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REVIEW ARTICLE

Preventable deaths after injury: why are the traditional 'vital' signs poor indicators of blood loss?

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The concept of preventable deaths[1] has stimulated debate about the identification and best ways of avoiding such undesirable outcomes. A constant feature of the debate has been the finding of unsuspected and/or underestimated haemorrhage as a major contributor to such deaths.[2–4] Why is the presence of occult bleeding so difficult to diagnose? In many undergraduate text books of physiology it can be read that an increase in heart rate (HR) is almost invariably an accompaniment of severe haemorrhage and a tachycardia is one of the most valuable indicators of concealed bleeding. The widely acclaimed Advance Trauma Life Support (ATLS) courses emphasize the importance of progressive increases in HR and decreases in arterial blood pressure as the hallmarks of hypovolaemic shock.[5] Also systolic blood pressure is included in the Revised Trauma Score (RTS),[6] the basis of the physiological assessment of the injured patient incorporated into TRISS methodology.[7]

The continuing problem with the diagnosis of haemorrhage should lead to a questioning of the relationship between pulse rate and blood pressure and the magnitude of blood loss. Even during the First World War it was noted that traumatic shock was not always accompanied by a tachycardia[8] and that 'blood pressure is of assistance in judging blood volume only when it is below a certain point, for there may be a considerable reduction of blood volume without any appreciable drop in the pressure'.[9] When blood pressure was recorded at very short intervals after the patient had been wounded two groups could be identified; hypertensive and hypotensive groups with 'practically none' occupying an intermediate (normal) group.[10] The occurrence of hypertension in injured patients was also noted in a study of 100 air-raid casualties during the Second World War.[11] In this study all the patients were 'shocked' and they were categorized on initial observation as hypertensive (9%), normotensive (28%) or hypotensive (63%). The normotensive group had suffered severe injuries and the mortality rate was 25%. The hypotensive group (systolic blood pressure <100 mmHg) was divided into those with a slow pulse rate (<70 beats min^{-1}, 14%), normal pulse rate (43%) or rapid pulse rate (>100 beats min^{-1}, 43%). Thus, only 27% of those patients observed within the first hours of injury had hypotension and tachycardia.

Grant and Reeve[12] summarized a large amount of war-time civilian and military data on the relationship between systolic blood pressure and blood volume. In 68 out of 70 patients with a systolic blood pressure above 100 mmHg, blood volume was a systolic pressure below 100 mmHg, blood volume was below 70% of normal. They concluded that after wound size (assessed as hand-fulls of tissue damage) systolic blood pressure was the most useful sign of blood loss. Pulse rate, colour, temperature, restlessness, thirst, dyspnoea and sweating were of little individual value as indicators of the severity of shock. In a separate review of war-time experience it was noted that 'even patients judged to be in severe shock can have a pulse rate as low as 60 beats min^{-1}.[13] The limited value of pulse rate in the assessment of blood loss after trauma confirmed previous findings.[14–16]

A series of studies in health volunteers of the effects of 'simple' blood loss demonstrated a slight tachycardia (seldom exceeding 100 beats min^{-1})

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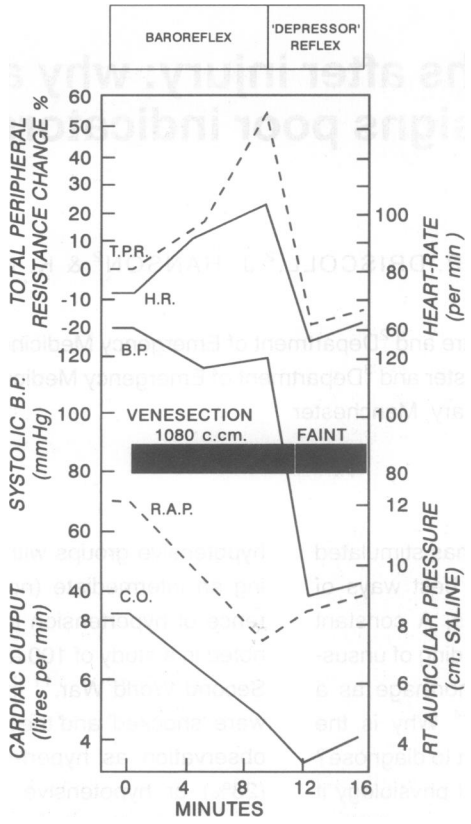

Fig. 1. Changes in HR, systolic arterial blood pressure, cardiac output, peripheral resistance and right atrial pressure during a controlled haemorrhage (venesection) and subsequent faint in a human volunteer (from 43).

and a well-maintained blood pressure up to losses of approximately 1 L.[17–19] However when losses exceeded 1 L syncope with a fall in blood pressure, bradycardia and vasodilation in skeletal muscle were frequently recorded (Fig. 1).[19] These findings suggested a biphasic heart rate response to blood loss (i.e. a tachycardia followed by a bradycardia) and seemed to have been forgotten until the mid 1980s.[20] Secher and his colleagues in Copenhagen reported bradycardia and hypotension in severe but reversible haemorrhagic shock in humans.[21,22] A feature of the patient in whom such a bradycardia was noted was that the haemorrhage was 'simple' (i.e. from ruptured varices, penetrating injury to a major vessel etc.) and not accompanied by concomitant direct tissue injury. These authors emphasized that the bradycardia was reversed by transfusion and they suggested that it was mediated by a reflex arising in the heart. More recently the biphasic HR response to 'simple' blood loss has been confirmed although it was noted that the magnitude of the bradycardia seemed to be attenuated in the presence of concomitant tissue injury[23] (Fig. 2a).

It seems that it is now appropriate to review the reflexes involved in the cardiovascular response to injury and to consider how they might be modified by injury. If this information can be applied to clinical situations and initial resuscitation rates can be improved then it will contribute to achieving the targets set in the Government proposals Health of the Nation, to reduce road casualties by one third by the year 2000.

