,51	0,47
T_s	Mean	28,5	37,4	39,0	40,7	40,3	40,6	41,1	41,3	41,5
	SD	1,11	1,32	0,53	3,01	0,44	0,45	0,48	0,32	0,22
T_m	Mean	34,3	37,3	38,3	39,1	39,8	40,4	41,0	41,4	41,8
	SD	0,47	0,62	0,36	0,44	0,49	0,48	0,49	0,42	0,34

Note: On the basis of an analysis of variance, the difference between the means was established to be significant at the 0,5% level of significance (Appendix 1) for all of the above measurements. Subsequent analysis (Polynomial regression) indicates a first order relationship for T_c, a second order for T_m and a third order for T_s. The fitted values are given below:

Measurement (°C)	Exposure Time (min) 0	10	20	30	40	50	60	70	80
T_c	36,9	37,5	38,2	38,8	39,5	40,1	40,8	41,4	42,1
T_s	29,4	35,7	39,3	40,9	41,2	40,9	40,4	40,6	42,1
T_m	35,0	36,6	37,9	39,0	39,9	40,7	41,2	41,5	41,6

while (c) T_s exhibits a third-order relationship. In each instance, fitted values for T_c, T_s, T_m and S were calculated. T_c and T_s are graphically displayed in Figure 4.10 at the end of this chapter.

An analysis of Table 4.1 indicates that at a point in time just prior to circulatory failure (0+70 minutes), T_s exhibits the greatest overall change, constituting an elevation of 45% of its initial value. In contrast, the most significant difference between means over the entire period of heat exposure pertains to T_m (Appendix 3). This observation may be readily explained by following the time-course for T_s: within 10 minutes after the onset of heat stress, T_s reaches a value of about 68% of its terminal value and, in fact, subsequently overshoots and exceeds T_c until just prior to circulatory failure. Thus, 20 minutes after the onset of heat stress, the time course for T_s only accounts for a further 19% of its overall change and hence the entire time-course assumes the shape of a rectangular hyperbola. The overall significance between means for T_m therefore appears to be related firstly to rapid changes in T_s while T_c remains relatively constant and secondly, during the latter stages, to a steady elevation in T_c while T_s remains relatively constant. It is therefore concluded that T_m represents the most sensitive overall index of changes in body temperature. Body heat storage, S, which exhibits a high level of significance between means over the period of heat exposure (Appendix 3), is represented by a second-order time-course and, in this sense, shows a close

correlation to T_m. In the context of the present study, however, the calculation of S does not appear to afford any advantage over that of T_m.

4.2 *CARDIOVASCULAR FUNCTION*

Cardiovascular function during heat stress was investigated in a group of 10 male albino rats (*Rattus norvegicus*) with a mean mass of 273,0±18,7g (Mean±SD). Measurements of cardiovascular function and body temperature were carried out concurrently. The electrocardiogram, phonocardiogram and arterial (carotid) blood pressure recordings were obtained at 10-minute intervals during heat exposure until circulatory failure occurred (*vide infra*).

The general circulatory response pattern to heat was remarkably similar in all animals despite considerable temporal variation. For example, peak arterial pressure was recorded after a mean exposure time of 75,0±14,3 minutes with a range of 60 to 100 minutes. In view of the fact that this variation could not be ascribed to animal size or the rate of change of body temperature, including body heat storage, the temporal variation was related to individual animal variation.

Individual variation obviously represents a complication in the interpretation of pooled data. In order to overcome this problem it was decided to choose a single event in time as a reference point instead of chronological time *per se*. The event chosen was a maximum elevation in systolic pressure prior

to the inevitable subsequent fall heralding the onset of circulatory failure. In as much as this study concerns the mechanism of circulatory failure, and in as much as arterial pressure changes would allow a distinction between events preceding failure and those following on failure, the choice of arterial pressure changes as a marker event was considered justifiable. In this sense the time-base referred to in this section could be regarded as "artificial time" in that it represents a mean time at which certain events occur. The exception to this is "0" minutes of heat exposure where the values reported truly represent control levels. With reference to the introductory paragraph and the identification of circulatory failure: the onset of circulatory failure was identified as that point where a decrease in systolic pressure first becomes noticeable after a sustained hyperkinetic circulation, overt failure being identified subsequently by a characteristic pressure pulse. Representative recordings of these phenomena are presented elsewhere in this section and will be specifically referred to.

A total of 45 measurements was made at each 10-minute interval for each animal. The raw data were punched into a Wang computer and at the outset, the respective means, standard deviations (SD) and standard errors of the means (SEM) were computed. The data were then subjected to an analysis of variance in order to establish the level of significance between the means of a particular measurement over time. The outcome of this treatment is presented in Table 4.2.1, the details of which are given in Appendix 3.

TABLE 4.2 *SUMMARY OF STATISTICAL ANALYSES OF CIRCULATORY RESPONSES*

4.2.1 *ANALYSIS OF VARIANCE*

F-value	LOS[1]	p-value	Measurement[2]
<2,05	NS[3]	>0,05	QT; EKG R-waves (mV); QRS (msec); QRS vector; summated R-waves; EKG S-waves (mV); summated S-waves; S_a/D_a; T; dP/dt_{max}; dP/dt_c; QS_{1-c}; QS_2/S_2Q, ET_c
>2,05	5%	<0,05	f/P_m; SV
>2,74	1%	<0,01	-
>3,033	0,5%	<0,005	f; PQ; QT_c; arterial pressures; dP/dt_{mean}; QS_1; PEP; ET; PEP/ET_c; DT; S_1S_2; QS_2; S_2Q; Q; R.

1 Level of significance.
2 Abbreviations explained in text and in separate list (See: Appendix 5).
3 NS: Not significant.

4.2.2 *POLYNOMIAL REGRESSION ANALYSIS*

Nature of Curve	Measurement
1st Order	f; arterial pressures; QS_1; PEP; ET_c; PEP/ET_c; DT; S_1S_2; QS_2; S_2Q; f/P_m; SV; Q; R.
2nd Order	PQ; QT_c; dP/dt_{mean}; P_s-P_{es}

All measurements which proved to be statistically insignificant were excluded from further analysis. The remainder was subjected to a polynomial regression analysis in order to establish the true nature of the differences between the means (Table 4.2.2). At the outset a first order equation (linear) was fitted to the data. This procedure was then repeated using a second order equation. On the basis of the significance of the increase in the multiple coefficient of determination, it could be established whether the contribution of the second order equation was significant, or not. If significant, the process was repeated for third, fourth, etc., order equations. The process terminated as soon as the added order did not contribute significantly.

Having thus established the appropriate order of the polynomial equation, fitted values were obtained for each exposure time. Differences between the observed means and fitted values reflect the closeness of fit. In some instances this procedure contributed significantly to the interpretation of results but it is equally clear that blind adherence to fitted values could create a false impression in certain circumstances. For example, systolic pressure is given as a first order equation; this ignores the fact that systolic pressure exhibits a definite fall at the onset of circulatory failure which, due to individual variation, cannot be demonstrated statistically.

4.2.1 ELECTROCARDIOGRAPHY

Electrocardiographic analyses were performed on the standard limb leads (EKG I-III) at a calibration of 2cm/mV and a recording speed of 250 mm/sec. The technique is detailed in Chapter 2. Apart from measuring the RR'-interval (cardiac cycle) in order to estimate heart rate (f=60000/RR in msec), the EKG was analysed to determine the PQ-, QRS- and QT-intervals as well as the respective amplitudes of the R- and S-waves in the standard leads. These basic measurements were then used to determine the corrected QT-interval ($QT_c=QT/\sqrt{RR'}$), and the direction and amplitude of the mean QRS-vector, the latter determination being based on Einthoven's equilateral triangle. Finally, the individual R- and S-waves in each lead were summated to respectively yield R_t and S_t. Normal electrocardiograms are presented in Figure 4.1.

The only electrocardiographic measurements which changed significantly (Table 4.2) were the PQ-interval and QT_c. The QRS-duration remained remarkably constant at 12 msec although a slight increase became noticeable in the terminal stage of heat exposure. None of the QRS-waves (R and S) changed significantly over the course of heat exposure so that the mean QRS-vector direction remained more or less constant at $+62,1\pm4,24^{o}$ (Mean ±SD) with a range of +55 to $+69^{o}$. The amplitude of the mean QRS-vector exhibited a tendency to increase to a peak just prior to circulatory failure whereupon an abrupt fall became

TABLE 4.3 ELECTROCARDIOGRAPHIC ANALYSES (1)

Measurement		Exposure time (min)								
		0	10	20	30	40	50	60	70	80
QT (msec)	Mean	49,0	48,0	48,2	47,6	46,0	46,6	46,4	49,0	49,8
	SD	3,2	3,9	2,4	3,9	3,0	3,4	3,9	5,6	7,6
R-I	Mean	6,7	7,2	6,8	6,9	7,1	6,8	7,8	7,3	6,7
	SD	2,3	2,1	2,7	2,2	2,6	3,1	4,1	3,0	3,2
R-II	Mean	12,9	12,8	12,1	12,1	12,2	12,4	13,3	12,6	10,2
	SD	3,2	3,3	2,7	1,7	2,2	2,2	2,1	2,2	2,8
R-III	Mean	8,2	7,9	8,0	7,7	7,5	7,8	8,5	8,2	7,6
	SD	2,3	2,2	2,2	2,2	2,2	2,4	2,7	2,5	2,9
R_t	Mean	27,8	27,8	26,9	26,7	26,7	27,0	29,1	28,1	24,4
	SD	5,9	5,4	5,0	3,7	4,3	3,9	4,0	4,0	5,5
S-I	Mean	4,9	4,2	4,5	4,3	4,4	4,0	4,0	4,2	5,3
	SD	2,1	1,6	1,9	1,7	1,7	1.8	1,6	2,4	4,8
S-II	Mean	6,2	6,2	5,6	5,0	5,2	5.9	5.2	5,2	5,8
	SD	2,3	1,8	1,8	2,1	1.6	2,5	1,5	2,0	3.3
S-III	Mean	5,2	5,1	4,0	4,1	4,0	4,2	5,1	5,5	5,7
	SD	2,3	2,6	2,3	2,4	2,4	2,0	2,5	2,9	3,4
S_t	Mean	16,3	15,5	13,1	13,5	13,6	13,4	14,3	14,9	16,7
	SD	4,2	4,1	2,7	3,5	3,0	2,4	2,7	3,9	7,2
QRS-vector	Direction (^{o})	+63	+55	+69	+60	+64	+64	+63	+58	+63
	Magnitude (mV)	0,58	0,66	0,64	0,72	0,75	0,64	0,76	0,68	0,40

Notes: 1. All amplitude measurements (R and S) are given in mm, 1 mm being equal to 0,05 mV.

2. In all instances the difference between the means was not regarded as statistically significant. (See Table 4.2).

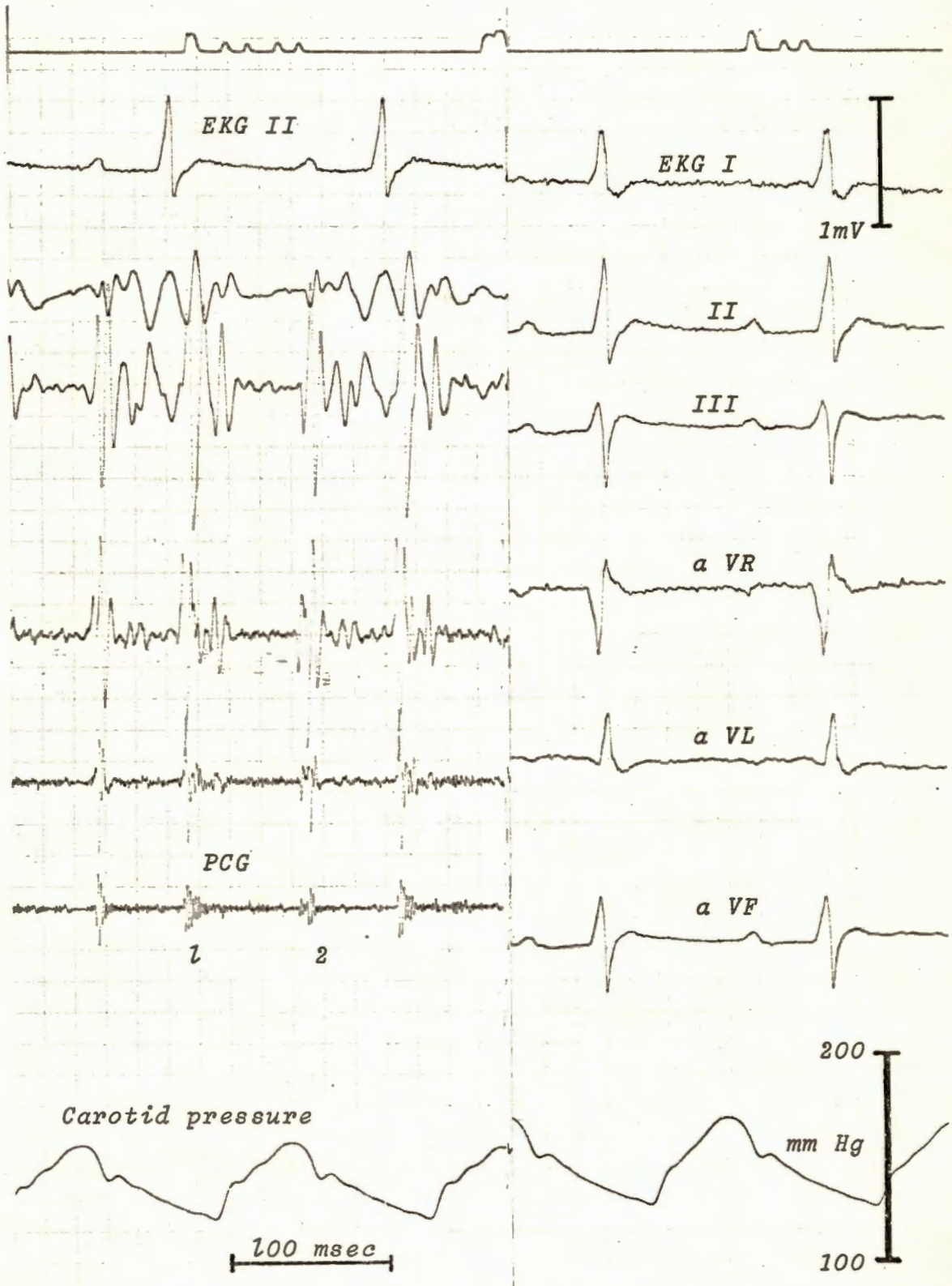
TABLE 4.4 ELECTROCARDIOGRAPHIC ANALYSES (2)

Measurement		Exposure Time (min) 0	10	20	30	40	50	60	70	80
PQ	Mean	47,6	45,4	44,6	43,0	41,0	41,2	41,2	41,6	41,4
(msec)	SD	2,3	3,7	3,3	3,9	4,2	3,2	3,3	3,4	4,6
QT_c	Mean	0,125	0,128	0,131	0,130	0,128	0,133	0,134	0,147	0,156
	SD	0,007	0,011	0,005	0,013	0,011	0,010	0,011	0,023	0,019

Note: On the basis of an analysis of variance, the difference between the means was established to be significant at the 0,5% level of significance, i.e. P<0,005 (Table 4.2). In both instances a polynomial regression analysis yields a second order relationship. The fitted values are given below:

Measurement	Exposure Time (min) 0	10	20	30	40	50	60	70	80
PQ	47,6	45,7	44,1	42,8	41,9	41,3	41,1	41,2	41,6
QT_c	0,125	0,128	0,130	0,130	0,130	0,131	0,136	0,144	0,157

FIGURE 4.1 *THE NORMAL EKG, PCG AND CAROTID PRESSURE PULSE*



evident. An opposite pattern was characteristic of R_t. Neither of these tendencies was considered significant from a statistical point of view. The above findings are presented in Table 4.3.

As mentioned above, the PQ-interval and QT_c were the only electrocardiographic measurements which exhibited significant differences between their respective means during heat exposure. An analysis of the data is presented in Table 4.4. With reference to the fitted values it is evident that the decrease in PQ is rapid during the initial stages of exposure and accounts for 89% of its maximum decrease within the first 40 minutes. There also exists a slight tendency for PQ to increase towards the terminal stages. A gradual increase in QT_c, initially, is followed by a dramatic terminal increase so that during the last 20 minutes the increase in QT_c represents 66% of the overall change.

A consistent finding was ST-segment depression. This event became evident just before circulatory failure and progressively more extensive. Evidence of this phenomenon is provided in Figures 4.1 - 5.

4.2.2. ARTERIAL PRESSURE

Arterial pressure was measured by catheterization of the left common carotid artery. The techniques employed, as well as the calibration procedures, are described in detail in Chapter

FIGURE 4.2 *CARDIOVASCULAR PERFORMANCE DURING MILD HYPERTHERMIA (0+40 MIN)*

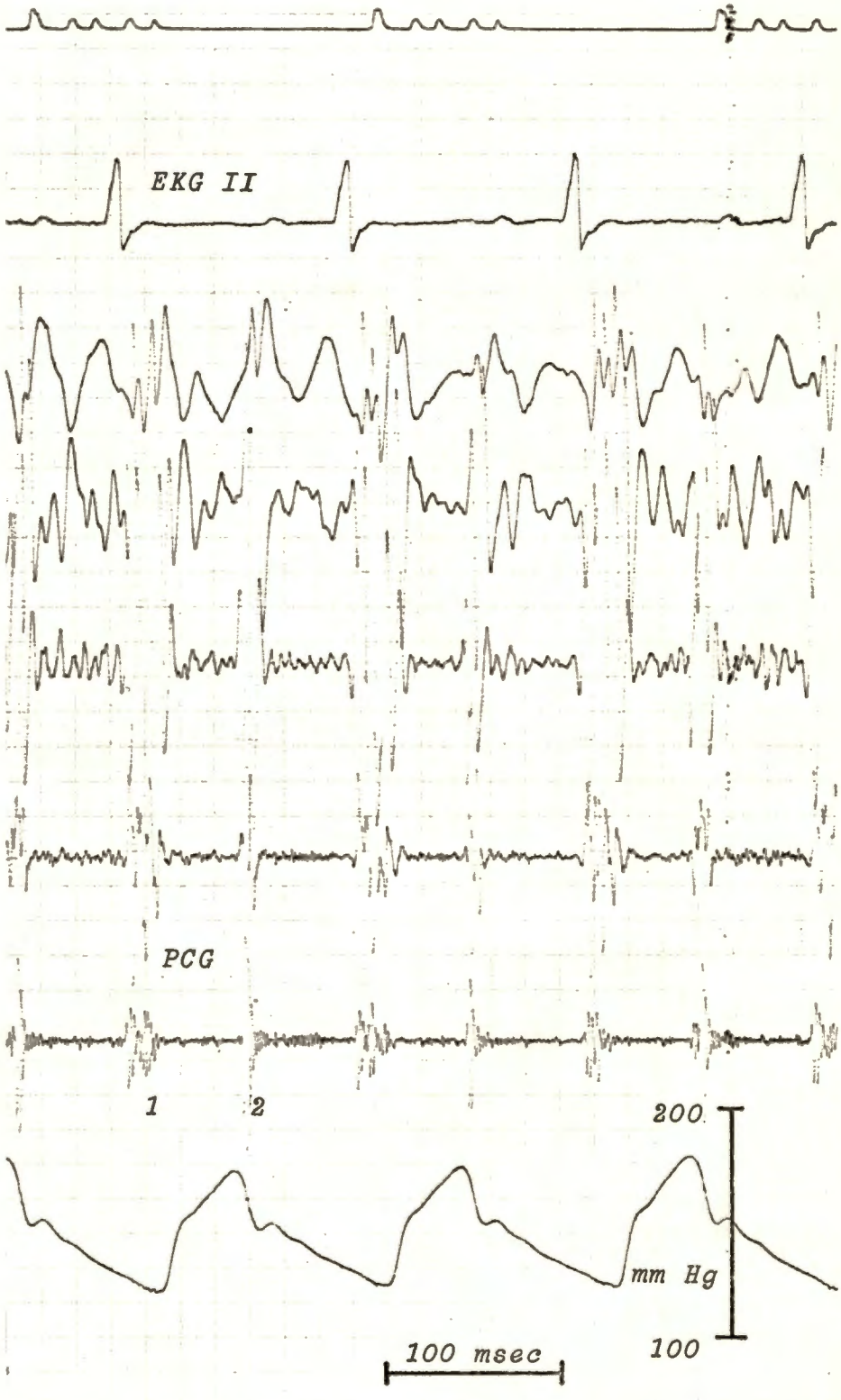


FIGURE 4.3 *THE HYPERKINETIC CIRCULATION*

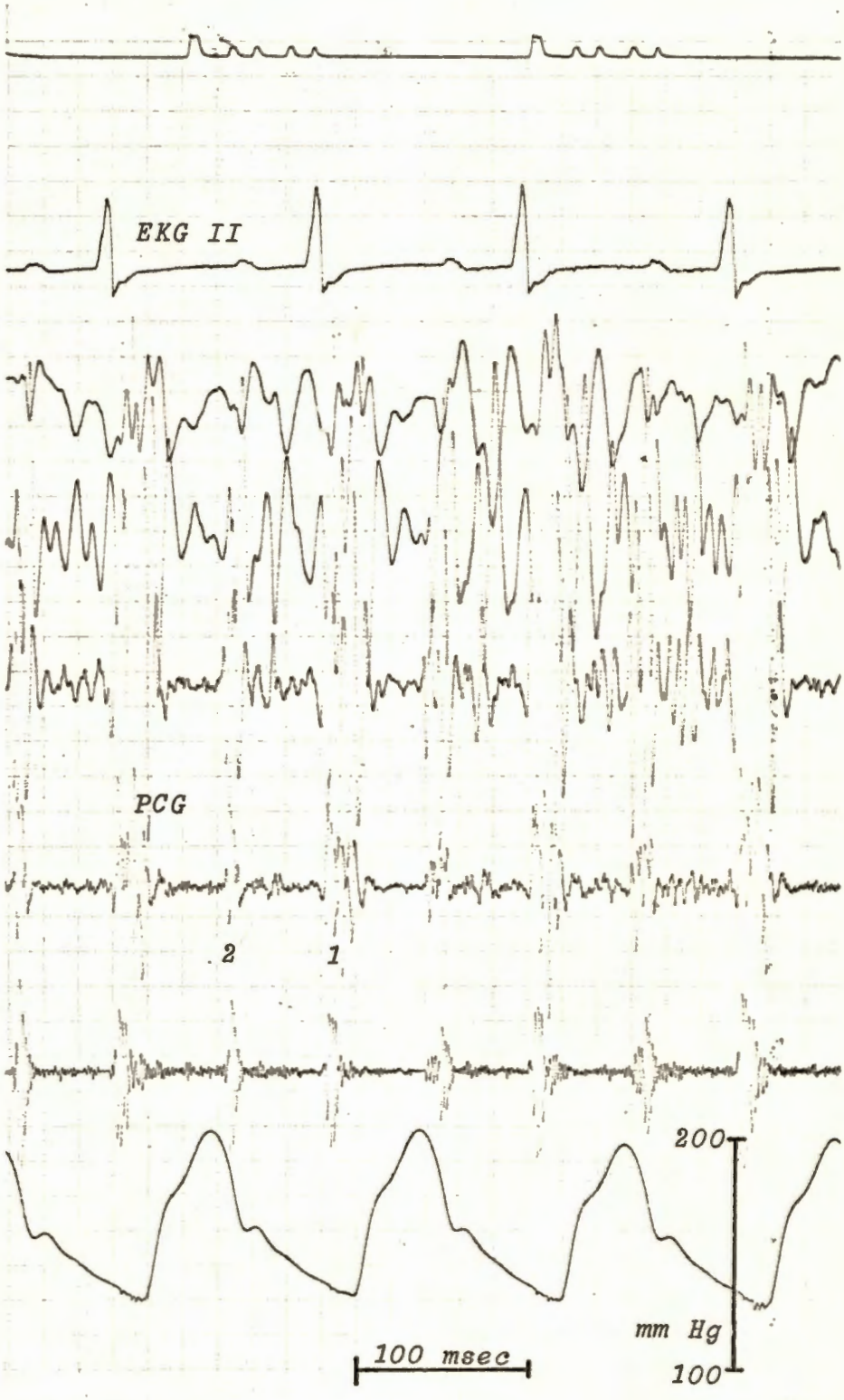


FIGURE 4.4 *THE COMMENCEMENT OF CIRCULATORY FAILURE*

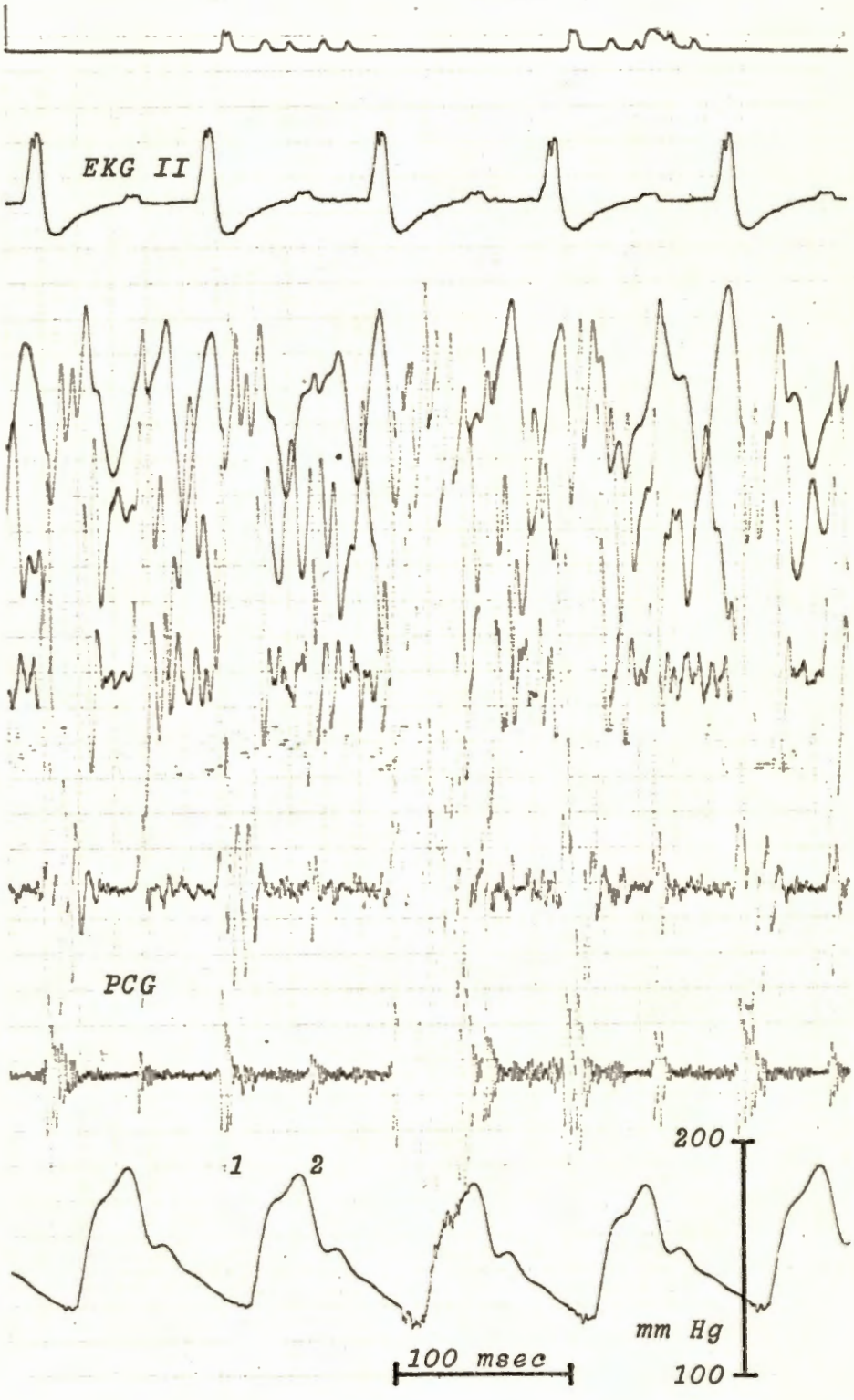
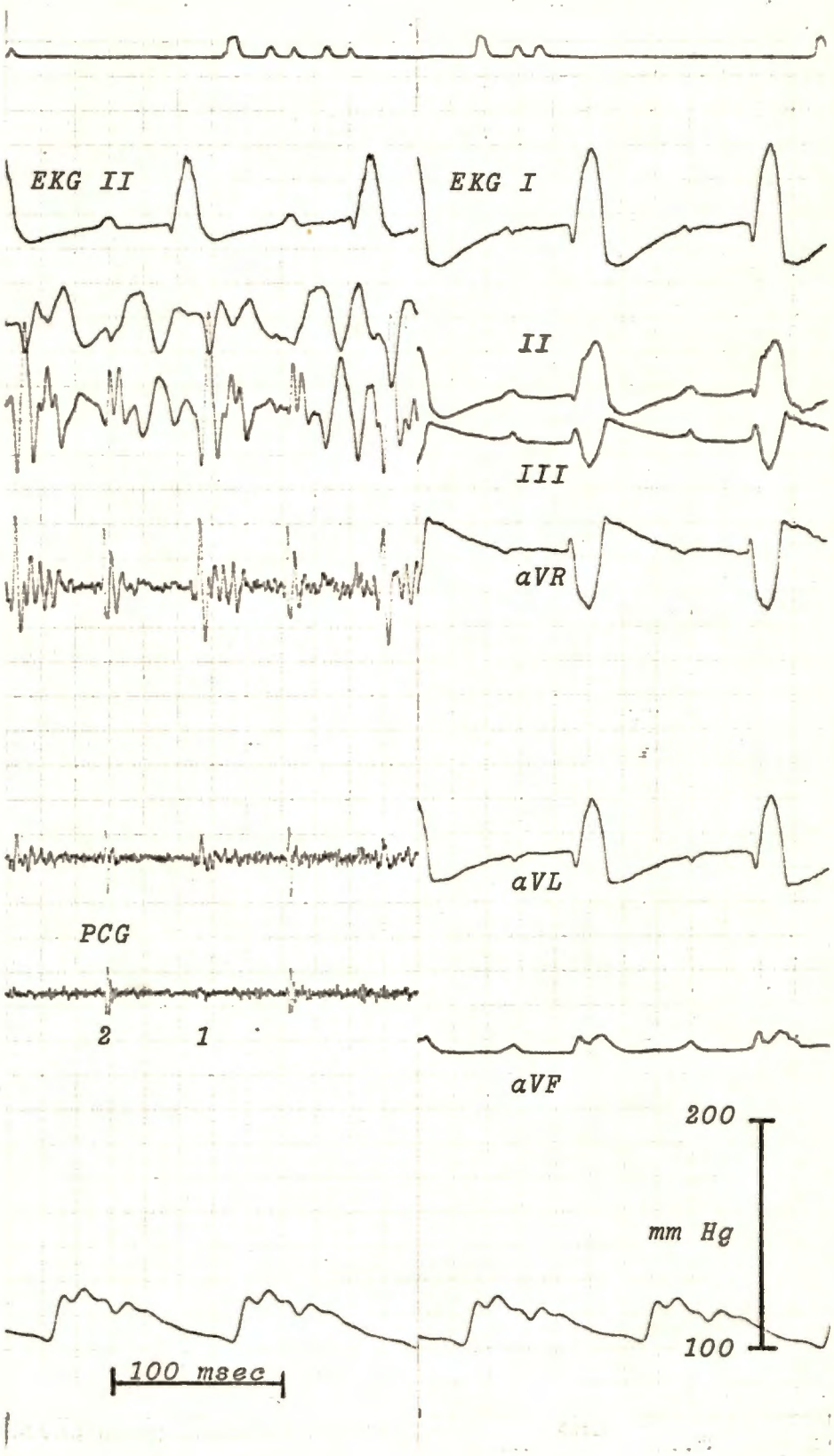


FIGURE 4.5 *PROFOUND CIRCULATORY FAILURE*



2. For analytical purposes a recording speed of 250 mm/sec and an amplification setting of 3mm Hg per 1 mm were used throughout. Apart from systolic (P_s) and diastolic pressure (P_d), the anacrotic shoulder pressure (P_x) on the ascending limb, and the end-systolic pressure (P_{es}) on the descending limb of the pressure pulse were also measured, P_{es} being measured at the dicrotic notch (incisura). Pulse pressure (P_p) was obtained by simply subtracting P_d from P_s. Finally, mean arterial pressure (P_m) was determined by multiplying the ratio of the ejection time-to-diastolic time and P_p, and adding this value to P_d. The terms ejection time and diastolic time, as applicable to this study, are defined in the next subsection (4.2.3). Since P_x was related to cardiac contractility, and P_{es} to peripheral resistance, these measurements will be referred to in subsections 4.2.4 and 4.2.6, respectively.

An analysis of Table 4.5 reveals general increases in all measurements until the commencement of circulatory failure, maximum levels coinciding at the same point in time. In all instances the difference between the respective means changed significantly over the period of heat exposure at a level of significance of 0,5% (Table 4.2).

Further analysis of Table 4.5 indicates that, with the exception of the terminal stage (0+80 minutes), two distinct phases exist. During the first 40 minutes the pressure increases are gradual while the subsequent phase is characterised by dramatic increases in pressure. The relative changes (% of overall maximum change) illustrate the difference between the two phases:

TABLE 4.5 ARTERIAL PRESSURE CHANGES DURING HEAT STRESS

Measurement (mm Hg)		Exposure Time (min) 0	10	20	30	40	50	60	70	80
P_s	Mean	156,5	166,3	156,2	167,1	167,4	179,5	192,2	211,0	186,3
(systolic)	SD	19,2	18,2	21,0	13,0	18,2	16,0	11,4	15,4	31,9
P_d	Mean	127,7	134,9	135,9	135,2	134,6	140,9	148,1	153,6	139,9
(diastolic)	SD	13,9	13,1	12,8	12,2	13,4	8,1	8,5	11,6	17,8
P_m	Mean	143,1	150,9	151,5	152,5	151,6	160,7	171,5	183,1	164,5
(mean)	SD	16,3	15,1	15,5	12,2	15,4	12,4	9,3	12,4	22,9

Notes:
1. On the basis of an analysis of variance, the difference between the means for each individual measurement is significant at the 0,5% level of significance.
2. A polynomial regression analysis reveals first order (linear) equations in each instance. Fitted values are omitted since this procedure obscures the advent of circulatory failure (0+80 minutes).
3. Pulse pressure (P_p) is omitted since its values may readily be derived (P_s-P_d).

TABLE 4.6 THE RATIO OF HEART RATE TO MEAN ARTERIAL PRESSURE

Measurement		Exposure Time (min)								
f/P_m	Mean	2,76	2,84	2,88	2,88	3,01	2,94	2,88	2,82	3,39
	SD	0,25	0,22	0,33	0,33	0,42	0,32	0,25	0,27	0,68

Note: Changes between means are significant at the 5% level of significance, the relationship being linear in general (Table 4.2).

Phase (minutes	Relative change (%) P_s	P_d	P_m
0-40	+20	+27	+40
40-70	+80	+73	+60

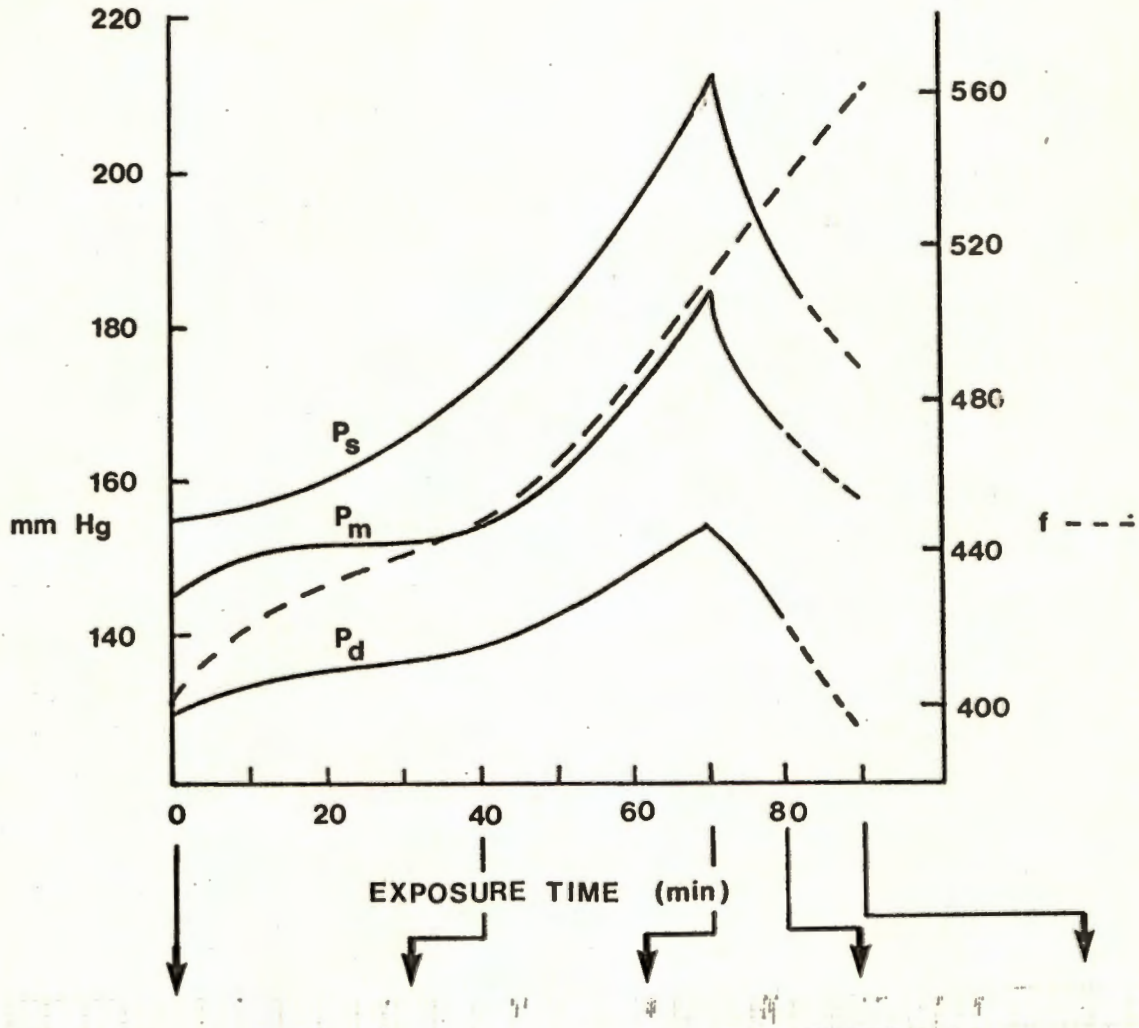
In view of the effect of heart rate on, especially, diastolic pressure (Rushmer, 1970), the above changes should also be related to corresponding changes in heart rate. Although specific reference to heart rate is made in the next subsection (4.2.3), the heart rate changes during the above phases account for 48 and 52%, respectively.

The most striking overall increase pertains to P_s (34,8% of control levels), followed by P_m (27,9%), and P_d (20,3%). These calculations are substantiated by the respective absolute F-values (Appendix 3).

The terminal stage is characterised by decreases in all pressure measurements and therefore represents the onset of circulatory failure. In most instances the experiments were terminated at this stage in order to estimate myocardial oxidative capacity (Section 4.3), thus preventing damage which would result in findings meaningless within the context of the objectives of this study.

In some instances, however, overt failure was allowed to occur in order to study the pressure pulse contour immediately prior to death. This pressure pulse is very unlike the normotensive

FIGURE 4.6 *ARTERIAL PRESSURE CHANGES DURING HEAT STRESS*



pulse and was not always associated with gross hypotension but rather with a particular circulatory status. The implication is that pressure levels *per se* may not necessarily serve as parameters of the integrity of overall cardiovascular function. This observation merits further discussion (Chapter 5).

The changes which occur in the pressure pulse contour, from normotension to overt circulatory failure, are presented in Figure 4.6 as a synopsis in order to facilitate direct comparisons. It is evident that during the first phase of heat exposure the changes in pulse contour may be regarded as subtle. In contrast, it is equally clear that the pulse contour subsequently changes in a most dramatic manner (50-70 minutes), eloquent of a massive hyperkinetic circulation. According to Hurst and Schlant (1978) this may be regarded as a typical "water hammer" pulse which is characterised by a rapid upstroke followed by an equally rapid downstroke, the latter also occurring in systole. Further analysis indicates the complete absence of bisferiens phenomena.

With the onset of circulatory failure (0+80 minutes) the pulse contour still exhibits the "water hammer" characteristics, albeit on a smaller scale. With the exception of heart rate, absolute pressure levels once again seem inadequate in providing a clear distinction between a physiologically elevated arterial pressure and levels associated with the advent of circulatory failure. In this respect the ratio f/P_m (heart rate to mean arterial pressure) appears to be of merit. An analysis

of Table 4.6 reveals that over the first 70 minutes of heat stress, the change in this ratio accounts for only 10% of the overall maximum change, a 90% change being recorded during circulatory failure. In the final stage (overt failure), the pressure pulse exhibits bisferiens phenomena.

4.2.3 TEMPORAL RELATIONSHIPS

Temporal relationships within the cardiac cycle were measured at a recording speed of 250 mm/sec. Each 1 mm of recording paper therefore represents 4 msec. All measurements were made in accordance with conventional procedures. These measurements comprised (a) ventricular electromechanical coupling time (QS_1), (b) the pre-ejection period (PEP), (c) the ejection time (ET), (d) diastolic time (DT), (e) mechanical systole (S_1S_2), (f) electromechanical systole (QS_2) and (g) electromechanical diastole (S_2Q). These intervals are discussed and presented semi-schematically in Chapter 2, Figure 2.7.

Although the RR'-interval (duration of the cardiac cycle) was measured, it is omitted from the results since it was primarily employed to estimate heart rate (f). The RR'-interval may, however, be readily derived from the following equation:

$$RR' = 60000/f \text{ msec.}$$

The RR'-interval was also employed to derive "rate corrected" measurements. This procedure applied to QS_1 (QS_{1-c}) and ET (ET_c) and was achieved by dividing the absolute value by the

square root of RR' according to standard practice. In addition to the above direct measurements, the QS_2/S_2Q-ratio was also determined while subtracting ET from S_1S_2 yielded the isovolumic contraction time (IVCT). With the exception of QS_{1-c}, ET_c and the QS_2/S_2Q-ratio, an analysis of variance (Table 4.2.1) indicates that in all instances the difference between the means over the period of heat exposure changed significantly at the 0,5% level of significance, the respective relationships conforming to a first order (linear) equation (Table 4.2.2). The relevant findings are presented in Table 4.7.

An analysis of Table 4.7 reflects a general shortening of all time intervals within the cardiac cycle which may be regarded as a logical sequel to an increase in heart rate. The relative (%) overall changes are given in Table 4.8. The RR'-interval decreases by 27,5% and it is evident that the relative decreases in PEP, DT and S_1S_2 are generally of the same order. It is also evident that QS_1 and QS_2 are relatively insensitive to an increase in heart rate while S_2Q and IVCT exhibit tendencies in the opposite direction. With the exception of IVCT it therefore seems as if the general decrease in the RR'-interval is achieved at the expense of electromechanical diastole (S_2Q) rather than decreases in systolic time intervals.

On the basis that the time-course of heat exposure prior to circulatory failure, may be divided into two distinct phases in terms of arterial pressure changes (Section 4.2.2), the relative overall changes were analysed to delineate changes

TABLE 4.7 TEMPORAL RELATIONSHIPS OF THE CARDIAC CYCLE DURING HEAT STRESS

Measurement (msec)		Exposure Time (minutes) 0	10	20	30	40	50	60	70	80
Heart rate - f*	Mean	394	427	432	437	451	470	493	515	544
(c.p.s.)	SD	41	25	21	35	31	37	42	48	43
QS_1	Mean	15,4	14,4	13,8	12,8	13,0	12,4	12,8	12,0	11,8
	SD	2,8	2,1	1,9	1,0	1,7	1,3	1,7	0,9	1,1
PEP	Mean	40,0	35,6	35,8	36,6	33,2	32,8	32,0	28,4	29,4
	SD	5,1	2,3	3,6	2,1	2,5	3,3	3,1	2,5	2,8
ET	Mean	56,6	55,0	54,6	53,0	52,2	49,0	48,8	49,2	43,6
	SD	5,5	5,1	2,9	3,4	4,7	4,3	4,1	5,3	7,8
DT	Mean	96,0	85,4	84,6	86,2	82,6	75,4	74,0	67,6	67,8
	SD	17,4	7,8	5,2	8,5	6,8	7,5	8,9	7,4	7,4
S_1S_2	Mean	73,4	70,2	68,8	66,6	64,4	60,6	60,0	59,2	53,6
	SD	7,1	4,5	4,1	3,5	3,5	5,3	4,9	4,9	7,4
QS_2	Mean	87,8	84,6	82,6	79,4	77,4	73,0	72,8	71,6	65,6
	SD	10,1	7,7	5,2	3,5	3,8	5,1	4,5	4,1	6,2
S_2Q	Mean	68,3	56,8	56,3	59,1	55,9	55,4	50,0	46,4	44,3
	SD	12,9	10,2	5,3	9,3	6,8	11,1	8,1	7,8	6,1
IVCT**	Mean	16,8	15,2	14,2	13,6	12,2	11,6	11,2	10,0	10,0

Notes:

1. On the basis of an analysis of variance, the difference between the means is significant at the 0,5% level of significance for all of the above measurements. Subsequent analysis (Polynomial regression) indicates first order equations in all instances.
2. * The cardiac cycle length, RR', is given by:

$$RR' = 60000/f \text{ in msec.}$$

3. ** IVCT represents derived data:

$$IVCT = S_1S_2 - ET$$

TABLE 4.8 RELATIVE CHANGES IN TEMPORAL RELATIONSHIPS OF THE CARDIAC CYCLE DURING HEAT STRESS

Interval	RR'	QS_1	PEP	ET	DT	S_1S_2	QS_2	S_2Q	IVCT
Max. change (%)	27,5	23,0	26,5	22,9	29,4	27,0	25,3	35,0	40
Phase 1 change (%)	46	67	59	34	47	45	47	52	68
Phase 2 change (%)	54	33	41	66	53	55	53	48	32

Notes:
1. In all instances the percentages are negative, thus reflecting decreases.
2. Phase 1 and 2 changes are expressed as percentages of the overall maximum change.
3. Phase 1 represents 0-40 minutes of heat exposure; Phase 2 representing 40-80 minutes.

TABLE 4.9 CARDIAC CONTRACTILITY VARIATIONS DURING HEAT STRESS

Measure		Exposure Time (min) 0	10	20	30	40	50	60	70	80
PEP/ET_c	Mean	8,83	7,75	7,74	7,55	7,41	7,66	7,36	6,23	7,38
	SD	1,49	1,06	0,79	0,46	0,83	1,29	1,27	0,60	1,97

Notes:
1. By convention, contractility is inversely related to PEP/ET_c.
2. Fitted values (first order equation) are omitted since terminal changes are obscured by this procedure.

which occur during the first 40 minutes of heat exposure from those which occur subsequently. This analysis is also presented in Table 4.8 where the relative (%) changes which occur during the first 40 minutes (Phase 1) are compared with those which occur during the latter half of the exposure time (Phase 2), the comparison being made in terms of the maximum overall change.

An analysis of the above treatment indicates that the RR'-interval decreases slightly more (54% of the overall decrease) during Phase 2 than during Phase 1 (46%). Virtually the same order of changes apply to DT, S_1S_2 and QS_2 and it would therefore appear that these time intervals are closely related to changes in the RR'-interval, irrespective of the phase of exposure. However, it is also evident that during Phase 1 QS_1, PEP, IVCT and, to a lesser extent, S_2Q, undergo extensive temporal decreases which are in sharp contrast to the corresponding decrease in the RR'-interval. During the same period, the decline in ET appears to be the least affected by the reduction in the RR'-interval. The initial phase of cardioacceleration (0 to 40 minutes) is therefore characterised by a dramatic decline in the pre-ejection time intervals (QS_1, PEP and IVCT) and a slight decline in electromechanical diastole, while ejection time remains relatively unaffected. Thus, while the initial reduction in the RR'-interval is chiefly related to pre-ejection and electromechanical diastole phenomena, it is equally true that the subsequent, and more extensive, reduction in the RR'-interval occurs chiefly at the expense of a reduction in ejection time.

In the final instance it is deduced that while the overall effect of cardioacceleration is manifested in a reduction in electromechanical diastole, a clear distinction exists between changes that occur during the initial phase of heat exposure and those characterising the terminal phase.

4.2.4 CARDIAC CONTRACTILITY

The assessment of cardiac contractility was initially based on two parameters, namely, the ratio of the pre-ejection period to ejection time (PEP/ET) and the initial rate of carotid pressure rise following ejection (dP/dt). These parameters, as well as certain theoretically derived modifications, were qualitatively evaluated by means of various pharmacological agents (Section 2.4.3) and employed in the current study. Of these, only two proved to yield statistically significant changes in contractility i.e., dP/dt_{mean} and PEP/ET_c (Appendix 3). Although dP/dt_{mean} represents statistically meaningful changes, its use as an index of contractility appears to be extremely limited in a physiological sense. For example, to anticipate matters, in the terminal stage (0+80 min) all parameters of cardiac function point to failure while dP/dt_{mean} indicates enhanced contractility. This finding suggests that dP/dt may be subject to misinterpretation during gross changes in the pressure pulse contour, especially when based on changes in P_x.

PEP/ET is widely held as a satisfactory index of cardiac contractility (Weissler *et al*, 1968; 1969; Garrard *et al*, 1970;

Ahmed *et al*, 1972; Martin *et al*, 1972; Cohn, 1978). However, since ET *per se* is generally corrected for rate, the index was modified to incorporate the corrected form (ET_c), i.e., PEP/ET_c. In the present study the difference between the means changed significantly over the time of exposure at a level of significance of 0,5% (Appendix 3), the changes in PEP/ET_c being represented by a first order (linear)equation on the basis of a polynomial regression analysis (Table 4.2). The original data is given in Table 4.9 (below Table 4.8) and graphically presented in Figure 4.10 at the end of this chapter.

By convention, PEP/ET_c is inversely related to cardiac contractility. An analysis of the means presented in Table 4.9 reflects four stages during the period of heat exposure, namely (a) an initial rapid increase in contractility, (b) a sustained enhanced level of contractility, (c) a further, dramatic increase in contractility and finally, (d) a terminal decrease. Further analysis reveals that the overall maximum increase in contractility constitutes 29,4% of the control level. Within the first 20 minutes of heat exposure the change in contractility accounts for 42% of the maximum overall change. It remains relatively constant for the following period of 30 minutes (3% further increase). During the last 20 minutes prior to circulatory failure (50-70 minutes), the contractility exhibits an increase of 55% of the maximum overall change achieving peak levels at 0+70 minutes of exposure. With the onset of circulatory failure the increase in PEP/ET_c reflects diminishing contractile power. These results do not therefore reflect any loss of contractile power prior to circulatory failure.

4.2.5 *CARDIAC OUTPUT*

The estimation of cardiac output was based on the Warner method of determining stroke volume from the arterial pressure pulse contour. The choice of this method and the details thereof are described in Chapter 2. A cursory evaluation of the Warner method, using flow rate as reference, indicates that the indirect method provides a sufficiently reliable method of estimating stroke volume within the context of this study.

The variations in cardiac output during heat stress are presented in Table 4.10 in conjunction with the components of this measure, stroke volume and heart rate. Table 4.10 indicates that over the period of heat exposure, a general increase in cardiac output occurs prior to an abrupt terminal decrease. These changes are closely related to changes in stroke volume and heart rate with the exception that the latter continues to rise during the terminal stage while cardiac output and stroke volume fall.

Further analysis of Table 4.10 reveals that prior to circulatory failure, the overall increase in cardiac output constitutes 122% of its control value. However, it is also evident that the increase in cardiac output during the initial stages of heat exposure (0-40 minutes) does not match the subsequent elevation (40-70 minutes). Thus, during the initial stages the increase in cardiac output constitutes only 29% of its overall maximum elevation, with stroke volume and heart rate exhibiting increases of 26 and 47% of their respective maximum elevations. During the subsequent stage (40-70 minutes) the converse applies in

TABLE 4.10 CARDIAC OUTPUT VARIATIONS DURING HEAT STRESS

Measurement (arbitrary units)		Exposure Time (min) 0	10	20	30	40	50	60	70	80
Cardiac Output (Q)	Mean	416	493	548	584	564	618	723	924	717
	SD	142	146	162	182	179	205	219	310	293
Stroke Volume (SV)	Mean	1,06	1,16	1,26	1,33	1,25	1,29	1,46	1,80	1,33
	SD	0,33	0,33	0,33	0,39	0,39	0,39	0,44	0,62	0,56
Heart Rate (f in c.p.s.)	Mean	394	427	432	437	451	471	493	515	544
	SD	41	25	21	35	31	37	42	48	43

Note: On the basis of an analysis of variance, the difference between the means was established to be significant at the 0,5% level of significance in the case of Q and f, respectively, and in the case of SV at the 5% level of significance. In all instances a polynomial regression analysis yields a first order equation. Fitted values are omitted in as much as this procedure obscures the decreases in Q and SV with the advent of circulatory failure (0+80 minutes).

terms of overall maximum elevations: cardiac output changes by 71%, stroke volume by 74%, and heart rate by 53%.

The above calculations clearly illustrate that the period immediately prior to failure (40-70 minutes) is characterised by relatively enormous changes in comparison with the initial stage. Moreover, whereas the initial increase in cardiac output is largely related to cardioacceleration, the most significant contribution during the subsequent stage is related to stroke volume elevations. Finally, it is also evident that when circulatory failure eventually occurs (0+80 minutes), the fall in cardiac output is referable to a fall in stroke volume.

In conclusion it appears that the variations in cardiac output during heat stress may be placed in three distinct but overlapping stages: (a) An initial heart rate stimulated increase of moderate dimensions, (b) a subsequent extensive elevation primarily associated stroke volume increases and (c) a terminal fall associated with a reduction in stroke volume despite sustained cardioacceleration.

4.2.6 PERIPHERAL RESISTANCE

Peripheral resistance, R, was primarily assessed by the analogy to Ohm's law:

Resistance = Pressure/Flow

In the current study, the above relationship was modified to

give the following equation:

$$R = (P_m - 20) / Q$$

Secondly, according to Hurst and Schlant (1978), the rapid pressure decline following peak systolic pressure ("collapsing pulse") signifies a fall in peripheral resistance. This feature of the pressure pulse was accordingly quantitated in terms of the difference between the peak systolic and end-systolic (dicrotic) pressure i.e., $P_s - P_{es}$. The changes in both these parameters of peripheral resistance are presented in Table 4.11.