REFLEXES INVOLVED IN THE RESPONSE TO HAEMORRHAGE

In explaining the biphasic response to blood loss three reflexes need to be considered; the arterial baroreceptor reflex, the reflex elicited by activation of cardiac C-fibre afferents and the arterial chemoreflex.

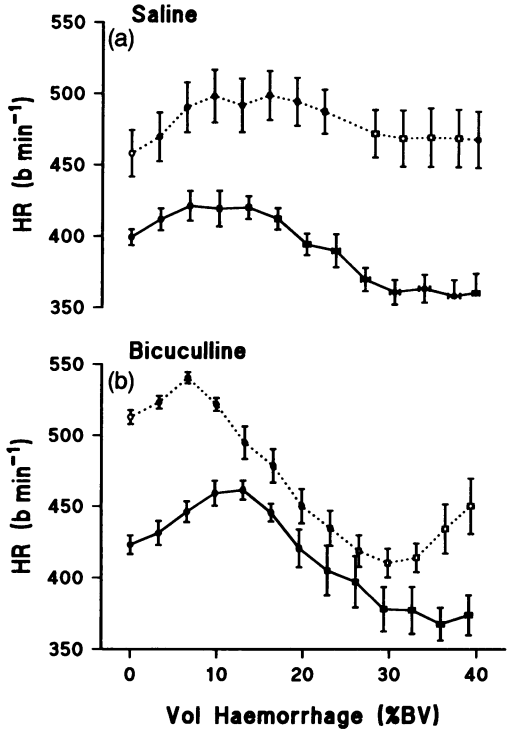

Fig. 2. Effects of progressive haemorrhage of 40% estimated total blood volume (%BV) at 2%BV min^{-1} in four groups of anaesthetized rats treated with either (a) saline or (b) bicuculline injected into the fourth cerebral ventricle. (●) 'Simple' haemorrhage; (○) haemorrhage on a background of bilateral hindlimb ischaemia (used as the model of injury). Values are mean ± SEM.

The arterial baroreceptor reflex

This reflex is thought to be responsible for the maintenance of arterial blood pressure following the loss of 10–15% of the blood volume. This reflex normally minimizes moment to moment variations in blood pressure around a given 'set-point', which itself can be altered.[24] The baroreceptor endings are located in the medio-adventitial border of the arterial wall in parts of the arterial system with a specialized elastic structure, mainly in the aortic arch and carotid sinus. The baroreceptors themselves are slow-adapting mechanoreceptors which respond to the degree of stretch of the arterial wall produced by the intraluminal pressure, rather than to the intraluminal pressure itself.[25] Furthermore, the baroreceptors are 'rate-sensitive' and can therefore respond to the rate of change of arterial blood pressure as well as to its absolute level.[26] Consequently, they can respond to a change in pulse pressure as well as to changes in mean pressure.

Thus, as pulse pressure diminishes during haemorrhage there is a decrease in baroreceptor afferent activity, even in the absence of a fall in *mean* arterial pressure. This change in baroreceptor afferent activity is signalled to the brain via the vagus nerve (from the aortic arch baroreceptors) and the sinus nerve, a branch of the glossopharyngeal nerve, (from the carotid sinus baroreceptors).[27] The efferent limb of the baroreceptor reflex is carried in the vagus and sympathetic nerves to the heart, and in the sympathetic vasoconstrictor nerves to the blood vessels.[27] When the baroreceptors are unloaded following a haemorrhage there is a resultant reflex withdrawal of vagal-cardiac and an enhancement of sympathocardiac activity. This leads to a tachycardia and an increase in the activity of the sympathetic vasoconstrictor fibres leading to an increase in total peripheral resistance. It should be emphasized that the activation of the sympathetic supply to the various vascular beds is not uniform, with some experiencing a more intense vasoconstriction than others.[27] The activity of the baroreceptor reflex at this time is augmented by a concomitant increase in its sensitivity.[28] The mechanism of this increase in sensitivity is unknown although it may result from increases in the plasma levels of vasopressin and renin activity which occur after haemorrhage.[29,30] Furthermore, the balance of pressures across the microvascular endothelium is changed in such a way that fluid moves from the extravascular to the intravascular compartment. As a consequence of these haemodynamic changes, any haemorrhage-induced falls in arterial blood pressure are minimized or prevented in the face of losses of up to 10–15% of the blood volume. Hence, the baroreceptor reflex serves to maintain blood flow to tissues critically dependent on oxygen delivery (e.g. brain) at the expense of flow to other organs (e.g. skeletal muscle) where oxygen delivery is less critical, at least in the short-term.

However, as blood loss exceeds 20% of blood volume, blood pressure falls dramatically. This is not because of a sudden failure of the baroreceptor reflex[28] or the imminent demise of the heart, but rather is because of the activation of a second reflex – possibly that elicited by activation of cardiac vagal C-fibre afferents.

The cardiac vagal C-fibre afferents

The cardiac vagal C-fibres form the afferent pathway from a group of receptors located mainly in the left ventricular myocardium. These receptors can be activated by mechanical and/or chemical means (e.g. prostaglandin E_2)[31] and lead to a profound reflex bradycardia, hypotension and reduction in skeletal muscle and renal vascular resistance:[32,33] the 'cardiac reflex'. The bradycardia results from increased vagal efferent activity to the heart, while the reduction in vascular resistance is because of a withdrawal of sympathetic vasoconstrictor tone.[32,33] Following a severe haemorrhage (>20% of the blood volume) it has been postulated that the mechano-sensitive receptor endings of the cardiac vagal C-fibre afferents are stimulated by deformations of the ventricular wall as the heart contracts vigorously around an incompletely filled chamber.[34] This is supported by the finding that sectioning the cervical vagi can reverse the bradycardia in experimental animals, and that the bradycardia and fall in blood pressure are attenuated markedly in animals, which are deficient in afferent C-fibres.[35] Furthermore, the reduction in renal sympathetic vasoconstrictor activity can be prevented by the instillation of procaine into the pericardial sac to block the afferent pathway.[36,37] However, more recent studies have questioned the precise nature of the afferent pathway mediating the 'depressor' response associated with severe haemorrhage, since the instillation of procaine into the pericardial sac may have more wide-ranging effects than simply blocking the cardiac neural pathways.[38] In addition a similar 'depressor' response has been reported in conscious dogs, which had been subjected to

cardiac denervation or acute cardiac nerve blockade.[39,40] Furthermore, a case report of sympatho-inhibition, following the infusion of a vasodilator agent in a cardiac transplant patient with no ventricular innervation, led the authors to suggest that 'stimulation of ventricular afferents is not the only mechanism that can trigger sympatho-inhibition during hypovolaemic hypotension'.[41] Finally, very recent evidence suggests that aspects of the central nervous pathways mediating the 'cardiac reflex' may be different to those involved in the 'depressor' response associated with severe haemorrhage. However, regardless of these questions relating to the nature of the afferent pathway, it must be stressed that there is very strong evidence suggesting that the 'depressor' response associated with severe haemorrhage is reflex in nature, and that the efferent limb of the reflex involves both increased vagal activity to the heart and reduced sympathetic tone to vascular beds, e.g. the kidney.

Since the efferent limb mediating the cardio-inhibitory component of the depressor reflex is carried in the vagus nerve (see above), it is not surprising that the bradycardia associated with severe haemorrhage can be prevented by treatment with atropine in both humans[42,43] and experimental animals.[35] However, the administration of atropine under these circumstances is not to be recommended (unless there is very severe bradycardia or asystole), since it has been suggested that the 'depressor' reflex may serve to protect the heart by reducing cardiac work at a time when coronary blood flow is compromised. Indeed there have been reports that the administration of atropine in these situations can jeopardize the patient's survival chances.[44] The logical treatment is to restore blood volume and hence reduce the activation of the reflex, whereupon the bradycardia should correct itself.

The arterial chemoreceptor reflex

The third reflex of importance in the cardiovascular response to haemorrhage is the arterial chemoreceptor reflex. The arterial chemoreceptors are found in the carotid and aortic bodies, close to the carotid sinus and aortic arch, respectively. They respond to changes in oxygen tension, a fall in oxygen tension increasing chemoreceptor afferent activity. In addition, increases in carbon dioxide tension and falls in arterial blood pH increase the sensitivity of the arterial chemoreceptors to hypoxia. Stimulation of arterial chemoreceptors produces an increase in respiration[46] while the primary cardiovascular effects are a vagally-mediated bradycardia and a vasoconstriction in, for example, skeletal muscle, which results from increased sympathetic vasoconstrictor tone.[47] This pattern of response is subsequently modified by the increased respiratory activity, which tends to inhibit both the vagal activity to the heart and the sympathetic vasoconstrictor activity.[48]

Following a severe haemorrhage the arterial chemoreceptors are activated as a result of a reduction in blood flow through the carotid and aortic bodies secondary to the fall in arterial blood pressure, and to sympathetic vasoconstriction in the bodies themselves[49,50] mediated by the local release of both noradrenaline and its co-transmitter neuropeptide Y.[51] Therefore, during the hypotensive phase of a severe haemorrhage, stimulation of the arterial chemoreceptors may prevent arterial blood pressure falling even further[52] and may be responsible for the increase in respiration following severe haemorrhage.[53] Since an increase in respiratory activity has been shown to reduce the reflex bradycardia produced by stimulation of cardiac C-fibre afferents[33] it is possible that the enhanced respiratory activity seen following a severe haemorrhage may attenuate the bradycardia seen under these circumstances. This interaction between the respiratory and cardiovascular responses to chemoreceptor stimulation may also have further implications for the treatment of injured patients. For example, procedures such as intubation which inhibit respiratory activity can unmask a dangerous bradycardia.[54] The role of the chemoreceptors in helping to maintain blood pressure will, of course, be increased in the injured patient with thoracic injuries which may impair pulmonary function.

THE CARDIOVASCULAR RESPONSE TO 'INJURY'

In direct contrast to haemorrhage, tissue injury/ischaemia produces an increase in arterial blood pressure accompanied by a tachycardia.[55–57] The increase in arterial blood pressure which accompanies 'injury' is largely mediated by an increase in sympathetic outflow to the vasculature and a consequent increase in total peripheral resistance. Thus the 'injury'-induced pressor response is unaffected by the complete cardiac autonomic blockade, but is abolished by the α-adrenoceptor antagonist phentolamine.[58] This intense sympathetically-mediated vasoconstriction induced by

'injury' could lead to a reduction in blood flow to vital organs such as the gut and kidney, and possibly lead to ischaemic damage of those organs[59] hence contributing to the pathophysiology of the response to 'injury' and its sequelae such as multiple organ failure.

The 'injury'-induced pressor response is accompanied by a tachycardia, rather than a bradycardia which would be expected were the baroreceptor reflex (see above) functioning normally. This pattern of response is possible because there is a concomitant reduction in the sensitivity and a rightward resetting (i.e. towards a higher arterial blood pressure) of the baroreflex following 'injury'[60] (Fig. 3a). The reduction in baroreceptor reflex sensitivity in humans is evident within 3 h of 'injury' of moderate severity (e.g. fracture of a long bone), and is persistent such that only partial recovery has occurred at 14 days after 'injury'[61] (Fig. 3b). This impairment of the baroreceptor reflex is accompanied by a persistent tachycardia which is not related to hypovolaemia, and a reduction in the variation in heart rate induced by respiration.