An analysis of Table 4.11 shows an initial (0-20 minutes) rapid decline in R which accounts for 46% of the overall maximum change, the latter change constituting a decrease of 38% of the control level. During the next 30 minutes (20-50 minutes), the change in R is a negligible 3% decrement. However, this period of constancy is followed by a further dramatic decrease in R (50-70 minutes) which accounts for a further 52% fall in terms of the maximum overall change. In the terminal stage (70-80 minutes) R exhibits an increase which, in as much as this period represents the advent of circulatory failure, is ascribed to the fact that the cardiac output is falling at a greater rate than mean arterial pressure.

The term $P_s - P_{es}$, as an index of peripheral resistance, is inversely related to resistance. The pattern of changes is slightly different from that of R in so far as prior to failure, only two distinct stages can be identified. The

TABLE 4.11 *PERIPHERAL VASCULAR RESISTANCE CHANGES DURING HEAT STRESS*

Measurement		Exposure Time (min) 0	10	20	30	40	50	60	70	80
R	Mean	0,314	0,286	0,259	0,255	0,268	0,256	0,231	0,194	0,225
(arbitrary units)	SD	0,082	0,090	0,078	0,106	0,132	0,087	0,083	0,066	0,080
P_s-P_{es}	Mean	10,2	11,7	11,0	11,9	13,8	17,2	20,7	30,2	25,5
(mm Hg)	SD	3,8	3,9	4,7	3,9	5,6	7,1	6,9	8,7	11,7
P_s-P_{es} (fitted values)*		10,2	10,5	11,4	12,9	14,9	17,6	20,8	24,7	29,1

Notes: 1. On the basis of an analysis of variance, the difference between the means was established to be significant at the 0,5% level of significance in both instances (Appendix 3). Subsequent analysis (Polynomial regression) indicates a first order relationship for R while P_s-P_{es} conforms to a second order equation* (Table 4.2.2)

2. The term P_s-P_{es} reflects the difference between peak systolic and end-systolic pressure.

first 40 minutes show a gradual fall in resistance which accounts for only 18% of the overall maximum change of 196%. The second stage (40-70 minutes) is characterised by a dramatic further reduction in resistance which accounts for 82% of the maximum overall change. In the terminal stage (failure) the term P_s-P_{es} reflects an increase in resistance which in this respect is related to a greater fall in P_s than in P_{es}.

Despite the slightly different response pattern, both parameters of peripheral vascular resistance exhibit similarities. Combining the two, it may be deduced that changes in resistance are characterised by three distinct stages. The first stage of heat exposure, identified as the first 40 to 50 minutes of heat exposure, is characterised by a moderate fall in vascular resistance, followed by the second stage wherein a further drastic reduction in resistance becomes manifest. The final stage (70-80 minutes) is characterised by an increase in peripheral resistance in the presence of circulatory failure. Of significance in this context is the observation that arterial pressure falls despite an apparent increase in vascular resistance. An analysis of the parameters employed reveals that the apparent increase in resistance is related to a decrease in cardiac output in the case of R, and a reduction in systolic pressure in the case of P_s-P_{es}.

SUMMARY

An analysis of the circulatory changes which occur during heat stress indicates the existence of three distinct, albeit over-

lapping, stages. The first stage (0-45 minutes, approximately) is associated with rapid changes of a moderate extent. The second stage (45-70 minutes) is characterised by dramatic further changes leading to the establishment of a true hyperkinetic circulation prior to the terminal stage of circulatory collapse.

4.3 MYOCARDIAL OXYGEN CONSUMPTION

Myocardial oxygen consumption (Q_{O_2}) was estimated in a group of animals exposed to varying degrees of heat stress. Strictly speaking, the term "myocardial oxygen consumption" is a misnomer within the context of this study since in actual fact it is a measure of the integrity or intactness of the overall oxidative capacity of the cell in the absence of the demands of contraction.

The methodology is described in detail in Chapter 2 (2.6.2). It is important, however, to point out that in this study heart slices were incubated at a temperature of 42°C and not at the more conventional level of 38°C. This choice is based on the findings of Burger (1972), namely, that a temperature of 42°C represents the optimum temperature for achieving maximum Q_{O_2} values for heart tissue. In as much as this temperature therefore appears to confer a greater measure of sensitivity, a temperature of 42°C was also adopted in this study.

In its entirety, this investigation had a dual purpose, namely, to establish (a) the influence of the anaesthetic agent on

TABLE 4.12 *THE INFLUENCE OF VARIOUS LEVELS OF HEAT STRESS ON MYOCARDIAL OXYGEN CONSUMPTION* (Q_{O_2})

Duration of heat stress (min)	Group*		Q_{O_2} Incubation Time (min) 10	20	30	40	50	60
40	C_2	Mean	2,835	2,640	2,222	2,121	1,951	1,855
	(n=10)	SD	0,354	0,305	0,270	0,289	0,353	0,249
		SEM	0,112	0,096	0,085	0,091	0,112	0,079
	E	Mean	2,839	2,658	2,258	2,077	1,907	1,801
	(n=10)	SD	0,293	0,200	0,153	0,313	0,304	0,330
		SEM	0,093	0,063	0,048	0,099	0,096	0,104
70	C_2	Mean	2,950	2,477	2,201	1,970	1,840	1,876
	(n=20)	SD	0,510	0,392	0,344	0,402	0,430	0,491
		SEM	0,114	0,088	0,077	0,09	0,096	0,11
	E	Mean	2,797	2,252	1,981	1,746	1,664	1,604
	(n=20)	SD	0,543	0,418	0,456	0,518	0,495	0,559
		SEM	0,121	0,093	0,102	0,116	0,111	0,125
80	C_2	Mean	2,726	2,274	1,979	1,933	1,761	1,705
	(n=20)	SD	0,642	0,632	0,496	0,441	0,392	0,321
		SEM	0,144	0,141	0,111	0,099	0,088	0,072
	E	Mean	2,323	1,952	1,569	1,464	1,393	1,282
	(n=20)	SD	0,497	0,448	0,458	0,294	0,326	0,272
		SEM	0,111	0,100	0,102	0,066	0,073	0,061

* C_2 : Anaesthetised control.

E : Anaesthetised, hyperthermic animal.

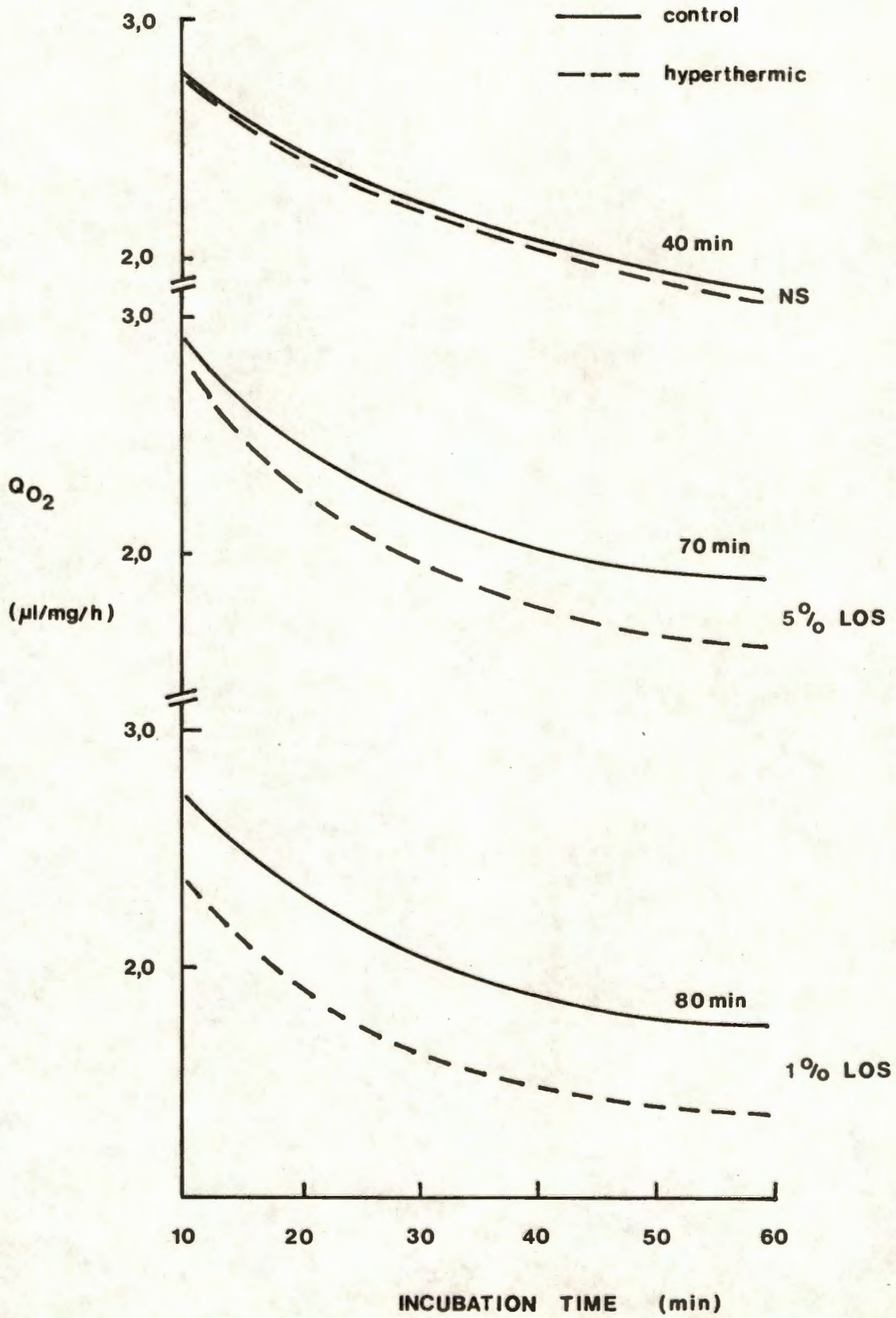
Note: Statistical analysis of the results is presented in Appendix 4.

myocardial oxygen consumption and (b) the influence of heat stress on myocardial oxygen consumption. The former study indicates that the effect of anaesthesia is completely abolished after a period of 40 minutes in both normo- and hyperthermic animals (Chapter 3).

Animals were subjected to three levels of heat stress, in each instance appropriate normothermic control levels being recorded simultaneously. The first level of stress constitutes an exposure time of 40 minutes. At this stage the animals are only slightly hyperthermic (Table 4.1) while the circulatory changes may be regarded as moderately hyperkinetic (Section 4.2). In view of the extent of individual variation referred to earlier on (Section 4.2: Introduction), the selection of subsequent levels was based on certain marker events rather than on a specific time interval *per se*. The second level of stress was therefore based on the attainment of maximal arterial pressure and the final level on the presence of definite signs of circulatory failure. The corresponding mean times for the latter events to occur were, respectively, 70 and 80 minutes after the commencement of heat stress.

The results of this investigation are given in Table 4.12 and are graphically displayed in Figure 4.7. Statistical analyses were performed by an analysis of variance, the particular treatment being regarded as conservative (Troskie, 1978). The details of this analysis appear in Appendix 4. The pertinent

FIGURE 4.7 *MYOCARDIAL OXYGEN CONSUMPTION* (Q_{O_2}) *DURING HEAT EXPOSURE*



findings are given below:

(a) For both control and experimental animals, irrespective of the level of stress, the changes in Q_{O_2} during the period of incubation conform to a second degree polynomial according to the method of orthogonal polynomials. (This relationship is exemplified in Figure 4.7 and is in general agreement with the findings of Webb *et al* (1949) and Burger (1972), according to whom the Q_{O_2} of heart slices, in contrast to most other tissues, exhibits a gradual decline throughout the period of incubation).

(b) The foregoing implies that during the period of incubation, the difference between the respective means for control and experimental values does not change significantly, i.e., irrespective of the level of stress, the respective Q_{O_2} curves run parallel to one another.

(c) At 0+40 minutes of heat exposure there is no statistical difference between control and experimental Q_{O_2} levels. At 0+70 minutes the difference is just significant at the 5% level of significance while at 0+80 minutes, at the 1% level of significance.

Seen in broader perspective, the above findings indicate that the reduction in Q_{O_2} during the latter two stages represents a general depression which, in both instances, is evident from the onset of the period of incubation. In other words, the significant reduction in Q_{O_2} cannot be ascribed to factors

which only become operative *during* the period of incubation. In terms of circulatory events it is also clear that during the initial period of heat exposure associated with moderate responses, myocardial Q_{O_2} is completely unaffected (-0,004% of control value). However, with the attainment of a peak hyperkinetic circulation, Q_{O_2} is already depressed by 9,5% and when circulatory failure becomes apparent, by 19,4%.

SUMMARY

Myocardial oxygen consumption is significantly reduced prior to circulatory failure, an event which is compounded at the onset of heart failure.

4.4 MYOCARDIAL ELECTROLYTES

An analysis of the results presented in Section 4.2 indicates that the circulatory responses to heat stress are characterised by three distinct stages (See "Summary" to 4.2), the first stage of which was associated with changes of moderate extent. The primary objective of this investigation was, therefore, to firstly establish the extent to which myocardial K^+ and Na^+ levels were altered and, secondly, to establish whether such changes were of reversible or irreversible nature.

Myocardial K^+ and Na^+ levels were determined by flame spectrophotometry. The methodology is detailed in Chapter 2 (2.6.1). Animals were subjected to heat stress for periods of 20, 30, 40 and 50 minutes, respectively. The choice of a maximum exposure

TABLE 4.13 MYOCARDIAL K^+ AND Na^+ LEVELS DURING HEAT STRESS

Exposure Time	Electrolytes (mEq/l) K^+		Na^+		Ratio K^+/Na^+		Deviation from control (%)	
(min)	Mean	SD	Mean	SD	Mean	SD	K^+	Na^+
0(control)*	66,95	2,14	31,12	3,77	2,24	0,19	-	-
0+20+	72,27	2,59	36,22	2,71	2,03	0,18	+7,9	+16,4
0+30+	75,82	2,94	35,47	4,06	2,19	0,21	+13,2	+14,0
0+40+	79,42	5,88	37,57	4,50	2,12	0,10	+18,6	+20,7
0+50+	78,30	7,21	37,57	3,56	2,09	0,23	+17,0	+20,7

*n = 12

+n = 4

TABLE 4.14 MYOCARDIAL K^+ AND Na^+ LEVELS FOLLOWING HEAT STRESS

Post-Exposure period	Electrolytes (mEq/l) K^+		Na^+		Ratio K^+/Na^+		Deviation from control (%)	
(hours)	Mean	SD	Mean	SD	Mean	SD	K^+	Na^+
24(30)*	75,15	4,17	35,32	2,01	2,13	0,06	+12,2	+13,5
48 (30)	66,30	3,52	31,35	4,51	2,16	0,02	- 0,01	+0,007
24 (50)	77,40	3,09	31,15	4,66	2,36	0,26	+15,6	+0,001
48 (50)	68,77	1,35	32,92	4,09	2,11	0,22	+ 2,7	+ 5,7

*n = 4 in each instance

Note: The figures in brackets indicate the period of heat exposure prior to a given survival period or post-exposure period.

time of 50 minutes was based on the observation that this period is representative of the stage of moderate circulatory changes. A second consideration was to ensure that the animals would be able to survive heat stress by at least 48 hours in order to establish the extent of reversibility. Since it was not anticipated that meaningful changes would become evident after only 10 minutes of exposure, this interval was omitted.

The results of this investigation are presented in Tables 4.13 and 4.14, the former pertaining to findings observed during heat stress; the latter to findings observed at various periods subsequent to exposure to heat. Statistical interpretation was simply based on whether particular means differ from the control by at least two standard deviations. Under such circumstances the chances that the two observations belong to the same population are 1 in 20. These aspects are graphically displayed in Figures 4.8 and 4.9.

An analysis of Table 4.13 and Figure 4.8 indicates a general direct relationship between myocardial electrolyte levels and the exposure time. In both instances peak values are achieved after 40 minutes of exposure. However, it is also clear that K^+ is already significantly elevated above control levels after 30 minutes while a similar elevation only becomes evident after 50 minutes in the case of Na^+. The changes in the K^+/Na^+ ratio were not considered to alter significantly.

Following heat stress (Figure 4.9) myocardial K^+ levels remain

FIGURE 4.8 *MYOCARDIAL K^+ AND Na^+ LEVELS DURING HEAT EXPOSURE (MEANS ± SD)*

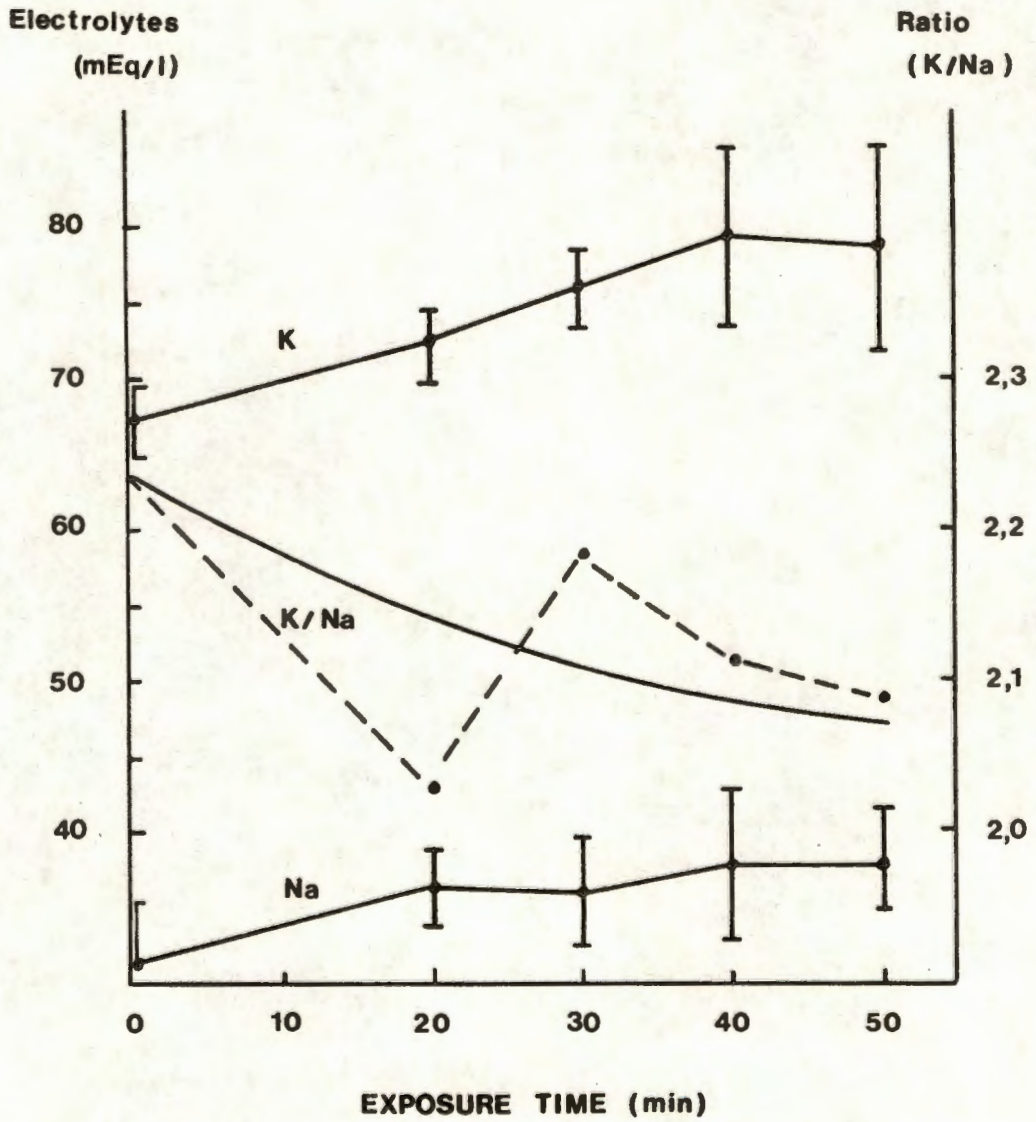
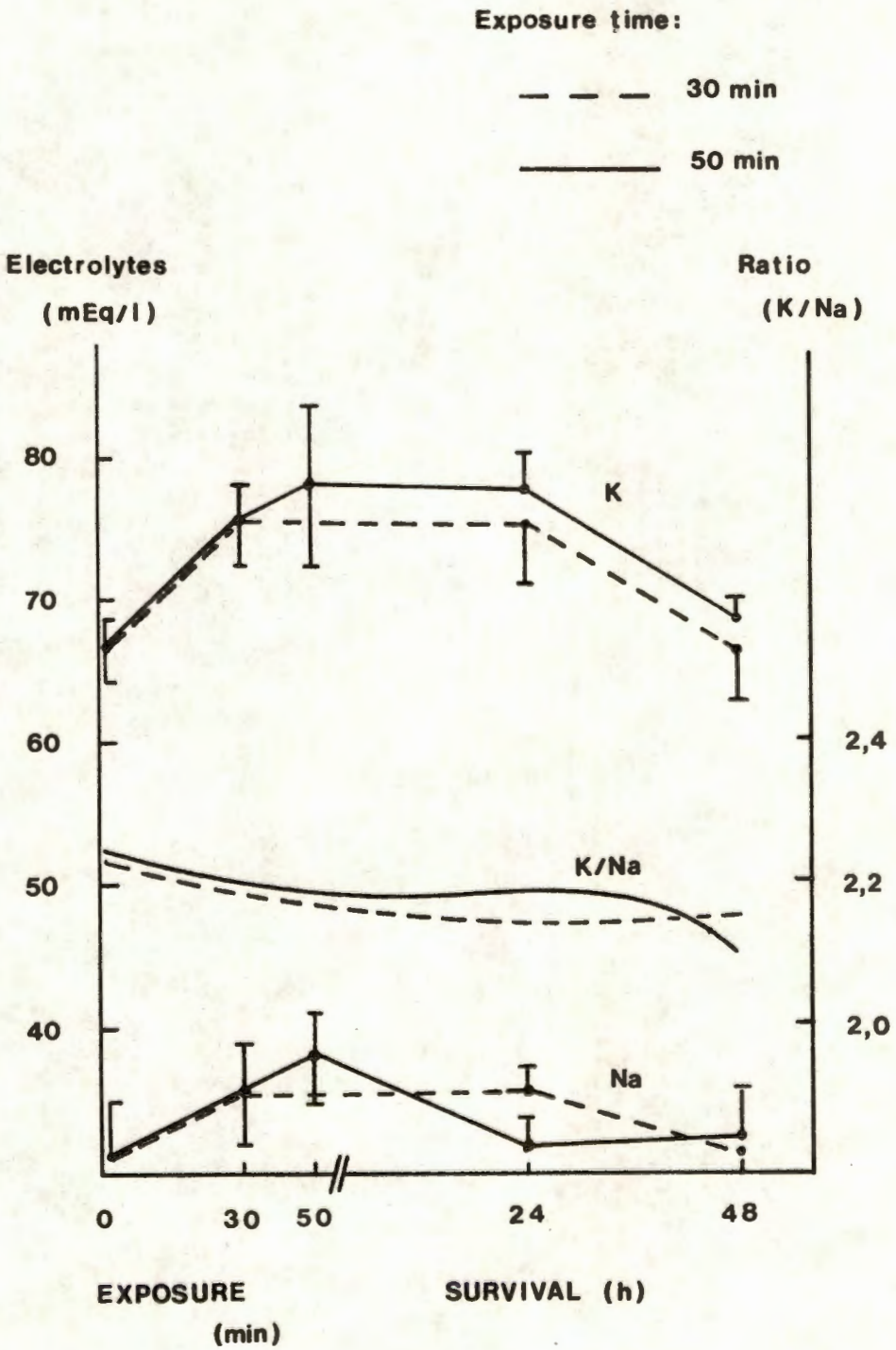


FIGURE 4.9 MYOCARDIAL K^+ AND Na^+ LEVELS FOLLOWING HEAT EXPOSURE (MEANS ± SD)



elevated 24 hours after exposure to heat stress, those animals having been subjected to a 50-minute exposure time exhibiting slightly higher levels than those having been subjected to a 30-minute exposure time. However, it is clear that after 48 hours, irrespective of the period of heat exposure, K^+ levels return to control levels.

The changes in myocardial Na^+ content following heat stress are also presented in Figure 4.9. In this instance it is clear that a return to control levels occurs within 24 hours following heat exposure, irrespective of the exposure time. This relatively rapid return to normal is in contrast with the rate at which K^+ levels return to control levels.

SUMMARY

The initial stages of heat stress, characterised by moderate circulatory changes, are associated with elevated myocardial K^+ and Na^+ levels which in the case of K^+ become significantly elevated after 30 minutes and in the case of Na^+, after 50 minutes of heat exposure. Following heat stress, Na^+ levels return to control levels within 24 hours, irrespective of the exposure time, while K^+ levels return to normal only after 48 hours following heat stress, again irrespective of the duration of exposure. In terms of myocardial electrolyte levels, the above findings indicate that the initial period of heat exposure (0-50 minutes) is not associated with changes of a permanent nature.

4.5 REVIEW

In reviewing the experimental findings presented in this chapter, a distinction can be made between measurements exhibiting significant changes over the period of heat exposure and those which were not subject to significant change. This distinction is given in Appendix 3.

With regard to measurements which essentially remained constant throughout the period of heat exposure, perhaps the most striking feature pertains to the constancy of the electrocardiographic QRS-complex as well as the uncorrected QT-interval. The significance of this finding is discussed in the next chapter.

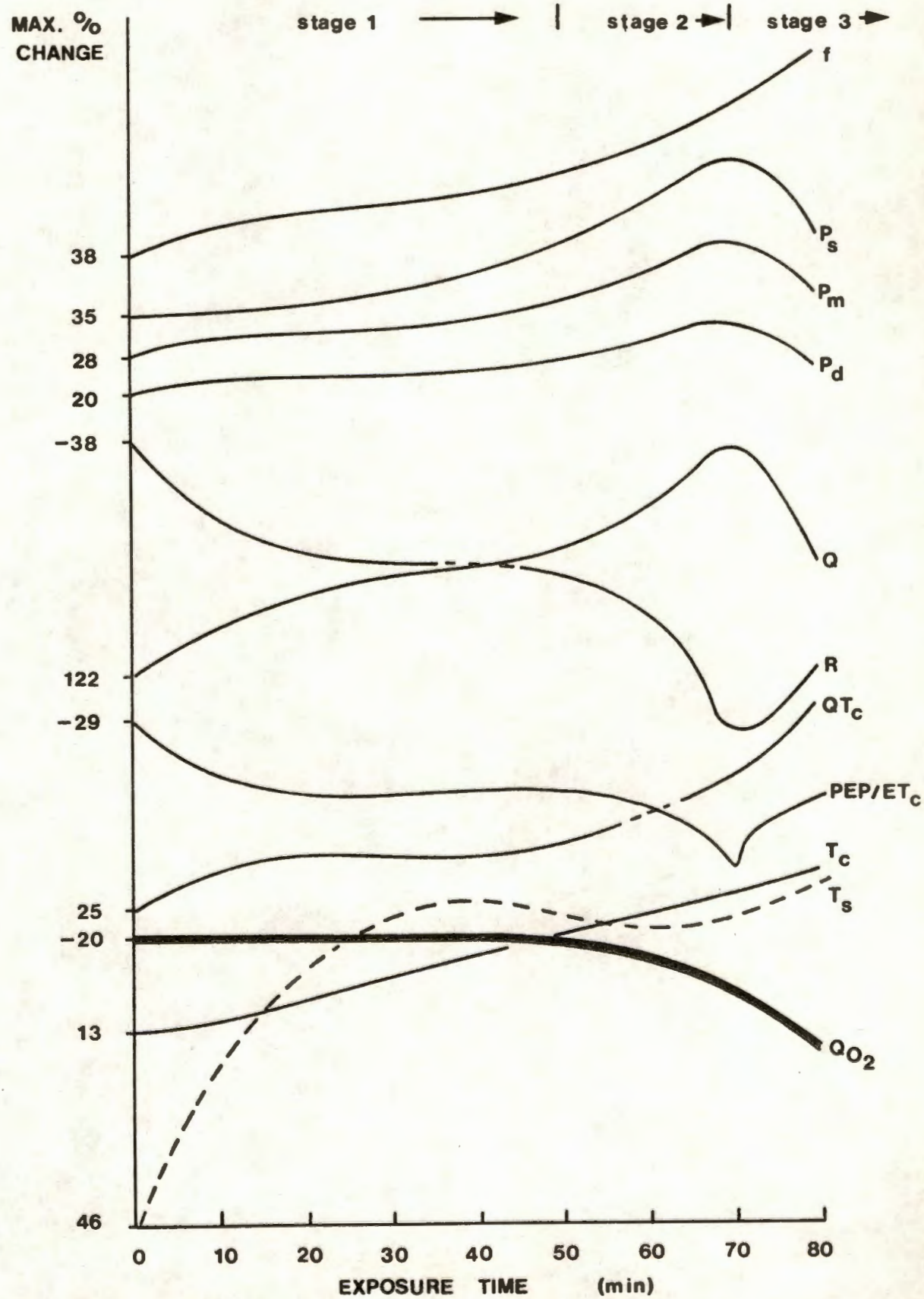
Of further interest was the fact that the ratio of the systolic area to the diastolic area of the pressure pulse (S_a/D_a) also did not change significantly. The implication of this finding is that, in as much as this factor is employed in the estimation of stroke volume, the significant changes observed in stroke volume are related to the factor dV in the Warner equation (Section 2.4.2.3) and not so much to the ratio itself. Of the various parameters employed to assess cardiac contractility (dP/dt_{max}, dP/dt_c, PEP/ET_c and dP/dt_{mean}), only PEP/ET_c proved to be of use. Further discussion of the above findings does not appear to have merit and is, therefore, dispensed with at this point.

The majority of measurements employed to evaluate cardiovascular function during heat exposure did, however, reflect

significant changes. The general pattern which emerges indicates the existence of three distinct phases: the first stage (a) is characterised by moderate circulatory changes and represents a period of approximately 45 (40-50) minutes following the onset of heat exposure. The second stage (b) is associated with the establishment of a hyperkinetic circulation which reaches a peak 70 minutes after the commencement of heat stress. During the final stage, (c) circulatory failure occurs. This review is, therefore, an attempt to describe the characteristics of each of the above stages in order to interrelate the most important observations in this study. A graphical synopsis of the more important observations is presented in Figure 4.10.

(a) The changes occurring in the first stage have been described as moderate. However, an analysis of these changes indicates that the term "moderate" may be qualified so as to distinguish between changes of moderate extent showing gradual change and those also of moderate extent exhibiting, however, rapid initial change. The former category is exemplified by the gradual increase in core temperature. The rate of change recorded is virtually of the same order as observed for systolic pressure, diastolic pressure and mean arterial pressure while the same also holds true for heart rate, stroke volume and cardiac output. It would therefore appear that a certain relationship exists between core temperature and the general haemodynamic status.

FIGURE 4.10 *INTERRELATIONSHIP OF MAJOR CIRCULATORY AND BODY TEMPERATURE CHANGES DURING HEAT EXPOSURE*



Further analyses reveal that (a) the initial increase in cardiac output is more significantly influenced by cardioacceleration than by stroke volume and (b) that the gradual elevation in mean arterial pressure is related more to an increase in diastolic pressure than to an increase in systolic pressure. The latter observation is in keeping with the fact that mechanical diastole is not shortened to a disproportionately greater extent than the reduction in the cardiac cycle.

In contrast with core temperature, skin temperature increases dramatically over the first 20 minutes of heat exposure, its rate of change subsequently tapering off. The consequence is that mean body temperature also exhibits a rapid, initial elevation. These rates of change are paralleled by an increase in contractility and a fall in peripheral vascular resistance. Of further significance is the fact that although the rate of cardioacceleration is gradual, the rate of decrease in the pre-ejection time intervals (QS_1, PEP and IVCT) exceeds the rate of decrease of the cardiac cycle. The fact that total electromechanical systole (QS_2) is not altered significantly by these reductions, is ascribed to the fact that the ejection time is reduced to a lesser extent than the reduction in the cardiac cycle. These findings suggest a possible relationship between, on the one hand, changes in skin and mean body temperatures and, on the other hand, cardiac contractility and the pre-ejection time intervals.

Although peripheral vascular resistance appears to exhibit an initial rapid decline, it should be borne in mind that, statistically, the changes in vascular resistance conform to a first order equation. This implies that the initial changes in vascular resistance conform to changes in core temperature rather than to changes in skin or mean body temperature. Such a deduction is substantiated by considering the initial changes in the term $P_s - P_{es}$: using this term as index of peripheral vascular resistance, it is evident that, statistically, the initial changes are indicative of a gradual decline in resistance rather than of a rapid reduction conforming to the initial time course of, for example, skin temperature.

At the end of this period, myocardial oxygen consumption is unaltered from control levels while myocardial K^+ and Na^+ content is significantly elevated. The QT_c-interval is only slightly increased.

(b) The second stage is characterised by the establishment of a hyperkinetic circulation. During this stage, the changes in body temperatures are gradual and generally linear (Table 4.1) and, therefore, do not appear to have any direct bearing on any of the events leading to the establishment of a hyperkinetic circulation. From Figure 4.10 it is evident, however, that with the exception of the initial period of heat exposure (0-10 minutes), body core temperature for the first time begins to exceed skin temperature. A sensitive plot of the fitted values for core and skin temperature (Figure 5.1) indicates a

cross-over point at an exposure time of 0+57 minutes, i.e., core temperature begins to exceed skin temperature. In as much as the establishment of a hyperkinetic circulation might have been referable to the above event, the observation that core temperature begins to exceed skin temperature at a point in time which practically coincides with the advent of the hyperkinetic circulation, is regarded as significant. The possible implications of this observation are discussed in the next chapter.

One of the most striking features of this stage, is the elevation in mean arterial pressure which in contrast with the first stage, is achieved by an increase in systolic pressure rather than through an increase in diastolic pressure. The increase in mean arterial pressure is therefore also related to an increase in pulse pressure. Of further note is the observation that the above events are associated with further cardioacceleration, an observation which merits further discussion in view of the relationship between heart rate and diastolic pressure.

The increase in mean arterial pressure is associated with similar changes in cardiac output but as shown previously (Section 4.2.5), the increase in cardiac output during this stage is largely referable to an increase in stroke volume rather than to an increase in heart rate. Since the elevation in mean arterial pressure is related chiefly to an increase in systolic pressure, and in view also of the relationship between flow and pressure, it seems likely that

a definite relationship exists between systolic pressure changes and stroke volume changes. Of further interest in this context is the observation that, on the basis of changes in PEP/ET_c, the above events probably are manifestations of an increase in cardiac contractility. It is also significant that whereas the reduction in the cardiac cycle during the initial stages occurred at the expense of pre-ejection intervals, as well as electromechanical diastole, the reduction in cycle length during this stage occurs chiefly at the expense of the ejection time (Section 4.2.3).

The prevailing haemodynamic status during this stage is also characterised by a further fall in peripheral vascular resistance. This observation is substantiated by an independent parameter (P_s-P_{es}), which is indicative of a rapid fall in peripheral vascular resistance during this stage (Table 4.11). In as much as resistance is equated to a pressure difference per unit change in flow, the fall in resistance means that from a mathematical point of view, flow rate (cardiac output) increases more than the pressure differential. To the extent that it may be argued that adequate compensation to a fall in peripheral vascular resistance could have been achieved by an augmented cardiac output without inducing hypertension, the current findings merit careful consideration since a cursory evaluation suggests an element of overcompensation. This deduction is based on the fact that a state of hypertension arose despite a fall in vascular resistance (Figure 4.10). This observation is of particular significance and will be specifically referred to in the next chapter.

Of a more ominous nature is the fact that although enhanced cardiac performance is reflected by at least two parameters (PEP/ET_c and systolic pressure), certain others point towards the advent of pump dysfunction. An analysis of the EKG presented in Figure 4.3, which is representative of this stage, reveals the development of ST-segment depression while a marked increase in the QT_c-interval also becomes apparent (Figure 4.10). Finally, immediately prior to the onset of failure (0+70 minutes), myocardial oxidative capacity is significantly depressed (Figure 4.10). The above findings merit careful consideration especially in view of the observation that enhanced mechanical performance is achieved in the face of signs indicative of pump dysfunction.

(c) The terminal stage represents the onset of circulatory failure. The fall in mean arterial pressure which characterised this stage, is related more to a fall in systolic pressure than to a fall in diastolic pressure. Concurrently, cardiac output also falls and it is apparent that this fall must be ascribed solely to a fall in stroke volume since cardioacceleration is maintained throughout (Figure 4.10).

The fall in systolic pressure and in stroke volume is also associated with diminished cardiac contractility and it is concluded that these events bear a definite relationship to one another. Two electrocardiographic parameters which also appear to have a direct relationship to the above observations

are (a) an extension of ST-segment depression (Figure 4.4) and (b) a further increase in the QT_c-interval (Figure 4.10). Of crucial importance in this context is the fact that myocardial oxidative capacity (Q_{O_2}), already compromised at the onset of the terminal stage, undergoes an extensive further reduction (Figure 4.10).

Although peripheral vascular resistance exhibits a tendency to increase, also in terms of the index P_s-P_{es}, the potential benefit of this response is clearly inadequate and in all probability is simply a manifestation of the fact that the reduction in cardiac output exceeds the reduction in mean arterial pressure.

While most experiments were discontinued at this stage, overt failure was allowed to occur in a selected number of animals. Immediately prior to death the pressure pulse contour was grossly distorted. Apart from hypotension, the major feature was the development of a typical bisferiens pulse (Figure 4.5) accompanied by a marked left axis deviation. Although Cheyne-Stokes breathing was most apparent, overt signs of convulsions were generally absent. A detailed analysis of these events was not, however, considered as being relevant to this study.

SUMMARY

The experimental findings presented in this chapter pertain to an analysis of cardiovascular function during acute, experimental heat stress with special reference to the development of circulatory failure. The general response pattern

indicates the existence of three distinct, albeit overlapping, stages. The essentials of each of these stages are described below:

STAGE 1 (0-45 MINUTES): One of the most dramatic events associated with this stage is the rapid change in skin temperature and, to a lesser extent, mean body temperature. The circulatory response to the higher body temperature may be described as rapid but of moderate extent. The general picture is one of well-adjusted compensation.

STAGE 2 (45-70 MINUTES): The second stage is characterised by the establishment of a hyperkinetic circulation. A major feature is a further decrease in peripheral vascular resistance which is accompanied by an increase in mean arterial pressure. The latter event was considered as being indicative of over-compensation to a fall in resistance and was related to a disproportionate increase in cardiac contractility and stroke volume. Despite enhanced mechanical performance, signs of pump dysfunction become evident during this stage.

STAGE 3 (70-80 MINUTES): This stage represents the advent of circulatory failure. The parameters investigated indicate that cardiac function is compromised.

This summary forms the basis for the subsequent discussion and interpretation of the results (Chapter 5).

C H A P T E R V

DISCUSSION

This study concerns an evaluation of cardiovascular function during acute experimental heat stress with particular reference to the mechanism of circulatory failure. By way of an introduction, the original objectives are restated (5.1) and the validity of the experimental model is discussed (5.2). Recommendations pertaining to possible further avenues of research are given in Appendix 6.

5.1 OBJECTIVES

Heatstroke is regarded as one of the few true medical emergencies (Eichler *et al*, 1969; Hubbard *et al*, 1976) and if effective treatment is not instituted promptly, carries a mortality rate of up to 80% (Kew, 1976). Under such circumstances, where treatment takes priority over investigation, and in view of the mercurial onset of the affliction, little or no knowledge of the prodromal period exists. The first objective, therefore, represents an attempt to elucidate an aspect of the prodromal stage of heatstroke, namely cardiovascular function.

The evaluation of cardiovascular function during the prodromal stage is based on the observation that the cardiovascular system "apparently takes the brunt of heat exposure" (Gold, 1960) and that it represents the "first line of defence" against the

threat of an elevated body temperature (Belding, 1967). An *a priori* deduction may therefore be made, namely , that the genesis of heatstroke is causally related to cardiovascular insufficiency and failure. Such a view is supported by the experimental findings (dogs) of Frankel *et al* (1963) and also by the autopsy findings in 125 fatal cases of heatstroke reported by Malamud *et al* (1946): "Most of the lesions apart from those in the brain can be attributed to the anoxia and circulatory failure incident to shock".

A critical review of the literature does not, however, unequivocally support a concept of cardiovascular insufficiency as primary factor in the pathogenesis of heatstroke. For example, according to Minard and Copman (1963), "circulatory failure... is an occasional complication of heatstroke but by no means an invariable finding". This view is in contrast to the findings of O'Donnell and Clowes (1972), namely that acute circulatory failure has been observed to precede death in more than 80% of cases of human heatstroke. In view of the vast number of interacting factors involved in the genesis of heatstroke, both environmental and physiological, it would therefore seem difficult to establish a clear causal relationship between circulatory failure and heatstroke, if such a relationship exists at all. In this respect the fundamental problem seems to concern whether thermoregulatory mechanisms fail or whether they are merely overloaded (Shibolet *et al*, 1967; Kew, 1976). In as much as the primary physiological strain experienced during heat exposure of the unacclimatised individual may be regarded

as circulatory (Hatch, 1963), the second objective represents an attempt to establish the particular sequence of circulatory events culminating in heat death against a background of circulatory failure or, conversely, circulatory overload.

The final objective concerns the mechanism of circulatory failure. The statement of this problem is by no means original. In 1948 Daily and Harrison posed the following questions: "What are the mechanisms of circulatory collapse which complicate stroke? Is it cardiac or peripheral? Obviously, rational treatment must depend upon an understanding of the type of failure present".

A review of the literature indicates that the general consensus of opinion supports the concept of peripheral blood pooling (peripheral vascular collapse) originally propounded by Daily and Harrison (1948). This view is indirectly supported by the extent of myocardial damage reported in heatstroke victims by Kew (1969): " ... in no case was the (myocardial) damage sufficiently severe for overt cardiac failure to occur". In contrast, according to Gold (1960), the primary event in circulatory failure is a high-output (forward) cardiac failure. This view, too, is not without support (Moore *et al*, 1966). Moreover, the data obtained by O'Donnell and Clowes (1972) fail to support either the concept of decreased venous return due to peripheral pooling or whether right heart failure is due to a myocardial defect or to elevated pulmonary vascular resistance. The latter authors were led to conclude that

the mechanism of cardiovascular collapse during heatstroke in man had not been established beyond doubt. It is also not insignificant that the therapeutic measures advocated by Knochel (1974) in the treatment of hypotension incident to heatstroke (Section 1.2.3) eloquently substantiate the conflicting views on the mechanism of circulatory failure. Although it is not implied that only a single mechanism exists, the final objective, therefore, represents a fresh attempt to shed light on this apparently controversial issue since it is evident that Daily and Harrison's original queries of 1948 are still largely unanswered.

5.2 *THE EXPERIMENTAL MODEL*

In a study of this nature, wherein it is intended to simulate a condition of acute heat stress which is probably akin to the prodromal period of heatstroke, it is obvious that the investigator must resort to an animal study. The relevant perspectives which govern this approach are stated in the introduction to this study (p. 1-2) and it is perhaps appropriate to quote Kew (1976) in this context: "Elucidation ... of the pathogenesis of heatstroke has been hampered by ... the high mortality, which rules out experimental induction of heatstroke in man". While the need for an animal model is amply justifiable in the present context, morphological and possibly other differences may preclude direct animal-to-man extrapolation. It is, therefore, necessary to assess the validity of the current experimental model.

In this particular study, the rat was used as experimental animal. This choice is motivated in Chapter 2 (2.1) and is largely based on the extensive use of rats in studies of this nature. Examples are: *in vitro* and *in vivo* tissue damage assessments (Burger and Fuhrman, 1964 a and b; Burger *et al*, 1970 a and b), heat tolerance studies (Baker and Horvath, 1964), circulatory responses (Daily and Harrison, 1948), cardiac function (Opie *et al*, 1965), metabolic studies (Burger, 1972) and tissue injury (Hubbard *et al*, 1976).

While the above choice may be justified simply on the basis of precedent, the experimental techniques employed in this study necessitated the use of an anaesthetic agent (Na-pentobarbitone). In as much as normal thermoregulatory activities may be suppressed by this intervention, the implication exists that so-called control animals may be rendered grossly abnormal, to such an extent, in fact, that the experimental model becomes meaningless in a physiological sense. For this reason a detailed preliminary investigation was carried out in order to establish the extent to which the experimental model is influenced (Chapter 3). The results of this investigation indicated that while most parameters are demonstrably affected, the adverse effects of anaesthesia are completely abolished after approximately 30 minutes following the onset of heat exposure. This may be ascribed to two factors, namely (a) that the particular dosage used (40 mg/kg body mass) represents the lower limit of the recommended dosage for rats (Chiueh and Kopin, 1978) and (b) that the induction of heat stress

apparently decreases the duration and effect of anaesthesia, probably by enhanced catabolism. In as much as the narcotic effect of hyperthermia becomes evident at a stage which practically coincides with the abolishment of the effects of Na-pentobarbitone, re-administration of the latter becomes superfluous. Moreover, since the initial responses to heat exposure were observed to conform largely to a "normal" response pattern, it was concluded that the discrete use of Na-pentobarbitone anaesthesia did not significantly compromise the overall efficiency of thermoregulation.

In this study the emphasis falls on cardiovascular function with particular reference to the heart. While a detailed description of various aspects of normothermic cardiovascular function may be extracted from the results reported in Chapter 4, the general circulatory status of the rat merits comment in a comparative sense. Firstly, the EKG of small mammals exhibits all the characteristics of larger mammals with slower heart rates (Kisch, 1953). The Q-wave is, however, absent from the normal EKG of a rat (Norman *et al*, 1961). Secondly, according to Chiueh and Kopin (1978), the mean resting heart rate of anaesthetised rats is 336 beats per minute with an arterial pulse fluctuation of 158/133 mm Hg. The current findings are in good agreement, namely 393 and 156/127, respectively. However, although arterial pressure is slightly hypertensive in relation to man, it is equally evident that the pulse contour (Figure 4.1) closely resembles that of man. Thirdly, experimental evidence also suggests that on the basis of ballistic accelerations, the higher dynamic functions of

the heart in all species of mammals are very similar (Južnič, 1973). Finally, according to Guyton (1963), it seems likely that cardiac output regulation in lower mammals (e.g. the rat) is both qualitatively and quantitatively identical to that in man.

In comparison with man, however, the results of the present study suggest that the extent of cardioacceleration exhibited by rats is not as extensive, and probably does not constitute more than a 100% increase, but that rats are capable of achieving arterial pressure elevations at least of the same order generally associated with man subjected to stress. The general impression is therefore that the rat does not exhibit the same flexibility of cardiovascular response as that observed in man. This deduction is probably related to the observation that the rodent heart is functioning closer to its maximum contractile range than the hearts of larger mammals (Henderson *et al*, 1974). On the other hand, according to Guyton (1963), tissue perfusion (cardiac output) per unit mass in the rat is three-fold that of man. It is therefore concluded that the characteristics of the rodent cardiovascular system are such that they do not preclude comparison with the cardiovascular system of man.

The penultimate question concerns the validity of the specific animal model. Until relatively recently, the major objection against animal models stemmed from the definition of heatstroke, in particular from the fact that the pathogenesis of heatstroke depended on sweat cessation. This has since been questioned (Shibolet *et al*, 1967; Eichler *et al*, 1969) and in subsequent

definitions (Kew, 1969; 1976) the terms "sweat cessation" and "failure of the sweat mechanism" are conspicuously absent. In as much as most laboratory mammals do not sweat, Bynum *et al* (1977) were led to conclude that "if heatstroke represents an absence of effective thermoregulation, an animal model permits a cautious comparison of organ system responses between species in which normal thermoregulatory mechanisms are markedly different". It remains but to point out that in this instance the laboratory rat is regarded as a suitable animal (Hubbard *et al*, 1976; 1977).

In the final instance, as has been stated at the outset (5.1), the current experimental model is intended to simulate the prodromal period of heatstroke. In order to delineate this period, it seems necessary to identify at least two transitional stages, namely (a) a point at which "normal" homeostatic responses herald the onset of a crisis, and which may be considered as a prelude to heatstroke, and (b) a point at which the ensuing crisis may be regarded as heatstroke proper. The prodromal period is therefore interposed between these transitions. On the basis of the current findings, the advent of the prodromal period is discernible by the dramatic rates of change in most parameters after a period of about 50 minutes following the commencement of heat exposure (Figure 4.10). However, defining the second transition is not as easy a task and for this purpose resort is made to the definition of heatstroke.

According to Kew (1976), heatstroke represents a condition in

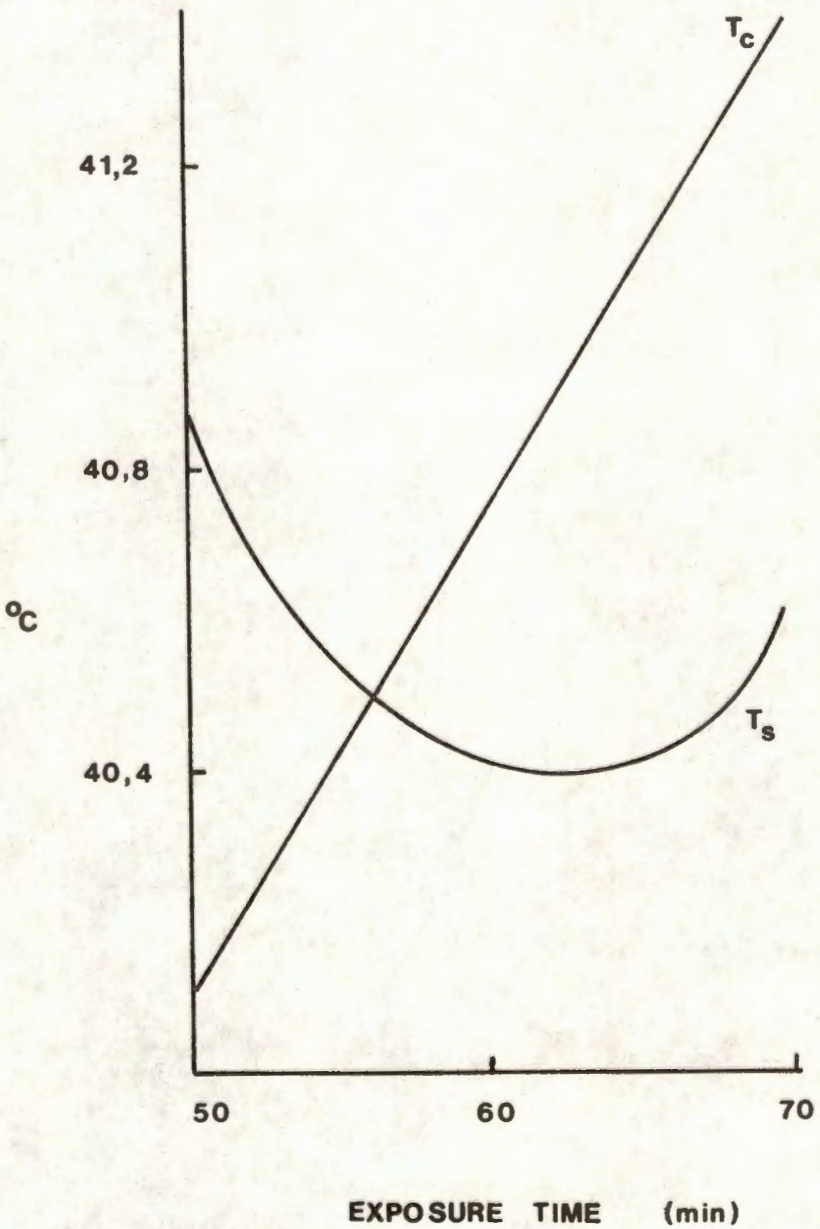
which elevated body temperature itself causes tissue damage. In the present study, the only criterion of tissue damage is related to the significant reduction in myocardial Q_{O_2} which is incurred at a core temperature of 41,5±0,51°C (Mean±SD). In this context the findings of Hubbard *et al* (1976) namely, that a mortality rate of 10% in rats exposed to core temperatures of 41°C changes to 48% on achieving core temperatures of 41,5°C, are of particular significance. Moreover, according to Bynum *et al* (1977) the point at which the cardiac output abruptly drops could be used to define the occurrence of significant heat injury. Since the present study revealed a similar fall in cardiac output immediately after the onset of myocardial "damage" (Figure 4.10), the views expressed by both Hubbard *et al* (1976) and Bynum *et al* (1977) coincide to support the belief that the onset of heatstroke in the present study occurs at a point in time approximately 70 minutes after the commencement of heat exposure and, hence, that the prodromal period encompasses the 50- to 70-minute period of heat exposure.

The preceding deduction cannot, however, be applied rigidly, the fundamental question being concerned with the relationship between core temperature, the duration of hyperthermia and the extent of tissue damage. For example, for a specific animal model (dog) it could be demonstrated that heatstroke occurred only at rectal temperatures in excess of 43°C (Shapiro *et al*, 1973) while in man, heatstroke has been reported to occur at a rectal temperature as low as 39,5°C (Kew, 1976). Moreover, in the present study, the assessment of tissue

damage rests on a single organ, the heart, which, in contrast to other tissues (e.g. the liver), is relatively insensitive to heat damage (Burger, 1972). The distinct possibility therefore exists that heatstroke, as defined in terms of significant tissue damage, could have resulted at a stage earlier than the 70-minute period. On the basis of survival studies (Section 4.4), however, it is equally unlikely that heatstroke could have commenced at a stage earlier than the 50-minute exposure time.

Of further importance in this context is the observation that the rate of fall in vascular resistance increases greatly after the 60-minute period of heat exposure. In view of the extreme heat sensitivity of the organs of the splanchnic area (Burger *et al*, 1970a), it is not inconceivable that the reduction in vascular resistance may be referable to the abolishment of splanchnic vasoconstriction, secondary to tissue damage in this area. A detailed discussion of these aspects is given in the following sections (5.3.1 and 5.3.2). The dramatic fall in vascular resistance at this stage may therefore be a manifestation of the onset of heatstroke. Moreover, with the exception of the initial stages of heat exposure (0+10 minutes), an analysis of Table 4.1 reveals that core temperature begins to exceed skin temperature only after about 65 minutes following the onset of heat exposure. Furthermore, it may be shown on a statistical basis that skin temperature actually exhibits a slight decline 50 minutes after the commencement of heat exposure (Figure 5.1), a finding also observed in a similar study (Hubbard *et al*, 1974). These findings are interpreted to

FIGURE 5.1 *FITTED BODY CORE AND SKIN TEMPERATURE CHANGES*



mean that at a crucial point, skin temperature is lowered at the expense of an elevated core temperature: It is as if the dermal circulation is "coupled" with the splanchnic circulation, an event which can only occur if compensatory splanchnic vasoconstriction is abolished.