The afferent pathway of the response to 'injury' appears to run in somatic (including nociceptive) fibres arising in the damaged tissues. Afferent information then ascends in the spinal cord (probably via the spino-thalamic tract) to the brain.[60] Little is known of the precise mechanism of the reduction in the sensitivity of the baroreflex. However, recent studies have shown that activation of somatic afferent Aδ fibres can lead to inhibition of baroreflex sensitive neurones within the nucleus of the tractus solitarius (NTS) via a GABA-ergic mechanism.[62] Furthermore, it has been argued that the response to injury is reminiscent of the visceral alerting response of the defence reaction[63] and that similar pathways are involved.

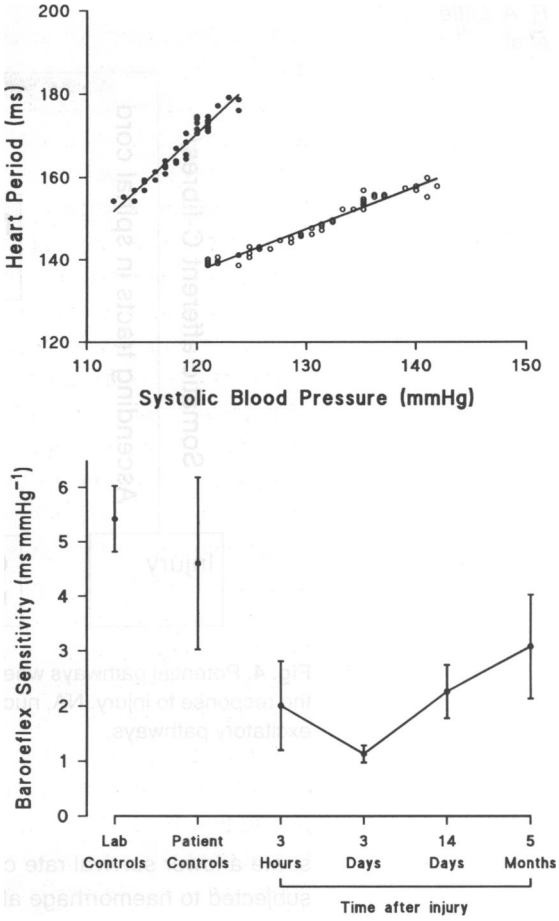

Fig. 3. (a) Relationship between systolic blood pressure and heart period in an anaesthetized rat (●) before and (○) 30 min after the induction of hindlimb ischaemia (which is a model of injury). The slope of this relationship provides a index of the sensitivity of the baroreflex while a lateral shift indicates a resetting of the reflex. (b) Baroreflex sensitivity in humans in control subjects and in injured patients treated at different times after injury (ISS range 9–17; median 9). Values are mean ± SEM. (From 61.)

THE CARDIOVASCULAR RESPONSE TO COMBINED HAEMORRHAGE AND TISSUE INJURY

The cardiovascular changes elicited by a progressive haemorrhage are markedly attenuated by the presence of concomitant tissue injury.[35] The initial tachycardia following a loss of 10–15% blood volume is reduced, and the vagal bradycardia following greater losses prevented. This may result from a central inhibition of vagal cardiac pre-ganglionic motorneurones via a GABA-ergic mechanism in the brainstem which can be blocked by the GABA-receptor antagonist bicucuilline (Fig. 2b). A long-lasting inhibition of vagal cardiac pre-ganglionic motorneurones in the nucleus ambiguus has also been demonstrated following electrical stimulation of nociceptive afferent fibres[64] (Fig. 4). Somatic afferent stimulation (e.g. of the sciatic nerve) is also able to block the vagal bradycardia evoked by stimulation of either the NTS[64] or cardiac C-fibre afferents (Kirkman & Little, unpublished observations). This attenuation of HR changes, normally associated with blood loss, seems to offer some degree of protection against the hypotensive effects of a severe haemorrhage.[35] However, this protection may be more apparent than real. Animals subjected to haemorrhage and concomitant electrical stimulation of the sciatic nerve (to simulate 'injury') demon-

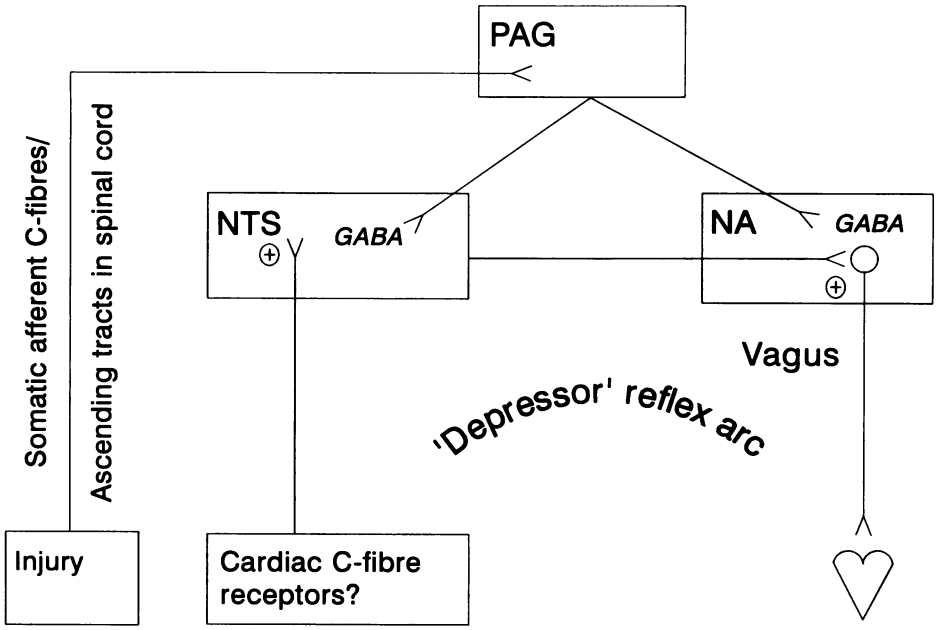

Fig. 4. Potential pathways whereby the 'depressor' reflex response to severe haemorrhage may be inhibited by the response to injury. NA, nucleus ambiguus: NTS, nucleus tractus solitarius; PAG, periadequactal grey; ⊕ excitatory pathways.