In the absence of any contradictory evidence, it is therefore assumed that the transition to heatstroke occurs within the 60- to 70-minute period of heat exposure.

5.3 CARDIOVASCULAR FUNCTION DURING EXPERIMENTAL HYPERTHERMIA

An analysis of the results presented in Chapter 4 indicates that the circulatory response pattern to heat exposure is characterised by three distinct, albeit overlapping, stages namely, compensation, crisis and failure. These divisions form the basis of the subsequent discussion.

5.3.1 INITIAL RESPONSES

During the initial 40 to 50 minutes of heat exposure, circulatory responses to an elevated body temperature present a picture of well-adjusted homeostatic compensation. This general impression is based on a review of the literature.

Within the context of the thermoregulatory role of the cardiovascular system, the primary circulatory event must be regarded as the rapid initial fall in total peripheral vascular resistance (Figure 4.10) which has its main origin in dermal vasodilatation (Belding, 1967). The resulting increase in skin

blood flow, which under these circumstances constitutes the functional equivalent of, if not a genuine, arterio-venous shunt (Gold, 1960), predisposes to heat dissipation. However, despite the beneficial effects of an augmented dermal perfusion rate, it is patently clear that dermal vasodilatation *per se* would precipitate a relative fall in circulating blood volume (functional hypovolaemia) in the absence of homeostatic compensation (Knochel, 1974; Hubbard *et al*, 1978).

The primary mechanism by which functional hypovolaemia is averted constitutes a repartitioning of the cardiac output (Rowell *et al*, 1966) by means of compensatory constrictions in other vascular beds, notably the splanchnic circulation (Robinson, 1963; Leithead and Lind, 1964; Rowell *et al*, 1965), non-exercising muscle (Hales and Dampney, 1975) and the kidney (Gilbert, 1978). Compensation may also occur in the form of an increased cardiac output but according to Robinson (1963), this is not a consistent finding.

The present findings indicate that the fall in vascular resistance is accompanied by an increase in cardiac output. On the basis of the view expressed by Knochel (1974) and Hales and Dampney (1975), it may be deduced that the occurrence of the latter event is indicative of inadequate compensatory vasoconstriction. The observation that the mean arterial pressure remains virtually unaltered (Figure 4.10) would support this deduction. However, it may also be argued that the thermoregulatory demands imposed on the circulation could not be met entirely be repartitioning of the cardiac output, and that

the concurrent increase in cardiac output provides additional augmentation of dermal perfusion. In this context, the increase in cardiac output is a manifestation of the severity of the physiological stress imposed by heat rather than of an inadequacy of compensatory constrictions. Further referance to this deduction will be made elsewhere in this section.

The overall increase in cardiac output during the initial stage of heat exposure was regarded as moderate (Chapter 4: 4.2.5). Further analyses reveal that the increase in cardiac output is achieved primarily by an increase in heart rate, stroke volume increases being of secondary importance. These findings are in agreement with the observation that the most simple and effective way of increasing cardiac output is by increasing heart rate (Schlant, 1978a) with moderate increases in stroke volume (Rushmer, 1970).

The reduction in cardiac cycle length during cardioacceleration generally occurs at the cost of the diastolic period (Rushmer, 1970). This was confirmed in the present study. However, it is also evident that the reduction in the cardiac cycle was associated with significant reductions in the pre-ejection periods viz., the conventional pre-ejection period (PEP), electromechanical systole (QS_1) and the isovolumic contraction time (IVCT). In as much as the ejection time (ET) decreased in direct proportion to the reduction in cardiac cycle length, the ratio PEP/ET was also reduced. Collectively, these reductions are indicative of enhanced cardiac contractility

(Weissler *et al*, 1969; Ahmed *et al*, 1972; Harris, 1974; Siegel, 1978) and are manifested in an increase in stroke volume. Although a physiologically induced positive inotropism (e.g. catecholamine release) cannot be excluded, the findings of Singh (1963) suggest that the enhanced contractility, and subsequent increase in stroke volume, may also be related to an elevation in body temperature *per se*. Of further note is the observation that the only significant electrocardiographic alteration pertains to a reduction in the PQ-interval. This reduction is especially evident during, and limited to, the initial stage of heat exposure and consequently the overall changes in the PQ-interval conform to a second order equation. According to Marriott and Meyerburg (1978), the reduction in the PQ-interval may be regarded as the normal sequel to an increase in heart rate.

The preceding considerations suggest that during the initial stage of heat exposure, cardiac function conforms to a response pattern which is closely related to that observed during mild physical exertion. Despite a marked decrease in vascular resistance, mean arterial pressure generally remains unaltered, an event which may be construed as being indicative of the overall competence of vasomotor control (Valbonna, 1974). The fact that diastolic pressure does not fall is referable to the proportionality between heart rate and diastolic pressure (Rushmer, 1970) and to the fact that diastolic pressure and vascular resistance are independent of one another in the presence of adequate compensatory mechanisms (O'Rourke, 1971).

Having thus established that the initial circulatory responses to heat exposure may be considered as "normal", it remains to relate these responses to changes in body temperature. Within the context of the scope of this study, it must be emphasised, however, that the respective temperature measurements may not be truly representative of what they are implied to be. The obvious shortcomings are related to the fact that (a) skin temperature was measured at a single, convenient site, (b) mean body temperature is no more than an arithmetical index and that (c) core temperature, although considered superior to rectal temperature measurements, is still only a substitute for the almost inaccessible hypothalamic temperatures.

With due recognition of the problems inherent in correlating body temperature inputs to the thermoregulatory system and thermoregulatory effector action, an attempt was nevertheless made to establish a relationship between body temperature changes and circulatory responses. This attempt is justified as follows: firstly, there appears to be general consensus that the regulated variable in mammalian thermoregulation is temperature *per se* (Hardy and Hammel, 1963). The second consideration is of a more practical nature, namely that the very nature of the hyperpyrexic state, including heatstroke, precludes accurate assessments of thermal gradients within the body and that much reliance falls on routinely employed measurements such as those used in the present study.

An analysis of the results reported in Chapter 4 (4.1) indicates that the most dramatic initial changes in body tem-

perature pertain to elevations in skin temperature and mean body temperature. Of especial significance is the fact that the initial changes in skin and mean body temperatures, respectively, exhibit second order characteristics.

Comparing changes in body temperatures and circulatory responses during the first 20 minutes of heat exposure (Figure 4.10), it is apparent that in the absence of any marked change in core temperature, none of the circulatory responses is governed by core temperature. However, in view of the doubt concerning the existence of afferent pathways for warm reception from the skin to the anterior hypothalamic regions (Benzinger *et al*, 1963), it is equally doubtful whether the initial circulatory responses are related to the dramatic skin temperature elevation. In agreement with the findings of Gonzalez *et al*, (1978), it is concluded that the initial changes in skin temperature merely represent a proportionality to the prevailing environmental temperature.

The relationship between skin temperature and ambient temperature should not, however, be seen in isolation since, irrespective of any weighting factor, changes in skin temperature are reflected in changes in mean body temperature. In as much as mean body temperature is regarded as an important input to the thermoregulatory system (Mitchell, 1972), it is evident that skin temperature must be implicated in the physiological effector action of the thermoregulatory centre. The preceding arguments lead to a tentative conclusion, namely that the initial general circulatory response to heat exposure is

governed by mean body temperature. This conclusion is also qualitatively substantiated by the findings of Mitchell (1972).

The changes in mean body temperature over the entire period of heat exposure are relevant to the present discussion. During the initial period of heat exposure it is evident that skin temperature changes account for the major alterations in mean body temperature while during the latter stage, when skin temperature remains virtually constant, the same may be said for core temperature (Section 4.1). It is therefore not surprising that, of the three measurements, mean body temperature exhibits the most statistically significant overall change and, in this respect, provides the most sensitive measure of the actual thermal state of the body. This conclusion is in complete agreement with the finding of Gonzalez *et al* (1978) that mean body temperature was considered as a significant indicator of physiological strain.

While mean body temperature may be regarded as an accurate reflection of physiological stress from a thermal point of view, it is equally clear that the only circulatory parameter of physiological stress is represented by heart rate changes. This deduction is based on the fact that although the heart rate response conforms to a first order equation statistically, it is the only circulatory measure which resembles the time-course for mean body temperature over the *entire* period of heat exposure. For example, the fall in cardiac output in the terminal stage would erroneously indicate alleviation of stress. The conclusion that heart rate also serves as an

index of physiological heat stress is in agreement with the views of others (Gold, 1961; Hatch, 1963; Berglund and Gonzalez, 1977).

An objective of this investigation was also to establish whether the combined effects of a hyperkinetic circulation and hyperthermia, during the initial stage of heat exposure (0-50 minutes), could induce changes in myocardial electrolytes of sufficient magnitude to explain, in part at least, subsequent circulatory failure. It was assumed that if such changes did occur at all, they need not necessarily become manifest immediately upon the termination of heat exposure; consequently certain animals were allowed to survive these subacute exposures to heat for fixed periods prior to assaying myocardial K^+ and Na^+ content. The results of this investigation are given in Chapter 4 (4.4).

Of fundamental importance is the fact that ischaemic injury of the myocardium results in K^+ loss, an event which might be due to a failure of energy producing mechanisms or K^+ retention mechanisms (Jennings *et al*, 1957; Corday and Lang, 1978). According to McVie (1970), one of the most sensitive methods for detecting inapparent myocardial infarction is the determination of the myocardial K^+/Na^+ ratio, which falls within minutes after the onset of anoxia. Changes in this ratio have also been shown to correlate well with other parameters of infarction and consequently the ratio (K^+/Na^+) provides a sensitive method to establish infarction at necropsy (Hearse *et al*, 1977).

The principle of the approach is based on the observation that after myocardial infarction, one of the first changes which occurs in cardiac cells is a loss of K^+ and a gain in Na^+ so that 24 hours after infarction, the intracellular electrolyte pattern resembles that of the extracellular fluid (Cherry and Meiners, 1971). In this study the approach was slightly different in so far as the K^+/Na^+ ratio was used more as an indicator of the reversibility of changes which may have occurred during heat stress, rather than in the detection of myocardial infarction.

An analysis of the results reported in the previous chapter (Section 4.4), with specific reference to Table 4.8, reveals a steady decline in the K^+/Na^+ ratio over the initial stage of heat exposure. This decline was not regarded as being statistically significant and consequently, in terms of a decrease in the K^+/Na^+ ratio as a marker for myocardial damage, inapparent myocardial failure in the initial stages of heat exposure may be ruled out as a factor contributing to the eventual circulatory failure. This view is also substantiated by the observation that a normal ratio is reinstated within 48 hours following heat exposure, an observation which also indicates total reversibility.

A more detailed analysis reveals absolute increases in both myocardial K^+ and Na^+ content over the initial stage of heat exposure. The slight decline in the K^+/Na^+ ratio is attributed to the fact that the myocardial Na^+ increase exceeds the myocardial K^+ increase in a relative sense. These absolute in-

creases in myocardial K^+ and Na^+ content are in general agreement with the findings of other investigators in the same field of study (Spurr and Barlow, 1959a; 1970). Since control levels for both K^+ and Na^+ are reinstated within 48 hours following heat exposure, the conclusion that irreversible electrolyte changes do not occur during the initial stage of heat exposure, is reaffirmed. This conclusion, that the inherent intactness of the cell membranes is maintained, is indirectly supported by the findings of Burger and Engelbrecht (1966) who observed that no leakage of K^+ and Na^+ occurred from heart slices (rat) subjected to supranormal temperatures.

The preceding discussion suggests that the changes in myocardial electrolytes merely reflect changes of a transient nature in membrane permeability, an event known to occur in the hyperpyrexic state (Spurr and Barlow, 1959a). However, to anticipate matters at this stage, the effect of elevated myocardial K^+ and Na^+ levels may be of crucial importance with regard to sustained cardiac function. In view of the competition between Na^+ and Ca^{++} for intracellular membrane-located receptor sites, an elevated Na^+ content may well shift the normal Ca^{++}/Na^+ ratio sufficiently so as to bring about reduced myocardial contractility (Nayler *et al*, 1971; Schlant, 1978b) and in this sense it may contribute, to an unknown extent, to the mechanism of circulatory failure. In this context it is perhaps of interest to note that although myocardial K^+ remains essentially unaltered during congestive cardiac failure, Na^+ increases significantly (Benson *et al*, 1956).

The increased myocardial K^+ content may be referable to increased plasma levels (Spurr and Barlow, 1959a), this finding often being associated with hyperthermia (Kanter, 1954; Barlow *et al*,1956; Spurr and Barlow, 1959a; 1959b; 1970; Burger *et al*,1970b; Kielblock, 1972). It is therefore unlikely that appreciable changes in the K^+ gradient could have occurred across the myocardial plasmalemma. This deduction is based on the complete absence of electrocardiographic evidence of disturbed ionic ratios throughout the entire period of heat exposure and is in agreement with the findings and deductions of Spurr and Barlow (1959a).

Although not measured in the present study, previous investigations under identical experimental conditions (Burger *et al*, 1970b; Kielblock, 1972) reveal extensive plasma K^+ elevations in the hyperthermic rat. In view of the vasodilatory effect of hyperkalaemia (Skinner and Powell, 1967; Schlant, 1978c), the possibility exists that a crucial abolishment of vasoconstriction could ensue, thereby potentiating circulatory failure. Hyperkalaemia also produces generalised muscle weakness and flaccid paralysis, the heart being more sensitive than skeletal muscle (Christy and Clements, 1978). However, in the absence of any direct evidence, these views concerning the potential reduction in cardiac contractility by Ca^{++} - Na^+ competition, and the possible role of hyperkalaemia in circulatory failure, must remain speculative.

A review of the events which characterise the initial stage of heat exposure, leads to a tentative conclusion that the

entire circulatory response to heat exposure is governed by the mean body temperature input to the thermoregulatory system. The primary circulatory event is a reduction in peripheral vascular resistance due to dermal vasodilatation, in order to enhance cutaneous blood flow and heat dissipation. The concurrent elevation in cardiac output is regarded as being indicative of the fact that repartitioning of the cardiac output is inadequate in itself to meet the thermoregulatory demands imposed by the environment. The overall competence of vasomotor control is exemplified in the constancy of mean arterial pressure. The changes in myocardial electrolyte content are regarded as consistent with the hyperpyrexic state, while the transient nature of these changes rules out inapparent myocardial damage during the initial stage of heat exposure. This finding is in keeping with the absence of any form of electrocardiographic abnormality. Myocardial oxidative capacity (Q_{O_2}) remains unimpaired at the end of this stage. The overall picture is one of well-adjusted compensation to the physiological stress of heat.

5.3.2 *THE HYPERKINETIC STAGE*

This stage commences approximately 50 minutes after the onset of heat exposure and lasts about 20 minutes. The major feature of this stage is the development of a hyperkinetic circulation of no uncertain dimensions (Figure 4.10). As mentioned earlier (5.2), it seems likely that this stage may be regarded as the prodromal period of heatstroke and, although the precise onset of heatstroke cannot be identified unequi-

vocally, it was concluded that the terminal stage is characteristic of heatstroke. It is likely, as in the initial stage, that the primary circulatory event may be regarded as a further dramatic fall in vascular resistance, a fall which constitutes over 50% of the overall maximum fall within a period of 25% of the total exposure time (Section 4.2.6). The fall in vascular resistance is substantiated by the significant increase in the difference between the systolic and end-systolic pressures, a feature which has been described as the "collapsing pulse", and which is indicative of a fall in vascular resistance (Hurst and Schlant, 1978). In this instance, however, the reduction in vascular resistance cannot be ascribed to dermal vasodilatation in as much as it may be assumed that the dermal vessels are maximally dilated. Under comparable experimental conditions, Daily and Harrison (1948) ascribed the reduction in vascular resistance in this critical stage to an abolishment of splanchnic vasoconstriction as a result of (a) thermal damage to the vasomotor centre and (b) the accumulation of acid metabolites during the period of diminished splanchnic blood flow.

However, according to Burger (1972), central nervous system tissue, in comparison with other tissue types, is remarkably insensitive to thermal damage *in vivo*. Burger (1972) could also demonstrate that while many tissues are damaged beyond doubt in experimental hyperthermia, the significance of damage to each specific tissue in the pathogenesis of heatstroke remains unanswered. Moreover, in the rat at least, it is unlikely that the primary cause could be ascribed to central nervous system damage in view of the relative heat insensitivity

of this tissue (Burger, 1972). It is therefore concluded that it is improbable that the reduction in vascular resistance is referable to impaired central control.

The preceding deduction implies that local factors are involved in the primary abolishment of splanchnic vasoconstriction. Although the precise mechanism is not clear, it seems likely that the abolishment of splanchnic vasoconstriction is referable to excess lactate (Daily and Harrison, 1948; Frankel *et al*, 1963; Burger *et al*, 1970b), direct thermal damage to the heat sensitive organs of the splanchnic circulation (Burger *et al*, 1970a; Burger 1972) and hyperkalaemia, the role of which has been discussed in the previous section (5.3.1). Moreover, it is also likely that the abolishment of splanchnic vasoconstriction may be explained by "autoregulatory escape" (Rushmer, 1970),whereby prolonged stimulation of intestinal vasoconstrictor fibers is followed by apparently spontaneous vasodilation. These observations provide the most plausible explanation for the marked reduction in vascular resistance.

The fall in vascular resistance is associated with an equally dramatic increase in cardiac output. At first glance the latter response may be regarded as a perfectly normal compensatory measure. However, the fact that the increase in cardiac output is also associated with a concurrent elevation in mean arterial pressure (Figure 4.10) is indicative of overcompensation. Moreover, as pointed out in the previous chapter (Section 4.2.5), the increase in cardiac output, and consequently also the extent of overcompensation, is predominantly

referable to a massive increase in stroke volume, rather than an increase in heart rate. This view is substantiated by a marked further increase in contractility (Section 4.2.4) and also by virtue of the fact that the increase in mean arterial pressure stems from a disproportionate rise in systolic and hence pulse pressure. According to Valbonna (1974) the latter event is a reflection of enhanced left ventricular contraction force.

The increase in stroke volume during this stage is not regarded as a normal response; more specifically, it is regarded as a supranormal response. In the present context, this phenomenon is associated with "extremely severe exertion" (Rushmer, 1970). The same phenomenon also occurs in chronically high output states resulting from anaemia, thyrotoxicosis, an arterio-venous fistula (Bishop *et al*, 1955; Gold, 1960), tissue injury, trauma and sepsis (O'Donnell and Clowes, 1972). It is therefore patently clear that the exaggerated rise in stroke volume observed in this study is a manifestation of some abnormality, specifically, the functional equivalent of a massive arterio-venous fistula.

These views lead to the conclusion that the disproportionate increase in stroke volume is directly attributable to the critical reduction in vascular resistance. Of interest is the fact that this increase in stroke volume occurs under circumstances which, potentially, are conducive to a decrease in venous return. This observation is not unique since it has been observed to occur during heat stress in man: "Despite

a fall in right sided filling pressure, stroke volume rises further suggesting some positive inotropic stimulation" (Gilbert, 1978). The importance of positive inotropism in this context requires extensive reference to Schlant (1978b): "One of the more important acute adjustments to heart failure is a reflex increase in autonomic sympathetic excitation to the heart .... The acutely increased sympathetic impulses to the heart stimulate the local release of norepinephrine and thereby produce beta stimulation with an increase in ... myocardial contractility. Norepinephrine also increases the rate of ventricular relaxation which further contributes to increased ventricular filling. In addition, the generalised increased sympathetic activity and the release of norepinephrine from the adrenal medulla ... contribute toward increasing myocardial contractility".

Thus, considering the entire interaction between, on the one hand, the detrimental reduction in vascular resistance and on the other, the disproportionate increase in stroke volume, it is clear that the link may be provided by excessive differential sympathetic discharge and/or catecholamine release. The extent of positive inotropism imparted is probably directly related to the magnitude of the crisis. Moreover, it is likely that excessive catecholamine release is directly responsible for the unwarranted erosion of the cardiac reserve which inexorably hastens the onset of circulatory failure (Section 5.3.2). This view is based on the findings of Mosinger *et al*, (1978) that the retrograde infusion of natural catecholamines induced irreversible morphological changes in the rat heart and

was preceded by lactate dehydrogenase release. These findings clearly demonstrate the potential cardiotoxic effect of catecholamines, an event which may not be unrelated to the present findings.

A point of extreme interest which emerges on analysis of the above reference to Schlant (1978b), is his observation that sympathetic discharge in this context is reflexly elicited by heart failure. The present findings tend to substantiate a view of imminent failure. A consistent finding prior to circulatory failure was progressive ST-segment depression, an event which has also been reported in dogs in an advanced state of hyperthermia (Goldberg *et al*, 1952). In the absence of hypokalaemia, ST-segment depression represents a non-specific imbalance between coronary arterial oxygen supply and haemodynamic demands; factors which may augment such demands are elevated systolic pressures and exertional tachycardia (Bruce and Irving, 1978). Since these are the very factors which characterise the haemodynamic status at the onset of ST-segment depression in the current study, and in the deduced absence of hypokalaemia, it is concluded that the observed depression in the ST-segment manifests the fact that myocardial oxygen demand exceeds the supply thereof. It is also a reflection of left ventricular strain (Castellanos and Meyerburg, 1978).

A second finding considered indicative of imminent cardiac failure, is related to changes in the QT_c-interval (Figure 4.10). During the last 30 minutes of heat exposure the change

in QT_c constitutes 74% of its maximum overall change (Table 4.4). Perhaps of greater significance is the fact that the changes in QT_c conform to a second order equation, so that the changes during the latter period of heat exposure are true reflections of the progressive delay in the corrected ventricular repolarization time. According to Rushmer (1970), QT is probably the only electrocardiographic sign of a metabolic disturbance of the myocardium. Although a prolonged QT-interval may also be associated with hypocalcaemia (Castellanos and Meyerburg, 1978), this explanation is rejected in view of the findings of Burger *et al* (1970b), namely that the blood calcium levels remained essentially unaltered during experimental hyperthermia. It is therefore concluded that the prolongation of the QT_c-interval, which becomes evident at the commencement of this stage, is a manifestation of a metabolic disturbance of the myocardium.

Apart from ST-segment depression and prolongation of the QT_c-interval, no electrocardiographic evidence indicative of myocardial dysfunction could be detected during this stage. This observation leads to the conclusion that cardiac conductivity remains essentially intact. Moreover, using the QS_1-interval as an index of electromechanical coupling (Table 4.7), and PEP/ET_c as an index of contractility (Table 4.9), it is patently clear that overall cardiac function is apparently unimpaired, despite progressive erosion of its reserve. In this context, the present findings suggest ST-segment and QT_c-interval changes may be of the most sensitive electrocardiographic parameters of a decrease in cardiac reserve. In as much as similar

changes have been observed to occur in cases of human heat-stroke (Kew, 1969; Kew *et al*, 1969), it seems likely that such changes may be of special significance when associated with a heat-induced hyperkinetic circulation.

The final indicator of imminent cardiac failure pertains to the reduction in myocardial oxygen consumption (Q_{O_2}) which becomes evident during this stage. At the commencement of this stage, myocardial oxygen consumption proceeded in a normal fashion. However, it is clear that at the end of this stage (50-70 minutes of heat exposure), myocardial oxygen consumption is severely depressed. It is likely that a progressive fall occurs during this stage (Chapter 4: 4.3).

According to Burger (1972), the measurement of Q_{O_2} by means of the Warburg technique may be regarded as an ideal method of assessing tissue damage, irrespective of the mechanism of damage. In the strictest sense of the word, Q_{O_2} is a reflection of the overall competence of the oxidative machinery of the cell i.e., cellular oxidative capacity. An analysis of the results presented in Chapter 4 (4.3) indicates that myocardial oxidative capacity is significantly reduced at the end of this stage (50-70 minutes). This reduction is barely significant at the 5% level of significance but, in view of the conservative nature of the statistical treatment (Troskie, 1978), the reduction is real and valid. It is therefore concluded that myocardial oxidative capacity only becomes significantly reduced 70 minutes after the commencement of heat exposure, and not at any prior stage.

From the preceding discussions it is clear that the progressive depletion in cardiac reserve, which ultimately culminates in a significant reduction in cellular oxidative capacity, proceeds in the complete absence of impaired mechanical performance. This finding is not without precedent: according to Schlant (1978b), most (cardiac) patients exhibit myocardial dysfunction prior to pump dysfunction and failure, and also prior to clinical signs of congestive cardiac failure.

A review of the events which characterise this stage indicates that the primary event is the dramatic reduction in vascular resistance. This reduction is ascribed to the abolishment of splanchnic vasoconstriction subsequent to a combination of autoregulatory escape of splanchnic constriction and local tissue damage. The fall in vascular resistance is countered by an increase in cardiac output with a concurrent reduction in cardiac reserve. Myocardial oxygen demand outstrips the supply thereof. Central recognition of an impending crisis is manifested in a further increase in stroke volume, most probably mediated through augmented sympathetic discharge. The resultant increase in cardiac output is in excess of the demands of homeostatic compensation. This leads to a further reduction in cardiac reserve and the consequent establishment of a vicious cycle.

5.3.3 THE TERMINAL STAGE: CIRCULATORY FAILURE

Circulatory failure becomes evident after a mean exposure time of 70 minutes. At this stage the pulse contour is still

typically hyperkinetic and the only initial sign of failure is a fall in mean arterial pressure. The fall in mean arterial pressure is ascribed to a greater fall in systolic than diastolic pressure and, according to Valbonna (1974), consequently signifies a reduction in left ventricular force of contraction. This interpretation is substantiated by a corresponding fall in stroke volume and, in terms of PEP/ET_c, decreased contractility which, according to Qureshi *et al* (1978), is also a manifestation of left ventricular failure. Despite sustained cardioacceleration, the cardiac output falls. The fall in cardiac output is therefore exclusively referable to a fall in stroke volume. Moreover, the rate of fall in cardiac output exceeds the rate of fall in mean arterial pressure and, in view of the apparent increase in total vascular resistance, it is unlikely that circulatory failure is solely related to peripheral vascular collapse. This deduction is supported by the establishment of a bisferiens pulse (Figure 4.5) which, according to O'Rourke (1971) and Hurst and Schlant (1978), may be associated with aortic stenosis i.e., an "obstruction" to flow. The development of a bisferiens pulse in the presence of low vascular resistance places emphasis on the extent to which cardiac mechanical function deteriorates.

In the absence of any electrocardiographic evidence of disturbances in cardiac conductivity (with the possible exception of a slight increase in the QRS-duration), it is clear that the mechanism of failure must reside elsewhere. In this respect it is probable that cardiac failure is referable to a

critical further reduction in myocardial oxidative capacity (Q_{O_2}). This event is reflected in a progressive prolongation of the QT_c-interval and an intensification of ST-segment depression. These findings collectively suggest that cardiac failure in the terminal stage is primarily due to a serious biochemical derangement of myocardial energy transformation mechanisms.

The patterns of changes in mean arterial pressure and heart rate observed during this stage are identical to those reported by Frankel *et al* (1963) in the terminal stage of progressive hyperthermia in dogs. Immediately prior to death, the haemodynamic status also shows a close correlation to that reported in several instances of fatal human heatstroke (Chapter 1: 1.3.1.3). The advent and establishment of metabolic malfunction has also been demonstrated to occur in isolated perfused rat hearts subjected to supranormal temperatures. (Opie *et al*, 1965).

The major feature of the terminal stage is cardiac failure.

5.4 *THE PATHOGENESIS OF HEATSTROKE IN TERMS OF CIRCULATORY FAILURE*

The pre-eminent role of the circulation in thermoregulation (Gold, 1960; Hatch, 1963; Belding, 1967; Knochel, 1974) and the apparent absence of gross cardiovascular malfunction (Ferguson and O'Brien, 1960; Minard and Copman, 1963; Kew, 1969), at first glance collectively constitute a contradiction. The general consensus is simply that circulatory failure, when

present, complicates heatstroke and in this sense, it seems as if circulatory failure is the result of heatstroke and not the cause thereof (Chapter 1: 1.2.4).

The results of this study indicate that tissue (cardiac) damage precedes overt circulatory failure, a finding which conforms to generally accepted views. However, a more detailed analysis reveals that overt circulatory failure is preceded by a severe reduction in total vascular resistance. Moreover, this fall is regarded as physiologically deleterious (Section 5.3.2) and its establishment may therefore be of fundamental importance to an understanding of the pathogenesis of heatstroke.

A review of the literature (Section 1.1.2) indicates that heatstroke is associated with wide-spread tissue damage, the kidney and the liver being damaged almost invariably (Kew *et al*, 1971). Animal analogies essentially reveal the same findings: according to Burger *et al* (1970a), the most sensitive tissues to *in vivo* heat damage are the liver, spleen, small intestine and skeletal muscle, the kidney being only slightly less sensitive. Thus, with the exception of the kidney and skeletal muscle, respectively, both clinical and experimental findings suggest that the organs of the splanchnic circulation are particularly sensitive to heat damage and if any particular organ may be singled out, it is likely to be the liver.

On the basis that the liver is representative of the organs

of the splanchnic circulation, the question arises as to which factors render the liver so sensitive to damage in heatstroke. That direct thermal damage is at least partly implicated may be deduced from the findings of Rowell *et al* (1968), namely that in young men subjected to environmental heat stress, the hepatic venous temperature rose to 41,6°C and in fact exceeded the concurrently recorded core temperature of 40,0°C. However, Burger (1972) could demonstrate that despite the *in vivo* heat sensitivity exhibited by hepatic tissue, the *in vitro* tolerance is remarkably high.

A clue to the reason for this discrepancy is provided by considering the circulatory adjustments to heat in the intact animal, specifically splanchnic vasoconstriction. While the beneficial effect of this adjustment is patently clear (Section 5.3.1), splanchnic vasoconstriction simultaneously imposes a restriction on the transfer of metabolic heat from the core to the periphery (*Vide supra*: Rowell *et al*, 1968). Such an adjustment is potentially conducive to thermal damage.

While the sensitivity of liver tissue to heat damage may be referable to a particular vasomotor adjustment, it is also interesting to consider cardiac tissue in this context. An analysis of the findings of Burger and co-workers (Burger and Engelbrecht, 1966; 1967; Burger *et al*, 1970a, Burger, 1972) indicates that while cardiac tissue is inherently susceptible to heat damage *in vitro*, it appears to be relatively insensitive to heat damage in the intact animal. The possibility once again occurs that the apparent discrepancy may be related

to the fact that during *in vivo* heat exposure, the rapid flow of blood through the heart would facilitate heat transfer as well as adequate oxygenation, thereby retarding the onset of thermal damage. In as much as a reduction in renal and non-exercising muscle blood flow has been demonstrated to occur in man exposed to heat (Gilbert, 1978), the likelihood exists that the susceptibility of these tissues to thermal damage may also be referable to inadequate heat dissipation. In view of the inherent susceptibility of renal and muscle tissue to thermal damage (Burger *et al*, 1970a), compensatory constriction of the respective vascular beds would simply aggravate the damage.

The preceding discussion indicates that tissue damage is likely to occur primarily in organs in which compensatory vasoconstriction occurs. This argument does not explain the high incidence of central nervous system disturbances in human heatstroke (Kew, 1976), but it also does not exclude the possiblity that brain damage may occur secondarily to damage in other areas. *In vivo*,rat brain tissue is regarded as relatively insensitive to heat injury (Burger, 1970a) but whether the same relative insensitivity applies to human brain tissue is, for obvious reasons, uncertain. However, if the above argument is valid, it may be concluded that the initial thermal damage associated with heatstroke is not the result of circulatory failure but, in fact, directly attributable to the competence of compensatory vasoconstriction. Moreover, in view of the extreme sensitivity of the liver to hypoxia (Burger, 1972), thermal damage may be aggravated by a hypoxic state incident to sustained vasoconstriction.

On the other hand, Daily and Harrison (1948) regarded the abolishment of compensatory splanchnic vasoconstriction during experimental hyperthermia as a significant event which, in the present study, is manifested in a dramatic secondary reduction in total vascular resistance (Section 5.3.2). The crucial abolishment of splanchnic vasoconstriction may be related to many factors e.g., observed hyperkalaemia under directly comparable experimental conditions (Burger, 1970b; Kielblock, 1972), local acidosis (Daily and Harrison, 1948; Rushmer, 1970), generalised acidosis (Burger 1972) or "autoregulatory escape" (Rushmer, 1970). Since the abolishment of splanchnic vasoconstriction may be regarded as an impairment of the circulation, it may "result in a further rise in core temperature" (Kew, 1976). The present findings substantiate this view in that the fall in vascular resistance at this stage is associated with a slight, but significant, reduction in skin temperature, an event which is interpreted to mean that the reduction in skin temperature occurs at the cost of a further elevation of core temperature (Section 5.3.2). In as much as this critical further elevation in core temperature may be directly attributable to the abolishment of splanchnic vasoconstriction, the ensuing tissue damage is the result of circulatory failure, as suggested by Frankel *et al*, (1963).

However, in view of the extensive damage which becomes evident in the organs of splanchnic circulation during experimental heatstroke (Burger, 1972), it is equally likely that the abolishment of splanchnic vasoconstriction may be explained solely in terms of local damage. In this sense, therefore, it would be

extremely difficult to establish a direct causal relationship between thermal damage and failure of splanchnic constriction in the light of the present experimental findings. In conjunction with the directly comparable studies of Burger (1972), the present findings do however suggest that the pathogenesis of heatstroke is related to an interaction of the preceding events. A tentative hypothesis is therefore presented that the initial sequence of events which lead to the establishment of heatstroke, is as follows: the beneficial effects of compensatory vasoconstriction during prolonged heat stress are largely cancelled by the development of local hypoxia, which is aggravated by a thermally stimulated increase in cellular respiration and consequent anaerobism. The liver appears to be the crucial organ in this context. Irrespective of the precise mechanism, splanchnic vasoconstriction is abolished. This results in a further increase in core temperature, which causes local tissue damage or compounds existing damage. This sequence is likely to constitute a primary vicious cycle and may occur in the *apparent absence of cardiovascular malfunction.*

5.5 *THE MECHANISM OF CARDIOVASCULAR FAILURE*

A review of the literature (Section 1.2.4) indicates that circulatory failure is not a consistent finding in heatstroke but rather the consequence of acute, prolonged exposure of the unacclimatised individual. The present findings (Section 5.4) suggest that while overt circulatory failure may not necessarily be a consistent finding, inapparent cardiovascular malfunction may constitute a significant event in the pathogenesis of heat-

stroke. On the other hand, gross cardiovascular failure has been observed to precede death in many instances of human heatstroke (O'Donnell and Clowes, 1972) and it therefore seems necessary to review the entire mechanism of cardiovascular failure in its widest perspectives.

The mechanism of cardiovascular failure during the physiological stress imposed by heat is explained in terms of two apparently contradictory mechanisms. Daily and Harrison (1948) were led to conclude that the observed collapse was primarily due to underfilling of a generally dilated capillary bed. This led to the concept of "peripheral pooling". In 1960, however, Gold postulated a novel hypothesis, namely that " ... the primary event in circulatory failure of heat pyrexia is high-output cardiac failure" and that "high-output failure is the triggering mechanism of circulatory failure". Further attempts to elucidate the precise mechanism of failure have not met with much success. For example, the data obtained by O'Donnell and Clowes (1972) fail to support either the concept of peripheral pooling or whether cardiac failure is due to a myocardial defect or to elevated pulmonary vascular resistance. The latter researchers concluded that the mechanism of cardiovascular failure still had not been established beyond doubt. Further confusion is apparently created when considering the treatment of hypotension incident to heatstroke. According to Knochel (1974) "the pronounced peripheral vasodilatation during hyperpyrexia will often respond to cooling alone (but) large quantities of ... plasma expanders ... may overload the central circulation" and "if hypotension persists after cooling,

appropriate agents used in therapy of cardiogenic shock should be administered since the patient may have myocardial damage ..."

Since there seems to be no reason to doubt the efficacy of the therapy advocated by Knochel (1974), it is likely that doubt should be cast on any view which rigidly implicates a specific mechanism to the total exclusion of any other. This in turn suggests that circulatory failure in heat may be explained in terms of a unified mechanism, albeit one more complex.

The present findings substantiate a unified concept of circulatory failure. Assuming that the current experimental model is representative of the entire spectrum of the physiological stress of heat, including its ill effects, the existence of a unified concept of circulatory failure may be deduced by relating the sequence of circulatory events observed in the present study to clinical and experimental correlates associated with heatstroke.

If animals had been withdrawn during the hyperkinetic stage (Section 5.3.2), the mean arterial pressure would have been normal or even hypertensive, as reported in heatstroke cases (Ferguson and O'Brien, 1956). Overt circulatory failure would have been absent (Minard and Copman, 1963) although signs indicative of slight cardiac impairment may have been present (Kew *et al*, 1969). The vascular resistance would have been low (O'Donnell and Clowes, 1972) probably as a result of splanchnic vasodilatation (Daily and Harrison, 1948). Body temperature would be consistent with levels reported in human

heatstroke (Shibolet *et al*, 1962) while both clinical and experimental analyses would have confirmed hepatic and renal damage (Kew, 1969; Burger, 1972).

The above is probably a fair description of most of the cardinal signs generally associated with heatstroke. The circulatory picture corresponds to peripheral pooling and a lowering of the cardiac reserve, which, according to Daily and Harrison (1948), constitutes the mechanism of circulatory failure in heat. Moreover, cardiac damage is "not sufficiently severe for overt cardiac failure to occur" (Kew *et al*, 1969). However, if the animals had been withdrawn subsequently, it is clear that the prognosis would have worsened considerably by the "occasional complication" of circulatory failure (Minard and Copman, 1963). The circulatory failure could have been referable to a high-output cardiac failure (Gold, 1960) or to a myocardial defect (Moore *et al*, 1966). Tissue damage would have been more extensive (Malamud *et al*, 1946), an observation which is substantiated by animal studies (Burger, 1972). Convulsions, Cheyne-Stokes breathing and profound hyperthermia associated with hypotension, precede death.

The preceding arguments are interpreted to mean that circulatory failure is not exclusively peripheral, nor is it exclusively central (cardiac). Moreover, the circulatory status during heatstroke is probably an indicator of the severity of heatstroke, the initial stages being characterised by inapparent "peripheral failure", with more advanced stages including cardiac failure. Thus, while overt circulatory

failure may be ascribed solely to a high-output cardiac failure, as proposed by Gold (1960), the present findings do not subscribe to the notion that it is the "primary event" in circulatory failure. In fact, the present findings suggest that cardiac failure is the result of vascular failure and it is deduced that the primary event in circulatory failure is the abolishment of splanchnic vasoconstriction. It remains but to point out that overt circulatory failure, in conjunction with the incident hypotension and cellular hypoxia, probably constitutes the final and fatal insult to already thermally-jeopardised tissues, as also reported by Kew (1969).

An internal redistribution of the cardiac output through the abolishment of compensatory splanchnic vasoconstriction, may lead to inadequate cardiac filling in the present circumstances and which, in turn, gives rise to a fall in cardiac output. According to Cohn (1978), this is the most common cause of shock, prompt clinical improvement being achieved by rapid plasma volume expansion (Cohn *et al*, 1967). While the above sequence of events is not disputed, it is equally clear that it does not explain the ultimate fall in cardiac output observed in the present study (*vide infra*).

The present findings indicate that a hyperkinetic circulation is established at the commencement of the crucial further fall in vascular resistance (Section 5.3.2). The concurrent elevation in mean arterial pressure is regarded as a manifestation of overcompensation. It is evident that the extent of overcompensation is chiefly related to a disproportionate increase

in stroke volume, which, under these circumstances, is in turn a manifestation of a circulatory crisis (Bishop *et al*, 1955; Gold, 1960; Rushmer, 1970). However, the consequence of this adaptation is that myocardial oxygen demand outstrips the supply thereof (ST-segment depression, QT_c-prolongation) which in turn elicits an augmented sympathetic discharge (Schlant, 1978b), as evidenced in a further increase in contractility (PEP/ET_c). A vicious cycle is initiated, the inevitable sequel to which is cardiac failure.

The present findings tend to substantiate the occurrence of cardiac damage, as judged by the significant terminal decline in myocardial oxidative capacity. The implication is that although direct thermal damage cannot be excluded, such damage may be compounded from a non-thermal origin. The underlying mechanism is probably related to excessive ATP-hydrolysis (Fleckenstein *et al*, 1974) which may eventually lead to irreversible catecholamine-induced cardiac damage and necrosis (Fleckenstein *et al*, 1974; Mosinger *et al*, 1978). However, it is clear that irrespective of the ultimate origin of cardiac damage, cardiac failure is primarily referable to excessive sympathetic/catecholamine discharge. The relevance of this observation is not restricted to the present study: according to Gilbert (1978), stroke volume has been observed to increase during hyperthermia in man despite a fall in right sided filling pressure, an event which suggested some "positive inotropic stimulation". In the light of the present findings the ominous portent of such an event, when associated with overcompensation, cannot be ignored.

One of the objectives of this study was to evaluate two radically opposed theories concerning the mechanism of circulatory failure in heat and the controversies that surround them. The present findings suggest that to explain the mechanism of failure as being either "peripheral" (noncardiac) or "cardiac" in origin is inadequate and inaccurate. It suggests that the mechanism of circulatory failure be explained in terms of a unified concept wherein different concepts are embraced within the principle of positive feedback. In essence the mechanism proposed is neither novel nor controversial. Although more complex, it is surely less rigid and certainly more definitive.

5.6 RESUMÉ

The clinical and experimental manifestations of heatstroke are well-documented and, although not established beyond doubt, it is clear that the pathogenesis of the widespread tissue damage is referable to a complex interlock of direct thermal effects and subcellular responses. This constitutes the so-called "multifactorial" hypothesis advocated by Bělehrádek (1967) and Burger (1972). In this sense, the present study is not directly concerned with the pathogenesis of tissue damage associated with heatstroke.

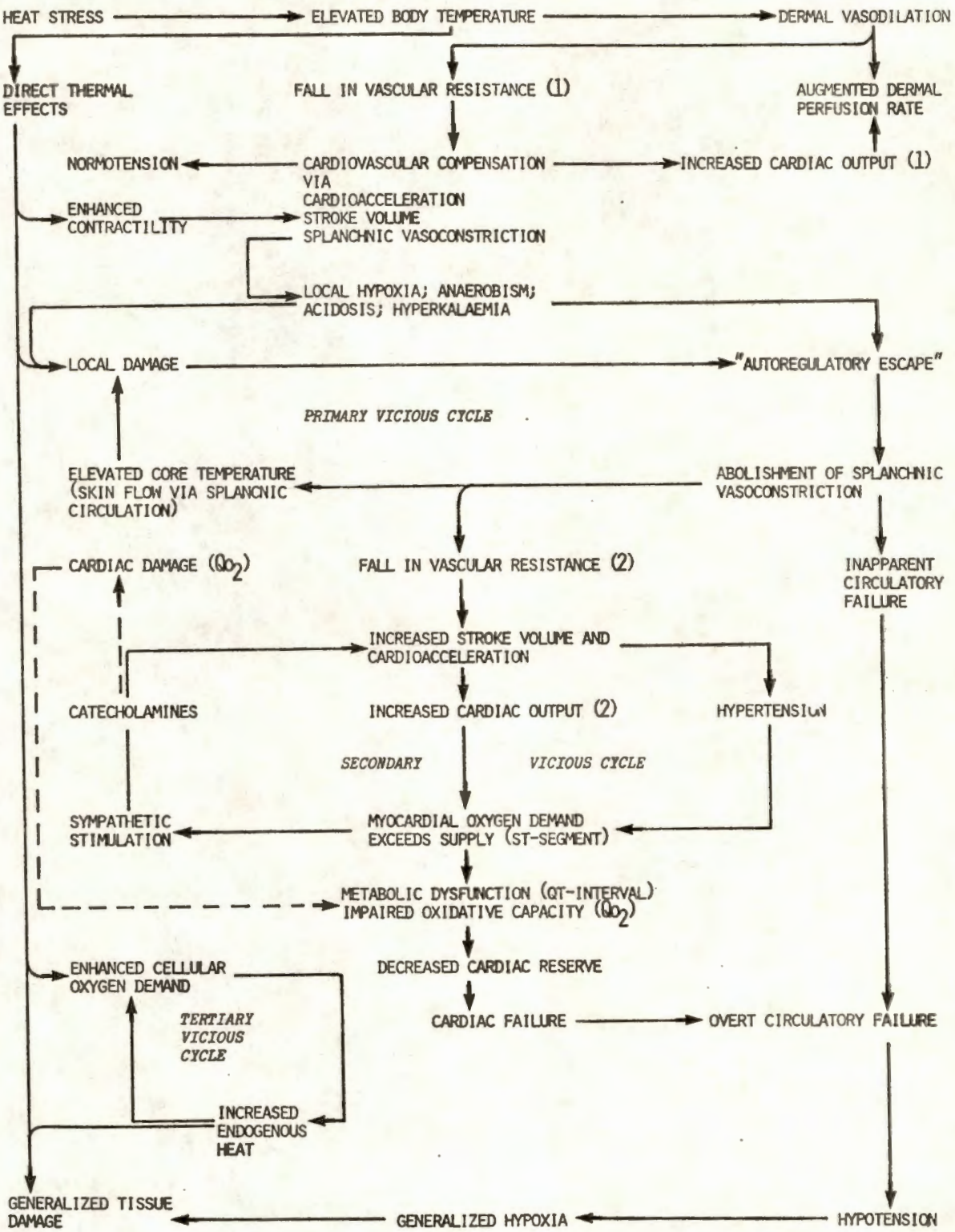
The objectives of this study stem from the fact that much of the enigma of heatstroke is seated in its notoriously mercurial onset. Despite the fact that the circulation constitutes the "first line of defence" against an elevation in

body temperature, it is not consistently implicated in heatstroke (Minard and Copman (1963), even in the presence of signs of cardiac damage (Kew *et al*, 1969). In as much as it was then argued that the genesis of heatstroke may be referable to a transient or "inapparent" failure of the circulation, this hypothesis was investigated. An analysis of cardiovascular function was consequently undertaken to include not only the normal response pattern to heat and ultimate failure, but also the prodromal period in particular. The objectives may now be stated with some clarity, namely (a) the relationship between heat exposure and cardiovascular performance (Section 5.3), (b) the possible role of circulatory malfunction in the genesis of heatstroke (Section 5.4) and (c) in view of certain controversial aspects, the mechanism of cardiovascular failure (Section 5.5). The use of an animal model is obvious.

A resumé of the major findings of this study is presented in Figure 5.2. The occurrence of certain events is deduced from the literature while certain others are based on directly comparable investigations, notably that of Burger (1972). The scheme presented is naturally not complete, nor is it intended to be so. Emphasis is placed on the establishment of three fundamental positive feedback loops (vicious cycles).

The primary vicious cycle is initiated by at least two independent inputs, namely local thermally-induced tissue damage during the period of diminished splanchnic blood flow, and such factors which may collectively elicit autoregulatory escape of splanchnic constriction. The former input implies

FIGURE 5.2 CARDIOVASCULAR FUNCTION AND MALFUNCTION DURING PROGRESSIVE HEAT STRESS



that the primary event in the genesis of heatstroke is direct thermal damage, which may be aggravated by local hypoxia. Both clinical (Herman and Sullivan, 1959; Kew, 1969) and experimental (Burger, 1972) evidence suggests that the liver is the primary site of damage. However, the possibility exists that the abolishment of splanchnic vasoconstriction by autoregulatory escape may well potentiate a critical increase in core temperature and subsequent damage. Daily and Harrison (1948) regard the abolishment of splanchnic vasoconstriction as a significant event and, in as much as it may constitute an "impairment" of the circulation (Kew, 1976), this event may be of equal significance in the genesis of heatstroke. That the primary failure may well be of circulatory origin, is in agreement with the views of Frankel *et al* (1963) as well as those of Hubbard *et al* (1978).

The findings of Burger (1972) may be interpreted to imply that the primary input is tissue damage to the organs of the splanchnic circulation. It is also conceivable that the crucial release of vasoconstrictor tone is referable to local damage. However, it is clear that although inapparent circulatory failure may not necessarily be implicated primarily, *its occurrence constitutes an important link in the genesis of tissue damage*. Circumstantial evidence therefore suggests that the establishment of the primary vicious cycle is of fundamental importance in the pathogenesis of heatstroke.

The fall in vascular resistance may be regarded as an important consequence of the establishment of the primary vicious cycle

in as much as it may potentiate the secondary vicious cycle. In its mildest form, the second vicious cycle is manifested in a slight decrease in cardiac reserve (Daily and Harrison, 1948), signs of cardiac damage (Kew *et al*, 1969) and normo- or hypertension (Ferguson and O'Brien, 1956). In the strictest sense of the word, this is not a vicious cycle but rather the manifestation of the extent of cardiac compensation. The prevailing situation substantiates the view that heatstroke may occur in the complete absence of signs indicative of circulatory failure (Minard and Copman, 1963). However, reduction in cardiac reserve, the extent of which is probably related to the intensity of the primary vicious cycle, may trigger the advent of the secondary vicious cycle, as indicated in Figure 5.2. The inevitable outcome is cardiac failure and consequently, overt circulatory failure.

The present findings suggest that the observed circulatory failure was directly attributable to the establishment of the secondary vicious cycle and its occurrence therefore supports the extent of cardiac involvement referred to by Gold (1960), Moore *et al*, (1966) and by implication, Gilbert (1978). The establishment of the secondary vicious cycle is likely to represent an advanced stage of heatstroke, as evidenced by the observation of O'Donnell and Clowes (1972), namely that in more than 80% of cases of human heatstroke, death was preceded by overt circulatory failure.

Although direct thermal effects cannot be excluded (Shibolet *et al*, 1967; Sohar *et al*, 1968), tissue damage may be

aggravated by the establishment of a tertiary vicious cycle (Figure 5.2) in accordance with the views of Belding (1967), and further compounded by a generalised hypoxic stage incident to hypotension (Kew, 1976).

An analysis of Figure 5.2 indicates that the reduction in vascular resistance through the primary vicious cyle provides links that possibly lead to the establishment of both secondary and tertiary vicious cycles. Although the tertiary cycle may be initiated independently of the primary, it is nevertheless concluded that the pathogenesis of heatstroke is fundamentally related to the establishment of the primary vicious cycle. In this sense, inapparent circulatory malfunction constitutes a significant factor in the advent of heatstroke, although it may not be the actual trigger mechanism.

The final question concerns the mechanism of circulatory failure. Firstly, circumstantial evidence does not support the contention that the primary factor in heatstroke is exclusively circulatory (*vide supra*). However, the present findings do suggest that the critical fall in total vascular resistance provides the most important link between those factors which potentiate the abolishment of splanchnic vasoconstriction and gross tissue damage. The primary circulatory event is therefore peripheral in origin; not cardiac. However, it is also evident that cardiac damage, either covert or overt, heat-induced or "self-inflicted" (catecholamines?), is intimately linked to the reduction in vascular resistance incident to the release of splanchnic vasoconstrictor tone. For this reason,

and in view of the controversies and confusion surrounding this aspect, it is proposed that the mechanism of overt cardiovascular failure in heat be explained in terms of a unified concept wherein cognizance is taken of the complexity of positive feedback interlocks.

The scheme presented in Figure 5.2 is not complete and is probably an oversimplification. It is based on an animal model which, by implication, is cautiously extrapolated to man. It considers neither variations in the environmental heat load nor the degree of physiological acclimatisation. It does not consider variables such as age or sex. It assumes an intact cardiovascular system. It is nevertheless concluded that it provides a simple, yet reliable framework which may serve to demonstrate clearly the association between the integrity of the cardiovascular system and the pathogenesis of heatstroke.

S U M M A R Y

Heatstroke is characterised by a notoriously mercurial onset so that little or no knowledge of the prodromal period exists. This study, therefore, represents an attempt to elucidate some aspects of the prodromal period of heatstroke. In as much as the integrity of the cardiovascular system may be regarded as the most critical determinant of man's defence against an environment-induced elevation in body temperature, the current emphasis falls on cardiovascular function and malfunction. The choice of an animal model is obvious.

In this study anaesthetised male albino rats of about 275g were subjected to an environmental temperature of 45^{o}C (ambient humidity) until circulatory failure occurred. During this period, body core and skin temperatures were monitored simultaneously with various electrocardiographic and haemodynamic parameters of cardiovascular function. Myocardial oxidative capacity was assessed by the Warburg technique. In order to establish whether irreversible, albeit inapparent, changes might occur during the initial period of heat exposure, myocardial electrolyte balance (K^{+} and Na^{+}) was measured (flame spectrophotometry) during heat exposure as well as up to 48 hours subsequent to heat exposure. Statistical analysis of the data was performed by an analysis of variance, statistically significant findings being further subjected to polynomial regression analyses.

The influence of Na-pentobarbitone anaesthesia on normal thermoregulatory activity was investigated over the entire spectrum of thermal stress (normo-, hypo- and hyperthermia). Although statistically significant changes were observed, the general impression is that the adverse effects of anaesthesia are abolished more rapidly during hyperthermia than in any other thermal condition. It was consequently concluded that the extent of suppression was negligible and that the experimental model, in a physiological sense, remained valid.

An analysis of the results of the main study reveals the existence of three distinct, albeit overlapping, stages of circulatory responses. The first stage (0+50 minutes) is characterised by well-adjusted homeostatic compensation. Despite significant elevations in myocardial K^+ and Na^+ content, these changes were found to be completely reversible on the basis of 48-hour survival studies. Myocardial oxidative capacity remained unimpaired.

The second stage (50-70 minutes) is characterised by the establishment of a hyperkinetic circulation. The elevation in mean arterial pressure, in the face of a further reduction in vascular resistance (abolishment of splanchnic vasoconstriction) is tantamount to overcompensation. Circumstantial evidence suggests that sympathetic discharge becomes excessive and, as such, may constitute the primary trigger in eventual cardiac failure. Myocardial oxygen demand exceeds the supply thereof (ST-segment depression) while signs indicative of a metabolic derangement become evident (QT_c-prolongation). At

the end of this period, myocardial oxidative capacity (Q_{O_2}) is significantly reduced. This stage was associated with the advent of heatstroke and it is therefore concluded that the prodromal period may constitute a very rapid transition between uncomplicated hyperthermia and heatstroke.

During the final stage, overt circulatory failure occurs. Myocardial oxidative capacity is severely depleted. The reduction in cardiac output exceeds the fall in mean arterial pressure, a finding which suggests that overt circulatory failure may be directly attributed to cardiac failure. In the absence of any electrocardiographic signs to the contrary (conductivity disturbances), it is concluded that cardiac failure is referable to acute metabolic dysfunction.