strate a lower survival rate compared with animals subjected to haemorrhage alone.[59] Recent studies have demonstrated that superimposition of somatic afferent nerve activity or a real injury, upon haemorrhage produces greater falls in cardiac index and systemic oxygen delivery than those produced by an equivalent 'simple' haemorrhage.[65,66] It is possible that the better maintenance of blood pressure is achieved at the expense of intense peripheral vasoconstriction leading to ischaemic organ damage which will exacerbate the severity of injury. It is tempting to speculate that the splanchnic circulation may be selectively vulnerable to such ischaemic damage leading to the release of blood-borne factors which may impair cardiovascular function. There is evidence that when haemorrhage is superimposed on a background of somatic afferent stimulation there is relative diversion of blood flow from the gut towards skeletal muscle[67] (Fig. 5). This diversion of blood flow away from metabolically active organs (such as the gut) towards relatively inactive resting skeletal muscle may explain the increase in critical oxygen delivery elicited by somatic afferent nerve stimulation[68] (Fig. 6). Intestinal permeability may also be increased leading to enhanced translocation of bacteria and endotoxin,[69,70] a suggestion that is reminiscent of Fine's endotoxin theory of shock.[71]

The neurotransmitters involved in the response to haemorrhage and injury are discussed in detail elsewhere.[72] However, there are a number of neurotransmitters which might be involved in the response to haemorrhage and injury, the manipulation of which could be useful in formulating new treatment regimens.

THE ENDOGENOUS OPIOIDS

There is a strong body of evidence suggesting that the endogenous opioid sytem may be involved in the response to severe hypovolaemia. Most of the evidence suggests a role for the opioid system in the sympatho-inhibitory response. However, there is also some evidence, albeit weaker, suggesting their role in the bradycardic response. Thus, the opioid antagonist naloxone, when given intravenously, was shown to attenuate the reduction in sympathetic efferent activity and the associated hypotension, and possibly the bradycardia which accompanies severe hypovolaemia.[36,73] Naloxone, in this case, is thought to exert its effect via an antagonist action at δ opiate receptors within the medulla.[37,74,75] It should be stressed here that although the administration of naloxone, or of a more specific δ opioid receptor antagonist (ICI 174864), clearly blocked the sympatho-

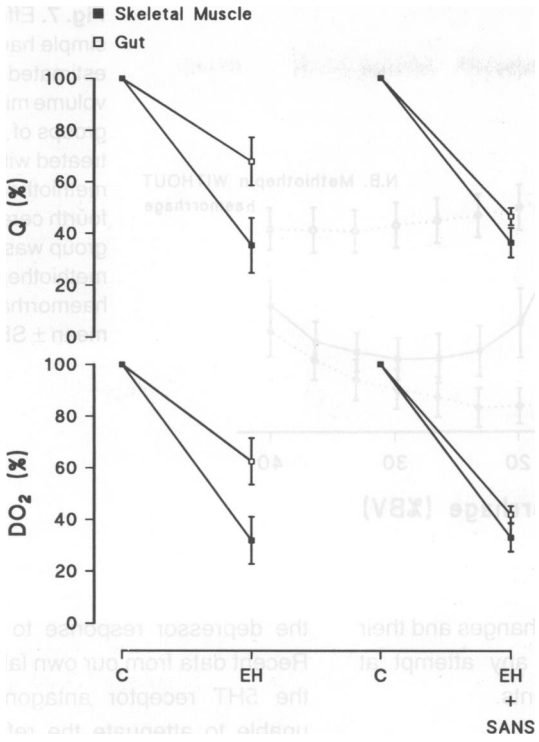

Fig. 5. Blood flow and oxygen delivery to the splanchnic and skeletal muscle vascular beds before(C) and after the loss of 30% estimated total blood volume at 1% min^{-1} (EH) in two groups of anaesthetized pigs: those subjected to haemorrhage alone, and those subjected to haemorrhage on background of somatic afferent stimulation (SANS) as a model of injury. Values expressed as a percentage of those recorded during the control phase, and presented as mean ± SEM.

the normal 'physiological' response to severe haemorrhage[75] although the use of μ receptor agonists, e.g. fentanyl and alfentanyl,[79] may provide a pharmacological means of inhibiting the depressor effect of a severe haemorrhage. Whether this would be beneficial or detrimental (bearing in mind the potential protective effects of this depressor reflex, and the consequences of blocking it) remains to be seen.

Since 'injury' is also known to activate the endogenous opioid system, and cell bodies which synthesize and release enkephalins are found in the peri-aqueductal grey[80] (Fig. 4), an area known to be involved in the cardiovascular response to 'injury', it is not surprising to learn that naloxone can modify the response to 'injury'. Thus, it has been demonstrated in experimental studies that the administration of naloxone, either centrally or intravenously, can prevent or reverse the reduction in baroreflex sensitivity produced by 'injury'.[81] Conversely, some of the effects of 'injury' on the baroreflex can be mimicked by the central administration of a long-lasting analogue of met-enkephalin (d-ala^2-met^5-enkephalinamide).[82]

Thus, it can be seen that both opioid agonists and antagonists can modify the cardiovascular response to haemorrhage and 'injury'. Clearly, the effects are complex, emphasizing the complexity of the underlying neural control mechanisms. Further studies are required to evaluate the role of individual opiate receptor subtypes in these responses,

inhibition,[74,76] the effects of δ antagonism on the bradycardia were less clear. This may be because of the relatively small bradycardic response to severe hypovolaemia even in the absence of δ antagonism in these studies, which were conducted on rabbits. Since δ opioid receptor antagonism appears to block *both* the vagal and the sympathetic component of the response to severe hypovolaemia, it is likely that the endogenous opioids are important early in the reflex pathway, before the two limbs diverge. One likely area is the NTS,[75] which contains a dense population of δ opioid receptors.[77,78]

In addition to the δ opioid receptors, the μ and the κ receptors also appear to be capable of modifying the response to severe hypovolaemia. Thus, μ and κ receptor *agonists* can also prevent the reflex sympatho-inhibition (and possibly the bradycardia) seen during severe hypovolaemia.[74–76] However, it is unlikely that the μ opioid receptor participates in

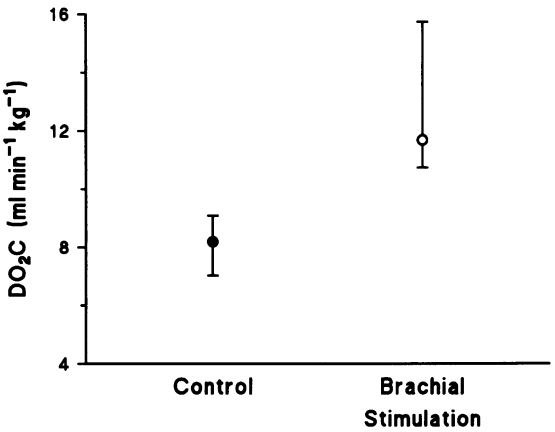

Fig. 6. Critical oxygen delivery (the point at which oxygen consumption becomes dependent upon supply and the tissues become ischaemic) in two groups of anaesthetized dogs: control, and those subjected to somatic afferent (brachial) nerve stimulation to simulate injury. Values are medians and interquartile ranges.

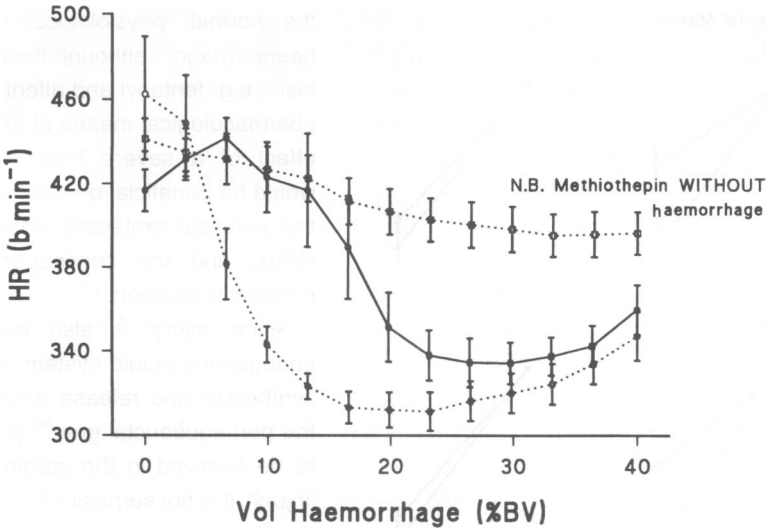

Fig. 7. Effects of a progressive simple haemorrhage (2% estimated total blood volume min^{-1}) on heart rate in two groups of anaesthetized rats treated with either saline (●), or methiothepin (○) injected into the fourth cerebral ventricle. A third group was treated with methiothepin but not subjected to haemorrhage (□). Values are mean ± SEM.

and the resultant haemodynamic changes and their consequences evaluated before any attempt at treatment are made with these agents.

5-HYDROXYTRYPTAMINE

There have been suggestions that this agent may be involved in the central nervous pathways mediating the response to severe haemorrhage. Thus, Bogle *et al.*[83] demonstrated that a response which includes the 'cardiac reflex' elicited by activation of cardiac-vagal C-fibre afferents could be blocked by methiothepin (a 5HT receptor antagonist) given centrally. Furthermore, blockade of the 5-HT system, either with p-chlorophenylalanine (PCPA, which blocks the synthesis of 5-HT), or with the 5-HT receptor antagonist, methysergide, has been reported to prevent or reverse both the sympathoinhibitory and the bradycardic response to severe blood loss, while leaving baroreflex control intact.[84] Although the 5-HT 'blocking' agents were given intravenously in this latter study, their sites of action are likely to be central, since any effect of 5-HT on the ventricular receptors is mediated via 5-HT_3 receptors,[85] where methysergide has little activity.[86]

However, the effects of 5HT 'blockade' on the response to severe blood loss are equivocal, since other studies have failed to show that PCPA blocks the depressor response to severe haemorrhage[87] and have suggested that the action of agents, e.g. methysergide, do not occur because of blockade of 5HT but rather because of *agonism* at 5HT receptors.[88] Thus, Evans *et al.*[88] concluded that there was no evidence of a physiological role for 5HT in the depressor response to severe haemorrhage. Recent data from our own laboratories indicate that the 5HT receptor antagonist methiothepin was unable to attenuate the reflex bradycardia which accompanies severe haemorrhage[89] (Fig. 7) unlike its effects on the 'cardiac reflex', suggesting that the two responses may be mediated via different central nervous pathways. Indeed, our studies indicate that 5HT antagonism may potentiate the depressor response to severe haemorrhage. Thus, our findings support and extend those of Evans *et al.*;[88] activation of central 5HT receptors does not appear necessary for the mediation of the depressor response associated with severe haemorrhage. In contrast 5HT could have a 'physiological' role in providing a tonic inhibition of this response.