The results of this study, in conjunction with the relevant literature, lead to the following final conclusions:

a. The data in this study may cautiously be extrapolated to man.

b. The primary sites of tissue damage are the organs of the splanchnic circulation.

c. The abolishment of compensatory splanchnic vasoconstriction is instrumental in the genesis of the characteristic, widespread tissue damage associated with heatstroke.

d. Inapparent circulatory failure may be masked by the general competence of the heart. Diastolic pressure

is a poor reflection of changes in vascular resistance during this stage.

e. Cardiac failure may be referable to a catecholamine-induced positive feedback loop, and damage may be compounded by the hyperpyrexic state.

f. It is proposed that the mechanism of circulatory failure in heat be explained in terms of a unified concept of failure which takes into account the successive interlock of several positive feedback loops, thus obviating the apparent confusion created by the term "cardiac *or* peripheral in origin."

O P S O M M I N G

Hittesteek word gekenmerk deur 'n uiters snelle ontstaan sodat weinig of geen kennis van die prodromale periode ingewin kan word. Die huidige studie verteenwoordig derhalwe 'n poging om sekere aspekte van die prodromale periode van hittesteek op te klaar. In soverre dat die integriteit van die kardiovaskulêre sisteem beskou mag word as die mees kritiese faktor in die mens se fisiolgiese verdedigingslinie teen 'n omgewing-geïnduseerde toename in liggaamstemperatuur, word kardiovaskulêre funksie en wanfunksie in die huidige studie beklemtoon. Die keuse van 'n diermodel spreek vanself.

In die huidige studie is genarkotiseerde manlike albino-rotte van ongeveer 275g blootgestel aan 'n omgewingstemperatuur van 45^{o}C (heersende humiditeit) totdat kardiovaskulêre ineenstorting plaasgevind het. Tydens hierdie periode is liggaamskern- en veltemperature gemonitor tesame met verskeie elektrokardiografiese en hemodinamiese parameters van kardiovaskulêre funksie. Miokardiale oksidatiewe kapasiteit is bepaal deur middel van die Warburg-tegniek. Om vas te stel of onomkeerbare, dog onopsigtelike veranderinge tydens die aanvanklike blootstellings-periode intree, is miokardiale elektrolietbalans (K^{+} en Na^{+}) bepaal (vlamspektrofotometrie) tydens hitteblootstelling asook tot 48 uur na blootstelling. Die resultate is statisties ontleed deur middel van 'n analise van variansie. Statisties betekenisvolle veranderinge is vervolgens onderwerp aan 'n polinomiale regressie-analise.

Die invloed van Na-pentobarbitoonnarkose op normale temperatuurbeheer is oor die hele spektrum van termiese spanning ondersoek (normo-,hipo- en hipertermie). Hoewel statisties betekenisvolle veranderinge waargeneem is, is die algehele indruk verkry dat die nadelige effekte van narkotisering sneller opgehef word tydens hipertermie as tydens enige ander termiese toestand. Die afleiding is derhalwe gemaak dat die omvang van onderdrukking minimaal is en dat die eksperimentele model in 'n fisiologiese sin geldig bly.

'n Ontleding van die resultate van die hoofstudie dui daarop dat die kardiovaskulêre reaksies tydens hitteblootstelling onderverdeel kan word in drie duidelik afgebakende, dog oorvleuelende fases. Die eerste fase (0+50 minute) word gekenmerk deur doeltreffende homeostatiese kompensasie. Ongeag die betekenisvolle toenames in miokardiale K^+- en Na^+-inhoud, dui die 48-uur oorlewingstudie op volkome omkeerbaarheid. Miokardiale oksidatiewe kapasiteit verloop normaal.

Die tweede fase (50-70 minute) word gekenmerk deur die totstandkoming van 'n hiperkinetiese bloedsomloop. Die toename in die gemiddelde arteriële bloeddruk, in die teenwoordigheid van 'n verdere afname in vaskulêre weerstand (opheffing van splangniese vaatvernouing), is verteenwoordigend van oorkompensasie. Omstandigheidsgetuienis dui op oormatige simpatiese ontlading wat, as sodanig, waarskynlik die primêre snellermeganisme tot uiteindelike hartversaking is. Miokardiale suurstofaanvraag oorskry die voorsiening daarvan (ST-segmentverlaging) terwyl tekens van metaboliese afwykings

waarneembaar word (QT_c-verlenging). Aan die einde van hierdie fase is miokardiale oksidatiewe kapasiteit betekenisvol ingekort. Hierdie fase is geassosieer met die totstandkoming van hittesteek en daar is gevolglik afgelei dat die prodromale periode 'n uiters snelle oorgang tussen ongekompliseerde hipertermie en hittesteek konstitueer.

Die finale fase word gekenmerk deur uitgesproke kardiovaskulêre ineenstorting. Miokardiale oksidatiewe kapasiteit ondergaan 'n verdere inkorting. Die afname in die kardiale omset oorskry die afname in die gemiddelde arteriële druk. Hierdie waarnemings dui daarop dat die uitgesproke ineenstorting van die bloedsomloop direk te wyte is aan hartversaking. In die afwesigheid van elektrokardiografiese tekens van geleidingsdefekte, is daar afgelei dat hartversaking toe te skryf is aan metaboliese wanfunksie.

Op grond van die huidige bevindings, asook die betrokke literatuur, is die volgende finale afleidings gemaak:

a. Die bevindings van die huidige studie is met voorbehoud ekstrapoleerbaar na die mens.

b. Die primêre setels van weefselskade is die organe van die splangniese omloop.

c. Die opheffing van kompensatoriese splangniese vaatvernouing is instrumenteel in die genese van die karakteristieke wydverspreide weefselskade geassosieer met hittesteek.

d. Onopsigtelike kardiovaskulêre ineenstorting mag verberg word deur die algemene intaktheid van hartfunksie. Onder hierdie omstandighede is diastoliese bloeddruk 'n swak parameter van vaskulêre weerstand.

e. Hartversaking mag herlei word tot 'n katesjolamiengeïndusserde positiewe terugkoppeling. Hartskade kan verder gekompliseer word deur direkte termiese effekte.

f. Daar word voorgestel dat die meganisme van kardiovaskulêre ineenstorting tydens hittespanning verklaar word in terme van 'n verenigde konsep van ineenstorting waarin die opvolgende aaneenskakeling van verskeie positiewe terugkoppelingsiklusse in ag geneem word, 'n beskouing wat die klaarblyklike verwarring geskep deur die begrip "kardiaal *of* perifeer", elimineer.

A P P E N D I X 1

STATISTICAL ANALYSES OF THE INFLUENCE OF SODIUM PENTOBARBITONE ANAESTHESIA ON METABOLIC RATE

	Metabolic Rate ($C/h/m^2$)					
	NU	NA	HU	HA	CU	CA
	24,60	16,25	15,89	8,18	17,21	19,87
	26,43	15,25	12,38	12,44	22,48	22,77
	21,69	13,10	13,77	11,97	21,40	17,40
	27,86	13,65	15,46	14,71	19,57	23,39
	20,95	15,25	17,92	13,71	19,85	20,18
	22,58	18,22	16,54	10,23	23,06	23,10
	22,33	16,28	14,62	8,95	15,22	20,75
Mean:	23,78	15,43	15,23	11,46	19,83	21,07

Prefix N: normothermia Suffix U: unanaesthetised

H: hyperthermia A: anaesthetised

C: hypothermia

The above data were treated as a 2×3 factorial experiment. For purposes of identification, the three temperatures (N,H and C) are referred to as T, the temperature factor, while A represents the anaesthesia factor with two levels, U and A. An analysis of variance of the data is given below:

Source of Variation	d.f.	Sums of Squares	Mean Square	F-ratio
T	2	421,9470	210,9735	40,00
A	1	138,1035	138,1035	26,18
TA	2	160,9560	80,4781	15,26
Error	36	189,8868	5,2746	
Total	41	910,8933		

From tables of the F-distribution it is clear that the main effects of T and A, and the interaction TA, are highly significant (at a level of significance of P = 0,01).

The significance of the interaction TA implies that the effect of anaesthesia on the mean metabolic rate of animals depends on the temperature. To determine the nature of the dependence, the following procedures were followed after having summarised the mean metabolic rates for the respective groups:

		Temperature		
		N	H	C
Anaesthesia	U	23,78	15,23	19,83
	A	15,43	11,46	21,07
Difference (U-A)		8,35**	3,77*	-1,24

** Significant at 1% level of significance.

* Significant at 5% level of significance.

These figures were compared with the critical values calculated using Scheffé's method of multiple comparisons (Scheffé, 1959):

The 1% critical value = 3,98

The 5% critical value = 3,14

A difference is significant if greater than the critical value. The following differences show the change in metabolic rate due to anaesthesia from one temperature to another:

	NU-NA-(HU-HA)	NU-NA-(CU-CA)	HU-HA-(CU-CA)
Difference:	4,50*	9,59**	5,01*

The critical value at a 1% level of significance is 5,62 and 4,44 at a 5% level of significance. The response to anaesthesia changes significantly from N to H, N to C and H to C.

A P P E N D I X 2

STATISTICAL ANALYSIS OF THE INFLUENCE OF SODIUM PENTOBARBITONE ANAESTHESIA ON MYOCARDIAL OXYGEN CONSUMPTION

For the purpose of subjecting the relevant data reported in Chapter 3 to an analysis of variance, the following designations were made:

a. G (groups): C_1 - normal control
C_2 - anaesthetised control

b. I (incubation times): 10; 20; 30; 40; 50 and 60 minutes.

c. E (experiments): 5 in each case, each experiment conducted in triplicate.

Source of variation	Degrees of freedom	Sums of squares	Mean square	
G	1	2,0694	2,0694***	
I	5	26,6263	5,3253***	
GI	5	0,5561	0,1112	NS
E	48	9,7832	0,2038	NS
Residual	114	14,7818	0,1296	
Total	173	53,8168		

*** Significant at the 0,1% level

NS Not significant.

The analysis indicates that the difference in myocardial oxygen consumption between the two groups is highly significant (G). Moreover, myocardial oxygen consumption changes significantly over the period of incubation (I) but this change is not influenced by anaesthesia (GI). Finally, repetitions within an experiment did not exhibit significant differences (E).

A P P E N D I X 3

OBSERVED F-VALUES FOR ANALYSIS OF VARIANCE OF BODY TEMPERATURE AND CIRCULATORY RESPONSES TO HEAT EXPOSURE

Measurement	F-value	Measurement	F-value	Measurement	F-value
T_c	129,60	QRS ^{o}	1,07^{NS}	QS_1	4,62
T_s	116,68	QRS(mV)	0,61^{NS}	QS_{1-c}	1,30^{NS}
T_m	262,25	P_s	8,98	PEP	12,19
S	59,09	P_d	3,80	ET	6,62
PQ	4,14	P_p	8,45	ET_c	1,79^{NS}
QT	0,91^{NS}	P_m	6,83	PEP/ET_c	3,23
QT_c	5,53	P_x	5,90	DT	10,64
R-I	0,16^{NS}	P_{es}	4,07	S_1S_2	14,59
R-II	1,21^{NS}	P_s-P_{es}	11,21	QS_2	14,42
R-III	0,18^{NS}	S_a/D_a	1,81^{NS}	S_2Q	6,46
R-t	0,77^{NS}	$T(S_a+D_a)$	1,33^{NS}	QS_2/S_2Q	1,80^{NS}
S-I	0,33^{NS}	dP/dt_{max}	1,40^{NS}	f/P_m	2,56
S-II	0,46^{NS}	dP/dt_c	1,09^{NS}	SV	2,36
S-III	0,71^{NS}	dP/dt_{mean}	12,26	Q	4,99
S-t	1,12^{NS}	f	16,67	R	3,46

F-value	2,05	2,74	3,03
Level of significance	5%	1%	0,5%

NS: Not significant

NOTE: The above abbreviations are explained in Appendix 5

A P P E N D I X 4

STATISTICAL ANALYSIS OF THE INFLUENCE OF HEAT STRESS ON MYOCARDIAL OXYGEN CONSUMPTION

For the purpose of subjecting the relevant data reported in Chapter 4 to an analysis of variance, the following designations were made:

a. L (levels of stress): B (40 min.); C (70 min.); D (80 min.).

b. I (incubation times): 10; 20; 30; 40; 50 and 60 min.

c. G (groups): C_1 - normal control
C_2 - anaesthetised control
E - experimental animals

d. E (experiments): 5 in the case of B (each in triplicate) and 10 each in the case of C and D (each in duplicate).

Source of Variation	Degrees of freedom	Sums of Squares	Mean square	
L	2	20,8453	10,4226	***
I	5	137,7342	27,5468	***
I_L	1	123,1945	123,1945	***
I_Q	1	13,9728	13,9728	***
Remainder	3	0,5670	0,1890	NS
LI	10	2,0890	0,2089	NS
G	2	18,9224	9,4612	***
LG	4	4,8710	1,2177	***
IG	10	0,7187	0,0719	NS
LIG	20	0,4395	0,0220	NS
E	396	121,8370	0,3077	*
Residual	450	38,4470	0,0854	
TOTAL	898	345,9041		

*		Significant at 5% level.
**		Significant at 1% level.
***		Significant at 0,1% level.
I_L	=	Linear component of fitted curve.
I_Q	=	Quadratic component of fitted curve.
NS	=	Not significant.

a. SIGNIFICANCE OF LEVELS OF STRESS

Levels	B	C	D
Means	2,28	2,22	1,93

TABLE OF DIFFERENCES

	C	D
B	0,06 NS	0,35 ***
C		0,29 ***

Scheffe's method of multiple comparisons were used to establish significant differences.

b. SIGNIFICANCE OF GROUPS

Groups	C_1	C_2	E
Means	2,52	2,41	2,13

	C_2	E
C_1	0,11 ***	0,39 ***
C_2		0,28 ***

Same as above

c. SIGNIFICANCE OF INCUBATION TIME

Using the method of orthogonal polynomials it was found that a second degree polynomial could be fitted to the incubation time means. The table below gives observed means and corresponding fitted values.

Time	10	20	30	40	50	60
Observed Mean	2,84	2,40	2,05	1,90	1,79	1,72
Fitted Value	2,82	2,41	2,09	1,88	1,77	1,74

d. SIGNIFICANCE OF LEVELS - GROUPS INTERACTION

Table of Means for LG Interaction

	B	C	D
C_1	2,32	2,43	2,07
C_2	2,27	2,22	2,06
E	2,26	2,01	1,66

Table of Differences

	B-C	B-D	C-D
C_1-C_2	-0.16	0,04	0,21 **
C_1-E	-0,36 ***	-0,35 ***	0,01
C_2-E	-0,20 *	-0,39 ***	-0,19 **

Differences were tested using Scheffe's method of multiple comparisons.

CONCLUSIONS

1. Levels of stress (L): There is a significant difference (P<0,1) between D and, B and C, respectively, but not between B and C with respect to mean Q_{O_2}. This applies to a combination of C_1,C_2 and E.
2. Groups (G): Each of C_1,C_2 and E differ significantly (P<0,1) from one another. (See also Note 4 below).
3. Incubation time (I): The mean decrease in Q_{O_2} over the time of incubation follows a quadratic curve (See Figure 4.7), and this pattern holds true for all groups irrespective of the level of stress.

4. Group and stress level interaction (LG):

   (a) The significant difference between C_1 and C_2 described in 2 above is mainly attributed to the difference between C_1 and C_2 at level C.

   (b) The relative difference between C_1 and C_2 does not change significantly from stress level B to C and from B to D, respectively.

   (c) The difference between C_1 and E is not relevant to this study.

   (d) The relative change in mean Q_{O_2} between C_2 and E at stress level B is not significant. However, this relative change becomes significant ($P<0,5$) when the level of stress is increased from B to C and even more so ($P<0,1$) when the level of stress is changed from B to D and from C to D, respectively.

A P P E N D I X 5

ABBREVIATIONS

A	:	Body surface area
ALT	:	Alanine aminotransferase (GPT)
AST	:	Aspartate aminotransferase (GOT)
$A\text{-}V\text{-}O_2$	:	Arteriovenous oxygen difference
CK	:	Creatine kinase
car	:	Carotid artery
cath	:	Catheter
D_a	:	Diastolic area of pressure pulse
DB	:	Dry-bulb temperature
DT	:	Diastolic time
dP	:	Change in pressure
dV	:	Change in volume
dP/dt_c	:	$(dP/dt_{max})\sqrt{P_d}$
dP/dt_{max}	:	Rate of pressure change to anacrotic shoulder upon left ventricular ejection
dP/dt_{mean}	:	Rate of pressure change to peak systolic pressure upon left ventricular ejection
EKG	:	Electrocardiogram
ET	:	Ejection time
f	:	Heart rate
F	:	Flow rate
IVCT	:	Intraventricular contraction time
LD	:	Lactate dehydrogenase
LOS	:	Level of significance
m	:	Body mass
NS	:	Not significant
PCG	:	Phonocardiogram
PEP	:	Pre-ejection period
P_s	:	Systolic pressure
P_d	:	Diastolic pressure
P_p	:	Pulse pressure

P_m	:	Mean arterial pressure
P_x	:	Anacrotic pressure
P_{es}	:	End-systolic pressure
Q	:	Cardiac output
Q_{O_2}	:	Myocardial oxidative capacity/oxygen consumption
QRS	:	Mean QRS vector
QS_1	:	Electromechanical coupling time
QS_2	:	Electromechanical systole
R	:	Total vascular resistance
RH	:	Relative humidity
R_t	:	Summated R waves (Leads I - III)
RR'	:	Cardiac cycle length
S	:	Body heat storage
S_a	:	Systolic area of pressure pulse
SD	:	Standard deviation
SEM	:	Standard error of the mean
S_1S_2	:	Mechanical systole
S_2Q	:	Electromechanical diastole
S_t	:	Summated S waves (Leads I - III)
SV	:	Stroke volume
T	:	Total area of pressure pulse
T_c	:	Core temperature
T_s	:	Skin temperature
T_m	:	Mean body temperature
WB	:	Wet-bulb temperature

A P P E N D I X 6

RECOMMENDATIONS

1. Despite having a common goal, many attempts to elucidate the pathogenesis of heatstroke result in apparent controversy. This seems largely referable to marked differences which encompass entire experimental models, and subsequent interpretations which are based only on such models and the specific parameters investigated, to the exclusion of others. The need for refined and flexible (animal) models is obvious, as evidenced in the recent studies of especially Hubbard and coworkers (Hubbard *et al*, 1974; 1976; 1977; 1978).

2. The current study indicates that cardiovascular malfunction may constitute a major factor in the genesis of heatstroke. Circumstantial evidence suggests that sympathetic discharge and/or catecholamine release becomes excessive. Further elucidation of these aspects seems to hold considerable merit.

3. The current study also places emphasis on the occurrence and implications of inapparent circulatory failure or alternatively, the extent of cardiovascular compensation, and the recognition thereof. The further development and application of non-invasive techniques to assess cardiovascular function, appears to be of paramount importance.

R E F E R E N C E S

AHMED, SS, GE LEVINSON, CJ SCHWARTZ & PO ETTINGER (1972):
Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man.
Circulation 46 : 559.

ANSARI, A, & GE BURCH (1969):
Influence of hot environments on the cardiovascular system.
Arch. Intern. Med. 123 : 371.

ASMUSSEN, E (1940):
The cardiac output in rest and work in humid heat.
Am. J. Physiol. 131 : 54.

AUSTIN, MG,& JW BERRY (1956):
Observations on 100 cases of heatstroke.
J.A.M.A. 161: 1525.

BAKER, AB,& SM HORVATH (1964):
The influence of water temperature on oxygen uptake by swimming rats.
J. Appl. Physiol. 19 : 215.

BARLOW, G, HP AGERSBORG & HE KEYS (1956):
Blood levels of 17-hydroxycorticosteroids in hyperthermic dogs.
Proc. Soc. Exp. Biol. Med. 93 : 280.

BASS, DE (1963):
Thermoregulatory and circulatory adjustments during acclimatization to heat in man.
In: Temperature. Its measurement and control in science and industry (Ed: CM Herzfeld). Vol. 3. Part 3. Biology and medicine, p. 299. Reinhold Publ. Corp.,New York.

BASS, DE,& A HENSCHEL (1956):

Responses of body fluid compartments to heat and cold. Physiol. Res. 36 : 128.

BAXTER, CR,& PE TESCHAN (1958):

Atypical heatstroke with hypernatremia, acute renal failure and fulminating potassium intoxication. Arch. Int. Med. 101 : 1040.

BELDING, HS (1967):

Resistance to heat in man and other homeothermic animals. In: Thermobiology (Ed: AM Rose), p. 479. Academic Press, London.

BĚLEHRÁDEK, J (1967):

Intermolecular aspects of the structural stability of protoplasm at the temperature extremes. In: The cell and environmental temperature (Ed: AS Troschin), p. 87. Pergamon Press, London.

BENSON, ES, EF FREIER, BE HALLAWAY & MJ JOHNSON (1956):

Distribution of fluid and electrolytes and concentration of actomyosin and other proteins in the myocardium of dogs with chronic congestive heart failure. Am. J. Physiol. 187 : 483.

BENZINGER, TH, C KITZINGER & AW PRATT (1963):

The human thermostat. In: Temperature. Its measurement and control in science and industry (Ed: CM Herzfeld). Vol. 3. Part 3. Biology and medicine, p. 637. Reinhold Publ. Corp., New York.

BERGLUND, LG,& RR GONZALEZ (1977):

Evaporation of sweat from sedentary man in humid environments.

J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 42 : 767.

BISHOP, JM, KW DONALD & OL WADE (1955):

Circulatory dynamics at rest and on exercise in hyperkinetic states.

Clin. Sci. 14 : 329.

BORDEN, DL, JF WADILL & GS GRIER (1945):

Statistical study of 265 cases of heat diseases.

J.A.M.A. 128 : 1200.

BLUMBERGER, KJ,& S MEINERS (1965):

Studies of cardiac dynamics.

In: Examination of the cardiac patient (Ed: AA Luisada), p. 4:372. McGraw-Hill, New York.

BRUCE, RA,& JB IRVING (1978):

Special electrocardiographic examination of the heart.

In: The heart, arteries and veins (Fourth edition) (Ed: Hurst *et al*), p. 336. McGraw-Hill, New York.

BURCH, GE (1946):

The influence of environmental temperature and relative humidity on the rate of water loss through the skin in congestive heart failure in a subtropical climate.

Am. J. Med. Sci. 211 : 181.

BURCH, GE,& A HYMAN (1957):

Influence of a hot and humid environment upon cardiac output and work in normal man and in patients with chronic congestive heart failure at rest.

Am. Heart J. 53 : 665.

BURCH, GE,& T WINSOR (1960):

A primer of electrocardiography (Fourth edition). Lea and Febiger, Philadelphia.

BURCH, GE, NP DE PASQUALE & AL HYMAN (1961):

Influence of temperature and oxygen concentrations in oxygen tents.

J.A.M.A. 176 : 1017.

BURGER, FJ (1972):

Die hittebeskadiging van die weefsels en van die intakte dier - 'n Biochemiese benadering.

D. Sc. Thesis. Potchefstroom University for C.H.E.

BURGER, FJ,& FM ENGELBRECHT (1966):

Metabolism of heart slices with special reference to the effect of hyperthermia.

S. Afr. Med. J. 40 : 124.

BURGER, FJ,& FM ENGELBRECHT (1967):

The tolerance of tissues to heat *in vitro*.

S. Afr. Med. J. 41 : 108.

BURGER, FJ,& FA FUHRMAN (1964a):

Evidence of injury by heat in mammalian tissues.

Am. J. Physiol. 206 : 1057.

BURGER, FJ,& FA FUHRMAN (1964b):

Evidence of injury to tissues after hyperthermia.

Am. J. Physiol. 206 : 1062.

BURGER, FJ, FM ENGELBRECHT & EM JORDAAN (1970a):

The *in vitro* oxygen uptake of tissues after hyperthermia.

S. Afr. Med. J. 44 : 148.

BURGER, FJ, FM ENGELBRECHT, EM JORDAAN & P BESTER (1970b):

Studies on the blood composition of hyperthermic animals.

S. Afr. Med. J. 44 : 524.

BURTON, AC (1935):

Human calorimetry: II. The average temperature of the tissues of the body.

J. Nutr. 9 : 261.

BYNUM, G, J PATTON, W BOWERS, I LEAV, D WOLFE, M HAMLET & M MARSILI (1977):

An anaesthetized dog heatstroke model.

J. Appl. Physiol. 43 : 292.

CASTELLANOS, A & RJ MEYERBURG (1978):

The resting electrocardiogram.

In: The heart, arteries and veins (Fourth edition)

(Ed: Hurst *et al*), p. 298. McGraw-Hill, New York.

CHARLIER, R (1971):

Antianginal drugs. Springer-Verlag, Berlin.

CHERRY, G,& MB MEINERS (1971):

The relationship to ventricular fibrillation of early tissue sodium and potassium shifts and coronary vein potassium levels in experimental myocardial infarction.

J. Thor. and Cardiovasc. Surg. 61 : 587.

CHIUEH, CC,& II KOPIN (1978):

Hyperresponsitivity of spontaneously hypertensive rats to indirect measurement of blood pressure.

Am. J. Physiol. 234 : H690.

CHRISTY, JH,& SD CLEMENTS (1978):

Endocrine and metabolic disorders.

In: The heart, arteries and veins (Fourth edition) (Ed: Hurst *et al*), p. 1734. McGraw-Hill, New York.

CLAGETT, AM (1944):

The electrocardiographic changes following artificial hyperpyrexia.

Am. J. Med. Sci. 208 : 81.

COHN, JN (1978):

Shock.

In: The heart, arteries and veins (Fourth edition) (Ed: Hurst *et al*), p. 716. McGraw-Hill, New York.

COHN, JN, MH LURIA, RC DADDARIO & FE TRISTANI (1967):

Studies in clinical shock and hypotension: V. Haemodynamic effects of dextran.

Circulation 35 : 316.

COLOCOUSIS, JS, LL HUNTSMAN & PW CURRERI (1977):

Estimation of stroke volume changes by ultrasonic Doppler.

Circulation 56 : 914.

COOK, EL (1955):

Epidemiological approach to heat trauma.

Milit. Med. 116 : 317.

CORDAY, E,& T-W LANG (1978):

Effect of arrythmias on the myocardium.

In: The heart, arteries and veins (Fourth edition)

(Ed: Hurst *et al*), p. 628. McGraw-Hill, New York.

DAILY, WM,& TR HARRISON (1948):

A study of the mechanism and treatment of experimental heat pyrexia.

Am. J. Med. Sci. 215 : 42.

DRILL, VA(1958):

Pharmacology in medicine (Second editon). McGraw-Hill, New York.

EICHLER, AC, AS McFEE & HD ROOT (1969):

Heat Stroke.

Am. J. Surg. 118 : 855.

EL HALAWANI, AW (1964):

Heat Illness. I. Heat illness during the Mecca pilgrimage.

World Health Org. Chron. 18 : 283.

ENGELBRECHT, FM (1964):

Praktiese handleiding vir fisiologiese chemie. AW Foyle, Cape Town.

FERGUSON, M,& MM O'BRIEN (1960):

Heatstroke in New York City: Experience with twenty-five cases. N.Y.J. Med. 60 : 2531.

FERRIS, EB, MC BLANKENHORN, HW ROBINSON & CE CULLEN (1938):

Heat stroke: Clinical and chemical observations on 44 cases.

J. Clin. Invest. 17 : 249.

FLECKENSTEIN, A, J JANKE, HJ DORING & O LEDER (1974):
Myocardial fibre necrosis due to intracellular Ca overload - A new principle in cardiac pathophysiology.
In: Recent advances in studies on cardiac structure and metabolism (Ed: NS Dhalla). Myocardial Biology 4 : 563.