Thus, 5-HT and its receptors may provide another avenue for pharmacological manipulation of the response to haemorrhage and injury, although, because of the complexity of the system, this possibility lies some way ahead.

EFFECTS OF ETHANOL

Ethanol is a drug taken socially, often preceding traumatic events, e.g. automobile accidents. The effects of ethanol on the cardiovascular response to haemorrhage and 'injury' are therefore of interest. Recent studies have shown that moderately raised blood levels of ethanol (100–200 mg%) can exacerbate the 'injury'-induced reduction in baroreflex sensitivity.[90] Explaining the action of ethanol on the cardiovascular response to injury is potentially simple. It has been reported that ethanol may potentiate the effects of endogenous GABA at both the

NTS and the vagal outflow nuclei.[91] Since the response to injury is thought to inhibit the baroreflex via a GABA-ergic mechanism within the brainstem nuclei, it is hardly surprising that ethanol augments the baroreflex-inhibitory effects of jury.

SHOCK INDEX

The obvious shortcomings of blood pressure and HR for assessing blood loss from the circulation stimulated the development of the Shock Index (SI – calculated by dividing HR by the systolic blood pressure).[92] It was predicted that combining the changes in HR and blood pressure would give a more sensitivie indication of blood loss and a low flow state than either variable used alone. It was found that there was a direct relationship between SI and the magnitude of blood loss in a group of patients with either gastro-intestinal bleeding, open wounds or intra-abdominal thoracic bleeding following blunt trauma.[92] Our own studies have confirmed the value of SI and suggested that it may be a more sensitive indicator of physiological status after injury than the more commonly used RTS. Thus, in a group of 160 trauma patients with a normal RTS, 69 had an abnormal SI.[93]

Shock Index (SI) has been further validated in a number of experimental studies. For example, despite the markedly biphasic HR response to simple haemorrhage in the rat, a progressive increase in SI was found as the magnitude of blood loss increased[93] (Fig. 8). A negative relationship between SI and both left ventricular stroke volume and cardiac output has been shown during haemorrhage in the anaesthetized pig.[93] Thus SI seems to be a simple, non-invasive means of evaluating cardiac function during acute hypovolaemia.

STROKE DISTANCE

Another non-invasive assessment of left ventricular stroke volume (LVSV) can be obtained by the measurement of stroke distance (SD) using continuous wave Doppler ultrasound via an ultrasonic probe placed in the suprasternal notch.[94] Technically, this is a very simple procedure requiring no more training than that needed to record blood pressure by sphygnomanometry. In a recent study in our laboratory, blood loss was simulated by pooling blood in the lower body using a negative pressure chamber.[95] A progressive haemorrhage was simulated by progressively increasing lower body negative pressure (LBNP). Mean arterial blood pressure did not change significantly at any level of LBNP (Fig. 9), unless the subject became pre-syncopal (Fig. 10a,b). Overall, pulse rate and shock index did not change at the first level of LBNP, but did increase progressively thereafter (Fig. 10) until presyncope, which occurred in a few subjects, whereupon HR fell dramatically and SI either continued to rise (Fig. 10a) or fell slightly (Fig. 10b) when the bradycardia and hypotension were extreme. By contrast SD fell significantly at each level of LBNP (Figs 9 & 10). However, with very marked reductions in HR there was a small increase in stroke distance, presumably related to improved cardiac filling as a result of the increased diastolic filling time. Thus, SD provides an effective early indicator

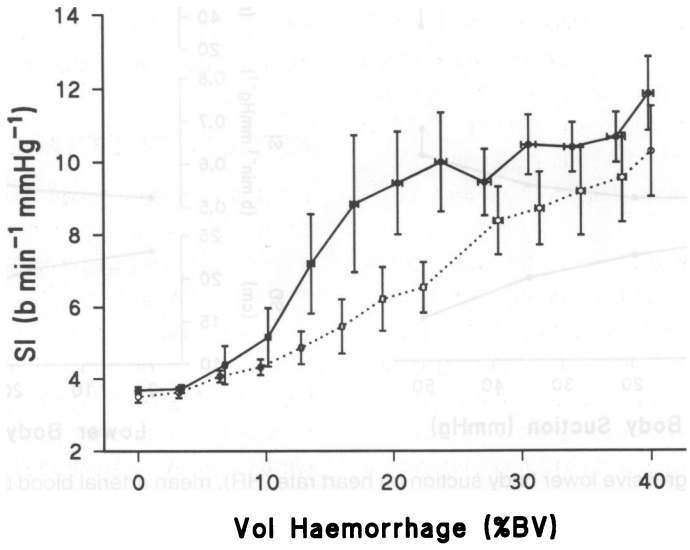

Fig. 8. Effect of progressive haemorrhage (2% estimated total blood volume min^{-1} on shock index in two groups of anaesthetized rats: (●) simple haemorrhage, (○) haemorrhage on the background of bilateral hind-limb ischaemia ('injury'). For HR data for the same animals, see Fig. 2a. Values are mean ± SEM.

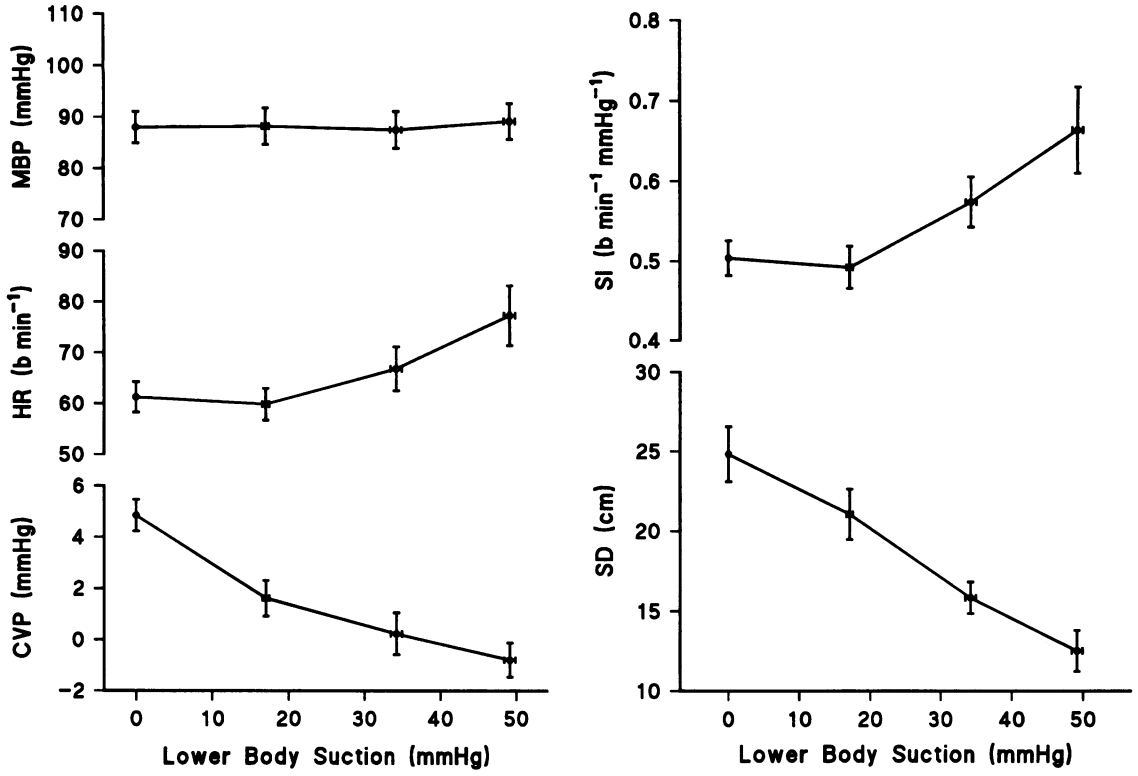

Fig. 9. Effects of progressive lower body suction on mean arterial blood pressure (MBP), heart rate (HR), central venous pressure (CVP), shock index (SI) and stroke distance (SD) in eight healthy volunteers. Presyncopal data were excluded. Values are mean ± SEM.

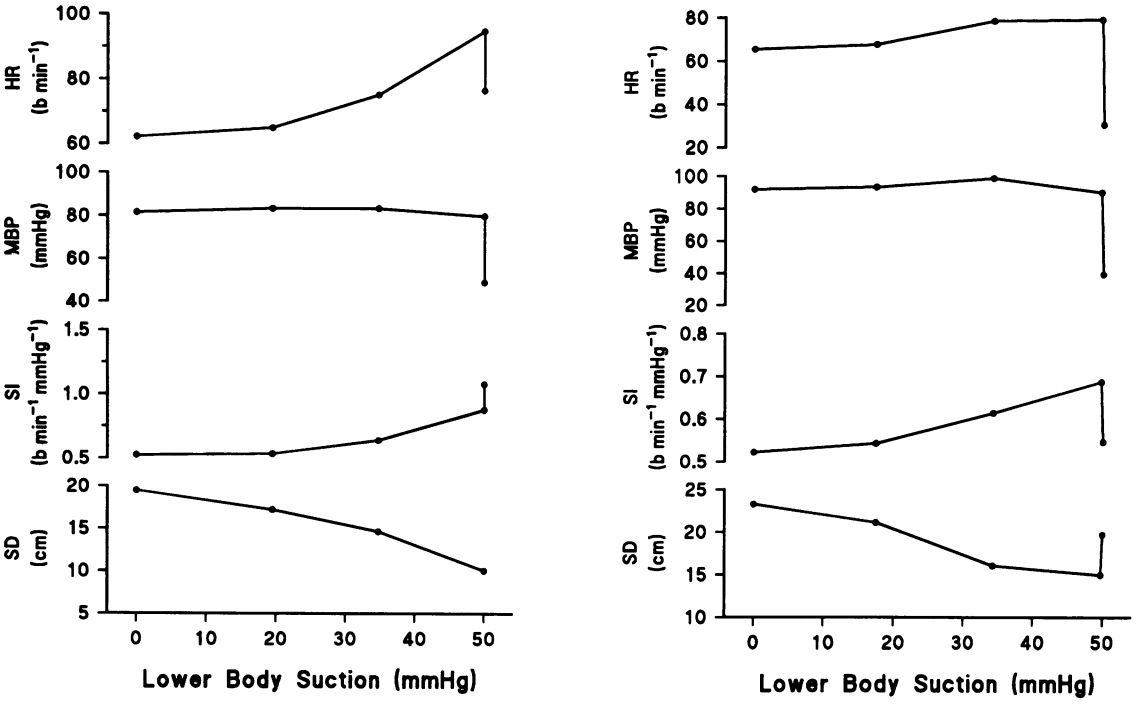

Fig. 10. Effects of progressive lower body suction on heart rate (HR), mean arterial blood pressure (MBP), shock index (SI) and stroke distance (SD) in two healthy male volunteers (a,b) who became presyncopal during suction at 50 mmHg.

of reductions in LVSV as a consequence of reduced central blood volume and venous return. These changes in SD can be detected before alterations in the classical vital signs – HR and blood pressure.

CONCLUSIONS

An increase in the understanding of cardiovascular responses to haemorrhage and injury will improve the interpretation of the injured patient's vital signs. The introduction of both the use of SI and measurements of stroke distance will provide simple, non-invasive means for detecting changes in cardiac output. Such developments will lead to a reduction in preventable trauma deaths.

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