FOLKOW, B, C HEYMANS & E NEIL (1965):
Integrated aspects of cardiovascular regulation.
In: Handbook of Physiology: Circulation Vol. 3
(Ed: WF Hamilton), p. 1787. Waverley Press, Baltimore.

FRANCH, RH (1978):
Cardiac catheterization.
In: The heart, arteries and veins (Fourth edition)
(Ed: Hurst *et al*), p. 479. McGraw-Hill, New York.

FRANKEL, HM, JP ELLIS & SM CAIN (1963):
Development of tissue hypoxia during progressive hyperthermia in dogs.
Am. J. Physiol. 205 : 733.

GARBUS, J, B HIGHMAN & PD ALTLAND (1964):
Serum enzymes and lactic dehydrogenase afer exercise and training in rats.
Am. J. Physiol. 207 : 467.

GARRARD, CL, AM WEISSLER & HT DODGE (1970):
The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease.
Circulation 42 : 455.

GELINEO, S (1964):

Organ systems in adaptation: The temperature regulating system.

In: Handbook of Physiology: Section 4: Adaptation to the environment (Ed: DB Dill), p.259. Waverley Press, Baltimore.

GILAT, T, S SHIBOLET & E SOHAR (1963):

Mechanism of heat stroke.

J. Trop. Med. Hyg. 66 : 204.

GILBERT, CA (1978):

Temperature and humidity, radiation, underwater environment, hyperbaric oxygen, and the cardiovascular system.

In: The heart, arteries and veins (Fourth edition)

(Ed: Hurst *et al*, p.1829. McGraw-Hill, New York.

GOLD, J (1960):

Development of heat pyrexia.

J.A.M.A. 173 : 1175.

GOLD, J (1961):

Unified system for evaluation and selection of heat stress candidates. II. Index for evaluation of subjects exposed to heat stress.

J. Appl. Physiol. 16 : 144.

GOLDBERG, LI, HK EZELL & RP WALTON (1952):

Electrocardiographic and serum potassium changes in fatal hyperthermia.

Am. Heart J. 44 : 754.

GOLDBERG, LI,& Y-Y HSIEH (1978):

Drugs acting on the autonomic nervous system.

In: The heart, arteries and veins (Fourth edition)

(Ed: Hurst *et al*), p. 1980. McGraw-Hill, New York.

GONZALEZ, RR, LG BERGLUND & AP GAGGE (1978):

Indices of thermoregulatory strain for moderate exercise in heat.

J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 44 : 889.

GORE, I, & NH ISAACSON (1949):

Pathology of hyperpyrexia: Observations at autopsy in 17 cases of fever therapy.

Am. J. Path. 25 : 1025.

GOTTWIK, MG, AF PARISI, J ASKENAZI & D McCAUGHAN (1978):

Computerized orthogonal electrocardiogram: Relation of QRS forces to left ventricular ejection fraction.

Am. J. Cardiol. 41 : 9.

GREENSPAN, K, CW WUNSCH & C FISCH (1965):

Relationship between potassium and vagal action on atrioventricular transmission.

Circulation Res. 17 : 39.

GUPTA, NN, RML MEHROTRA, & NLJ AGARWAL (1963):

Evaluation of functional and morphological status of liver during pyrexia.

J. Assoc. Physicians India 11 : 747.

GUYTON, AC (1963):

Circulatory physiology: Cardiac output and its regulation.

WB Saunders, Philadelphia.

GUYTON, AC, GG ARMSTRONG & PL CHIPLEY (1956):

Pressure-volume curves of the arterial and venous systems in live dogs.

Am. J. Physiol. 184 : 253.

HALES, JRS,& RAL DAMPNEY (1975):

The redistribution of cardiac output in the dog during heat stress.

J. Thermal Biology, 1 : 29.

HARDY, JD,& HT HAMMEL (1963):

Control system in physiological temperature regulation.

In: Temperature. Its measurement and control in science industry (Ed: CM Herzfeld). Vol. 3. Part 3. Biology and Medicine, p. 613. Reinhold Publ. Corp., New York.

HARLEY, A, CF STARMER & JC GREENFIELD (1969):

Pressure-flow studies in man. An evaluation of the duration of phases of systole.

J. Clin. Invest. 48 : 895.

HARRIS, WS (1974):

Systolic time intervals in the noninvasive assessment of left ventricular performance in man.

In: Cardiac mechanics: Physiological, clinical and mathematical considerations (Ed: Mirsky *et al*).

John Wiley and Sons, New York.

HASEEB, MA, & A FAYIZ (1958):

Fatal effects of heat on man.

J. Trop. Med. Hyg. 61 : 280.

HATCH, TF (1963):

Assessment of stress.

In: Temperature. Its measurement and control in science and industry (Ed: CM Herzfeld). Vol. 3. Part 3. Biology and medicine, p. 307. Reinhold Publ. Corp., New York.

HEARSE, DJ, LH OPIE, IE KATZEFF, WF LUBBE, TJ VAN DER WERFF, M PEISACH & G BOULLE (1977):

Characterization of the "border zone" in acute regional ischaemia in the dog.

Am. J. Cardiol. 40 : 716.

HELLMAN, K,& JS WEINER (1953):

Antidiuretic substance in urine following exposure to high temperatures.

J. Appl. Physiol. 6 : 194.

HENDERSON, AH, DL BRUTSAERT, R FORMAN & EH SONNENBLICK (1974):

Influence of caffeine on force development and force-frequence relations in cat and rat heart muscle.

Cardiovasc. Res. 8 : 162.

HERMAN, RH,& BH SULLIVAN (1959):

Heatstroke and jaundice.

Am. J. Med. 26 : 154.

HERNDON, RF, WH MERONEY & CM PEARSON (1955):

The electrocardiographic effects of alteration in concentration of plasma chemicals.

Am. Heart J. 50 : 188.

HILL, L (1920):

The nature, prevention and treatment of heat hyperpyrexia. The physiological aspect.

Brit. Med. J. 1 : 397.

HORVATH, SM,& CD HOWELL (1964):

Organ system in adaptation: The cardiovascular system. In: Handbook of Physiology. Section 4: Adaptation to the environment (Ed: DB Dill), p.153. Waverley Press, Baltimore.

HUBBARD, RW, WD BOWERS & M MAGER (1974):

A study of physiological, pathological and biochemical changes in rats with heat and/or work induced disorders. Intern. Congr. Physiol. Sci., 26th Jerusalem Staellite Symp. Temp. Regulation.

HUBBARD, RW, WT MATTHEW, JD LINDUSKA, FC CURTIS, WD BOWERS, I LEAV AND M MAGER (1976):

The laboratory rat as a model for hyperthermic syndromes in humans.

Am. J. Physiol. 231 : 119.

HUBBARD, RW, WD BOWERS, WT MATTHEW, FC CURTIS, REL CRISS, GM SHELDON & JW RATTEREE (1977):

Rat model of acute heatstroke mortality

J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 42 : 809.

HUBBARD, RW, WT MATTHEW, REL CRISS, C KELLY, I SILS, M MAGER, WD BOWERS & D WOLFE (1978):

Role of physical effort in the etiology of rat heatstroke injury and mortality.

J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 45 : 463.

HURST, JW,& RC SCHLANT (1978):

Examination of the arteries and their pulsation.

In: The heart, arteries and veins (Fourth edition)

(Ed: Hurst *et al*), p. 183. McGraw-Hill, New York.

IAMPIETRO, PR (1963):

Heat-induced tetany.

Fed. Proc. 22 : 884.

JENNINGS, RB, JR CROUT & GW SMETTERS (1957):

Studies on distribution and localization of potassium in early myocardial ischaemic injury.

Arch. Pathol. 63 : 586.

JUŽNIČ, G (1973):

Haemodynamic stress and relief of the heart in the light of comparative physiological investigations.

Bibl. cardiol. 30 : 31.

KANTER, GS (1954):

Effect of heat on regulation of body fluids and electrolytes in dogs.

Am. J. Physiol. 178 : 259.

KELLER, AD,& WK HARE (1932):

The hypothalamus and heat regulation.

Proc. Soc. Exptl. Biol. and Med. 29 : 1069.

KEW, MC (1968):

Heatstroke.

Lancet 7558 : 31.

KEW, MC (1969):

Renal, cardiac and hepatic damage in heatstroke.

The Leech 39 : 50.

KEW, MC (1976):

Temperature regulation in heatstroke in man.

Isr. J. Med. Sci. 12 : 759.

KEW, MC, I BERSOHN, J PETER, CH WYNDHAM & HC SEFTEL (1967a):

Preliminary observations on the serum and cerebrospinal fluid enzymes in heatstroke.

S. Afr. Med. J. 41 : 530.

KEW, MC, C ABRAHAMS, NW LEVIN, HC SEFTEL, AH RUBENSTEIN & I BERSOHN (1967b):

The effects of heatstroke on the function and structure of the kidney.

Quart. J. Med. 36 : 277.

KEW, MC, RBK TUCKER, I BERSOHN & HC SEFTEL (1969):

The heart in heatstroke.

Am. Heart J. 77 : 324.

KEW, MC, C ABRAHAMS & HC SEFTEL (1970a):

Chronic interstitial nephritis as a consequence of heatstroke.

Quart. J. Med. 39 : 189.

KEW, MC, I BERSOHN, H SEFTEL & G KENT (1970b):

Liver damage in heatstroke.

Am. J. Med. 49 : 192.

KEW, MC, I BERSOHN & HC SEFTEL (1971):

The diagnostic and prognostic significance of serum enzyme changes in heatstroke.

Trans. Roy. Soc. Trop. Med. Hyg. 65 :325.

KIELBLOCK, AJ (1972):

'n Eksperimentele ondersoek na die invloed van akute hittespanning op hartfunksie.

M. Sc. Thesis. University of Stellenbosch.

KIELBLOCK, AJ (1973):

The mechanism of circulatory failure of acute, experimental hyperthermia.

J. Univ. Durban-Westville. 2 : 23.

KILBURN, KH (1966):

Muscular origin of elevated plasma potassium during muscular exercise.

J. Appl. Physiol. 21 : 675.

KISCH, B (1953):

The heart rate and electrocardiogram of small animals.

Exp. Med. Surg. 11 : 117.

KJELLMER, I (1965):

Potassium ion as a vasodilator during muscular exercise.

Acta Physiol. Scand. 63 : 460.

KNOCHEL, JP (1974):

Environmental heat illness.

Arch. Intern. Med. 133 : 841.

KNOCHEL, JP, WR BEISEL, EG HERNDON, ES GERARD & KG BARRY (1961):

The renal, cardiovascular, hematologic and serum electrolyte abnormalities of heatstroke.

Am. J. Med. 30 : 299.

KNOCHEL, JP, FD FOLEY JR., & HL WALKER (1970):
Effect of potassium (K) depletion on cardiac output and lactate response to exercise in the dog.
Clin. Res. 18 : 92.

KREBS, HA (1950):
Body size and tissue respiration.
Biochem. Biophys. Acta. 4 : 249.

KUBICEK, WG, WD ANDERSON & LF GEBER (1958):
Effects of hypoxia on the course of induced fever in dogs and monkeys.
Am. J. Physiol. 195 : 601.

KUMAR, P, CK RATHORE, AM NAGAR & MP METHROTRA (1964):
Hyperpyrexia with special reference to heatstroke.
J. Ind. Med. Ass. 43 : 213.

KUNO, Y (1956):
Human perspiration. Thomas Books, Springfield, Ill.

LAURELL, H,& J PERNOW (1966):
Quoted by Rovic and Randall (1967) in the section "Systemic circulation", An. Rev. Physiol. 29 : 225.

LAURENCE, B (1973):
Clinical Pharmacology (Fourth Edition), p. 17.4. Churchill Livingstone, New York.

LEITHEAD, CS (1960):
Dehydration and death in the desert.
Trans. Roy. Soc. Trop. Med. Hyg. 54 : 297.

LEITHEAD, CS,& AR LIND (1964):
Heat stress and heat disorders. Cassell, London.

LEVIC, JJ (1859):

Remarks on sunstroke.

Am. J. Med. Sci. 37 : 40.

LEVINE, JA (1969):

Heat stroke in the aged.

Am. J. Med. 47 : 251.

LIND, J (1768):

An essay on diseases incidental to Europeans in hot climates.

T Becket Publ.Co.,London (Quoted by Leithead & Lind, 1964).

LIND, AR,& DC BASS (1963):

The optimal exposure time for the development of acclimatization to heat.

Fed. Proc. 22 : 704.

LINING, - (1748):

Quoted by Leithead and Lind (1964).

LOGUE, RB,& JF HANSON (1946):

Electrocardiographic changes following heat stroke, report of a case.

Ann. Intern. Med. 24 : 123.

MALAMUD, N, W HAYMAKER & RP CUSTER (1946):

Heatstroke: A clinico-pathological study of 125 cases.

Milit. Surg. 99 : 397.

MANOACH, M (1971):

The influence of bleeding on the amplitude of the QRS complex in the electrocardiogram of different vertebrates.

Ph.D. Thesis. University of Tel-Aviv, Israel.

MARS, A (1975):

"Unbroken": The story of a submarine. Corgi, London.

MARTIN, CE, JA SHAVER & JJ LEONARD (1972):

Physical signs, apexcardiography, phonocardiography and systolic time intervals in Angina Pectoris.

Circulation 46 : 1098.

MARRIOTT, HJL,& RJ MEYERBURG (1978):

Recognition and treatment of cardiac arrythmias and conduction disturbances.

In: The heart, arteries and veins (Fourth edition) (Ed: Hurst *et al*), p. 637. McGraw-Hill, New York.

McVIE, J (1970):

Postmortem detection of inapparent myocardial infarction.

J. Clin. Path. 23 : 203.

METZ, E (1940):

Herzschädigung durch Hitzshlag im elektrocardiogram.

Klin. Wschr. 19 : 247.

MICHAELI, D (1969):

Heatstroke (Correspondence)

Brit. Med. J. 1 : 844.

MINARD, D,& L COPMAN (1963):

Elevation of body temperature in disease.

In: Temperature. Its measurement and control in science and industry (Ed: CM Herzfeld). Vol. 3. Part 3. Biology and Medicine, p.253. Reinhold Publ. Corp., New York.

MITCHELL, D (1972):

Human surface temperature: Its measurement and its significance in thermoregulation.

Ph.D. Thesis. University of the Witwatersrand.

MIRVIS, DM, GS KOPF & EW POTALLA (1978):

Harmonic analysis of the left ventricular pressure waveform of the primate.

Cardiology 63 : 79.

MOORE, FT, SA MARABLE & E OGDEN (1966):

Contractility of the heart in abnormal temperatures.

Ann. Thorac. Surg. 2 : 446.

MORRIS, RO,& TE KING (1962):

Thermal denaturation of heart muscle preparation with respect to its capacity for DPNH oxidation.

Biochemistry 1 : 1017.

MOSINGER, B, J STEJSKAL, M TUTTEROVA & H VAVTINKOVA (1978):

Myocardial lesions induced by natural catecholamines *in vitro*.

Europ. J. Cardiol. 6 : 389.

NAYLER, WG, J STONE, V CARSON & D CHIPPERFIELD (1971):

Effect of ischaemia on cardiac contractility and calcium exchangeability.

J. Mol. Cell. Cardiol. 2 : 125.

NAYLER, WG,& JULIE SZETO (1972):

Effect of sodium pentobarbital on calcium in mammalian heart muscle.

Am. J. Physiol. 222 : 339.

NOBLE, MIM, D TRENCHARD & A GUZ (1966a):

Left ventricular ejection in conscious dogs; measurement and significance of the maximum acceleration of blood from the left ventricle.

Circulation Res. 19 : 139.

NOBLE, MIM, D TRENCHARD & A GUZ (1966b):

Effect of changing heart rate on cardiovascular function in the conscious dog.

Circulation Res. 19 : 206.

NORMAN, SJ, RE PRIEST & EP BENDETT (1961):

The electrocardiogram in the normal rat and its alteration with experimental coronary occlusion.

Arch. Res. 9 : 282.

O'DONNELL, TF,& GHA CLOWES (1972):

The circulatory abnormalities of heat stroke.

New Engl. J. Med. 287 : 734.

OPIE, LH, FJ BURGER, AJ BRINK & A LOCHNER (1965):

Hyperthermic damage to isolated rat heart tissue.

Clin. Sci. 28 : 461.

O'ROURKE, MF (1971):

The arterial pulse in health and disease.

Am. Heart J. 82 : 687.

PAPADOPOULOS, NM, AA LEON & CM BLOOR (1967):

Effects of exercise on plasma and tissue levels of lactose dehydrogenase and isoenzymes in rats.

Proc. Soc. Exp. Biol. Med. 125 : 999.

PATON, WDM & JP PAYNE (1968):

Pharmacological principles and practice. J & A Churchill, London.

PIEMME, TE, GO BARNETT & L DEXTER (1966):

Relationship of heart sounds to acceleration of blood flow. Circulation Res. 18 : 303.

PIGOTT, VM, DH SPODIC, EH RECTRA & AH KHAN (1971):

Cardiocirculatory responses to exercise: Physiologic study by noninvasive techniques.

Am. Heart J. 82 : 632.

PRETORIUS, PJ, JJ VAN DER WALT & LF RADEMEYER (1966):

The ultra-low frequency acceleration ballistocardiogram of the albino rat.

Proc. 1st World Congr. Ballistocard. Cardiovasc. Dynamics, Amsterdam. Karger, Basel.

PRYOR, R,& SG BLOUNT (1966):

The clinical significance of true left axis deviation.

Am. Heart J. 72 : 391.

QURESHI, S, HN WAGNER, PO ALDERSON, DF HOUSHOLDER, KH DOUGLASS, MG LOTTER, EL NICKOLOFF, M TANABE & LG KNOWLES (1978):

Evaluation of left-ventricular function in normal persons and patients with heart disease.

J. Nucl. Med. 19 : 135.

RADEMEYER, LJ (1969):

Experimental investigations of the higher dynamic functions of the heart in the albino rat.

D.Sc. Thesis. Potchefstroom University for C.H.E.

RIEKE, WO,& NB EVERETT (1957):

Effect of pentobarbital anaesthesia on the blood values of rat organs and tissues.

Am. J. Physiol. 188 : 403.

ROBINSON, S (1963):

Circulatory adjustments of men in hot environments.

In: Temperature. Its measurement and control in science and industry (Ed: CM Herzfeld). Vol. 3. Part 3. Biology and medicine, p. 287. Reinhold Publ. Corp., New York.

ROBINSON, S, & SC GERKING (1947):

Thermal balance of men working in severe heat.

Am. J. Physiol. 149 : 476.

ROWELL, LB, JR BLACKMAN, R MARTIN, JA MAZZARELLA & RA BRUCE (1965):

Hepatic clearance of indocyanine green in man under thermal and exercise stresses.

J. Appl. Physiol. 20 : 384.

ROWELL, LB, HJ MARX, RA BRUCE, RD CONN & F KUSUMI (1966):

Reductions in cardiac output, central blood volume and stroke volume with thermal stress in normal men during exercise.

J. Clin. Invest. 45 : 1801.

ROWELL, LB, GL BRENGELMANN, JR BLACKMON, RD TWISS & F KUSUMI (1968):

Splanchnic blood flow and metabolism in heat-stressed man.

J. Appl. Physiol. 24 : 475-484.

RUSHMER, RF (1970):

Cardiovascular dynamics (Third edition).WB Saunders, Philadelphia.

SCHEFFÉ, H (1959):

The analysis of variance. J Wiley & Sons, Inc., New York.

SCHLANT, RC (1978a):

Normal physiology of the cardiovascular system.

In: The heart, arteries and veins (Fourth edition)

(Ed: Hurst *et al*), p. 71. McGraw-Hill, New York.

SCHLANT, RC (1978b):

Altered physiology of the cardiovascular system in heart failure.

In: The heart, arteries and veins (Fourth edition)

(Ed: Hurst *et al*), p. 532. McGraw-Hill, New York.

SCHLANT, RC (1978c):

Metabolism of the heart.

In: The heart, arteries and veins (Fourth edition)

(Ed: Hurst *et al*), p. 107. McGraw-Hill, New York.

SCHMIDT, HD, & H HOPPE (1978):

The influence of the contractile state of the heart on preload dependence of the maximal rate of intraventricular pressure rise dP/dt max.

Cardiology 63 : 112.

SCHMIDT-NIELSEN, K (1964):

Terrestrial animals in dry heat: Desert rodents.

In: Handbook of Physiology. Section 4: Adaptation to the environment (Ed: DB DILL), p.493. Waverley Press, Baltimore.

SCHRIER, RW, J HANO, HI KELLER, RM FINKEL, PF GILLILAND, WJ CIRKSENA & PE TESCHAN (1970):

Renal, metabolic and circulatory responses to heat and exercise.

Ann. Int. Med. 73 : 213.

SCHRIRE, V (1963):

Clinical cardiology. Staples Press, London.

SELLERS, EA,& SS YOU (1950):

Role of the thyroid in metabolic responses to a cold environment.

Am. J. Physiol. 163 : 81.

SETNICAR, I,& O TEMELCOU (1961):

Effect of temperature on toxicity and distribution of pentobarbital and barbital in rats and dogs.

J. Pharma. 135 : 213.

SHAPIRO, Y, T ROSSENTHAL & E SOHAR (1973):

Experimental heatstroke. A model in dogs.

Arch. Intern. Med. 131 : 688.

SHARPLESS, SK (1966):

Hypnotics and sedatives. I. Barbiturates.

In: The pharmacological basis of therapeutics (Third edition). (Ed: LS Goodman & A Gilman). The Macmillan Co., New York.

SHIBOLET, S, S FISHER, T GILAT, H BANK & H HELLER (1962):

Fibrinolysis and hemorrhage in fatal heatstroke.

N. Engl. J. Med. 266 : 169.

SHIBOLET, S, R COLL, T GILAT & E SOHAR (1967):

Heatstroke; its clinical picture and mechanism in 36 cases.

Quart. J. Med. 36 : 525.

SIEGEL, W (1978):

Examination by external pulse recording and phonocardiography.

In: The heart, arteries and veins (Fourth edition) (Ed: Hurst *et al*), p. 422. McGraw-Hill, New York.

SINGH, I (1963):

Starling's law of the heart in cardiac and unstriated muscle killed by heat.

Experientia 19 : 34.

SJÖSTRAND, T (1976):

Regulation of blood volume (Editorial)!

Scand. J. Clin. Lab. Invest. 36 : 209.

SKINNER, NS,& WJ POWELL (1967):

Action of oxygen and potassium on vascular resistance of dog skeletal muscle.

Am. J. Physiol. 212 : 533.

SOHAR, E, D MICHAELI, U WAKS & S SHIBOLET (1968):

Heatstroke caused by dehydration and physical effort.

Arch. Internal Med. 122 : 159.

SPURR, GB, & G BARLOW (1959a):

Influence of prolonged hypothermia and hyperthermia on myocardial sodiu, potassium and chloride.

Circulation Res. 7 : 210.

SPURR, GB,& G BARLOW (1959b):

Plasma and erythrocyte Na, K, Cl and water in hypothermic and hyperthermic dogs.

Am. J. Physiol. 197 : 648.

SPURR, GB,& G BARLOW (1970):

Tissue electrolytes in hyperthermic dogs.

J. Appl. Physiol. 28 : 13.

STREETEN, DHP, JW CONN, LH LOUIS, SS FAJANS, HS SELTZER, RD JOHNSON, RD GITTLER & AH DUBE (1960):

Secondary aldosteronism.

Metabolism 9 : 1071.

TIETZ, NW (1970):

Fundamentals of clinical chemistry. WB Saunders, London.

TROSKIE, L (1978):

Personal communication.

UMBREIT, WW, RH BURRIS & JF STAUFFER (1964):

Manometric techniques. (Fourth edition). Burgess Publ. Co., Minneapolis.

VALBONNA, C (1974):

Physiologic monitoring in children.

In: Medical engineering (Ed: CD Ray), p. 624.

Year Book Medical Publishers, Inc., Chicago.

WALLACE, J,& SRM BUSHBY (1944):

Hazards of hypertherm treatment.

Lancet 2 : 459.

WARNER, HR (1954):

Quantitation of stroke volume changes in man from the central pressure pulse.

Minnesota Med. 37 : 111.

WARNER, HR (1966):

The role of computers in medical research.

J.A.M.A. 196 : 944.

WARNER, HR, JHC SWAN & EH WOOD (1952):

Quantitation of rapid stroke volume changes in man from aortic pulse pressure changes.

Am. J. Physiol. 171 : 777.

WARNER, HR, JHC SWAN, DC CONNOLLY, RG TOMPKINS & EH WOOD (1953):

Quantitation of beat-to-beat changes in stroke volume from the aortic pulse contour in man.

J. Appl. Physiol. 5 : 495.

WEBB, P (1959):

Human thermal tolerance and protective clothing.

Ann. N.Y. Acad. Sci. 82 : 714.

WEBB, JL, PR SAUNDERS & CH THIENES (1949):

The metabolism of the heart in relation to drug action. I. The endogenous aerobic metabolism of rat heart slices.

Arch. Biochem. 22 : 444.

WEISSLER, AM, WS HARRIS & CD SCHOENFELD (1968):

Systolic time intervals in heart failure in man.

Circulation 37 : 149.

WEISSLER, AM, WS HARRIS & CD SCHOENFELD (1969):

Bedside technics for the evaluation of ventricular function in man.

Am. J. Cardiol. 23 : 577.

WERKÖ, L (1962):

The dynamics and consequence of stenosis or insufficiency of cardiac valves.

In: Handbook of Physiology: Circulation. Volume 1.

(Ed: WF Hamilton), p.645. Waverley Press, Baltimore.

WHITEHEAD, RW,& RW VIRTUE (1965):

Anaesthesia. II. Intravenous agents.

In: Drill's parmacology in medicine (Third edition).

(Ed: JR DiPalma). McGraw-Hill, New York.

WILDENTHAL, K, DS MIERZWIAK, RW MEYERS & JH MITCHELL (1968):

Effects of acute lactic acidosis on left ventricular performance.

Am. J. Physiol. 214 : 1352.

WILLIAMS, CG, GAG BREDELL, H WYNDHAM, NB STRYDOM, JF MORRISON, J PETER, PW FLEMING & JS WARD (1962):

Circulatory and metabolic reactions to work in heat.

J. Appl. Physiol. 17 : 625.

WILSON, G (1940):

The cardiopathology of heatstroke.

J.A.M.A. 114 : 557.

WINSOR, T (1968):

Electrolyte abnormalities and the electrocardiogram.

J.A.M.A. 203 : 347.

WOOD, JE,& DE BASS (1960):

Responses of the veins and arterioles of the forearm to walking during acclimatization to heat in man.

J. Clin. Invest. 39 : 825.

WOOTTEN, JDP (1964):

Micro-analysis in medical biochemistry (Fourth edition)

J and A Churchill, London.

WYNDHAM, CH, AJA BENADE, CG WILLIAMS, NB STRYDOM, A GOLDIN & AJA HEYNS (1968):
Changes in central circulation and body fluid spaces during acclimatization to heat.
J. Appl. Physiol. 25 : 586.

WYNDHAM, CH, MC KEW, R KOK, I BERSOHN & NB STRYDOM (1974):
Serum enzyme changes in unacclimatized and acclimatized men under severe heat stress.
J. Appl. Physiol. 37 : 695.

YAGLOU, CP,& DP MINARD (1957):
Control of heat casualties at military training centres.
Arch. Industr. Hlth. 16 : 302.

ZARROW, MX, JM YOCHIM & JL McCARTHY (1964):
Experimental endocrinology. A sourcebook of basic techniques
Academic Press, New York.

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