CARDIAC PERFORMANCE IN
SURGICAL SHOCK

An essay submitted for the
William Leslie Prize in Surgery, 1971
by
Anthony J. Strong, B.A., M.B., Ch.B., F.R.C.S.E.

Department of Surgical Neurology,
The Royal Infirmary,
Edinburgh.
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
</tr>
<tr>
<td>Historical</td>
<td>1</td>
</tr>
<tr>
<td>Clinical evidence of cardiac failure</td>
<td>4</td>
</tr>
<tr>
<td>Haemodynamic evidence of cardiac failure</td>
<td>5</td>
</tr>
<tr>
<td>Methods of treatment</td>
<td>6</td>
</tr>
<tr>
<td>The measurement of cardiac performance</td>
<td>7</td>
</tr>
<tr>
<td>The present studies</td>
<td>8</td>
</tr>
<tr>
<td><strong>EXPERIMENT I</strong></td>
<td></td>
</tr>
<tr>
<td>Methods</td>
<td>9</td>
</tr>
<tr>
<td>Experimental procedure</td>
<td>10</td>
</tr>
<tr>
<td>Results</td>
<td>13</td>
</tr>
<tr>
<td>Discussion</td>
<td>16</td>
</tr>
<tr>
<td>Summary</td>
<td>23</td>
</tr>
<tr>
<td><strong>EXPERIMENT II</strong></td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td>24</td>
</tr>
<tr>
<td>Methods</td>
<td>24</td>
</tr>
<tr>
<td>Experimental procedure</td>
<td>26</td>
</tr>
<tr>
<td>Results</td>
<td>29</td>
</tr>
<tr>
<td>Discussion</td>
<td>32</td>
</tr>
<tr>
<td>Conclusions</td>
<td>37</td>
</tr>
<tr>
<td><strong>PATHOPHYSIOLOGY</strong></td>
<td></td>
</tr>
<tr>
<td>Enhancement or impairment of cardiac performance?</td>
<td>39</td>
</tr>
<tr>
<td>Enhanced/</td>
<td></td>
</tr>
<tr>
<td>Topic</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Enhanced cardiac performance in shock</td>
<td>39</td>
</tr>
<tr>
<td>Causes of myocardial depression</td>
<td>40</td>
</tr>
<tr>
<td>Intracellular damage</td>
<td>41</td>
</tr>
<tr>
<td>METABOLIC AGENTS IN THE TREATMENT OF CARDIAC FAILURE IN SHOCK</td>
<td>44</td>
</tr>
<tr>
<td>SUMMARY</td>
<td>45</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>47</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>48</td>
</tr>
<tr>
<td>TABLES</td>
<td>52</td>
</tr>
<tr>
<td>FIGURES</td>
<td>58</td>
</tr>
</tbody>
</table>
INTRODUCTION

**Historical**

The physiological basis for the treatment of surgical shock has been well recognised since the early years of this century, when Starling and Yandell Henderson first observed that the principal factor determining the cardiac output is the diastolic filling of the ventricle by venous blood. Military surgeons during World War I were aware that the venous return was diminished in most cases of shock, and this was reflected in the loss of venous pressure and constriction of peripheral veins observed clinically. The value of early restoration of an effective blood volume with a plasma expanding solution and of correction of acidosis with sodium bicarbonate was established at this time as the result of the work of Cannon and others. The possible role of cardiac failure in the genesis of shock as it presented in battle casualties also came under scrutiny at this time. Cannon, reviewing the evidence for a defect in cardiac function in 1919, concluded that although there was no primary cardiac deficit, low arterial pressure and acidosis could in time impair the performance of the heart. There was little further advance until World War II, when Cournand and his group studied haemodynamic changes in shock in the first clinical application of the technique of cardiac catheterisation. They confirmed/
confirmed the reduction of cardiac output, and interpreted this as due to a reduction in venous return: they found no evidence of cardiac failure.

During World War I Wiggers commenced his classical studies on experimental haemorrhagic shock in the dog; it is a tribute to the quality of his work that his techniques and conclusions have been adopted as a starting point for many subsequent experimental studies of haemorrhagic shock. He showed that if a dog is heparinised and allowed to bleed through an arterial cannula into a reservoir, the arterial pressure can be lowered to a desired level by setting the reservoir to the corresponding height. He found that after the initial withdrawal of blood to the desired level of hypotension, arterial pressure tended to recover although further slow blood loss into the reservoir prevented this from actually occurring. After a time interval which was predictable within broad limits and which was shorter for greater degrees of hypotension, arterial pressure started to fall spontaneously and this could easily be recognised as a reversal of blood flow so that the animal reinfused itself from the reservoir, at first slowly but later more rapidly. Animals in which hypotension had been maintained beyond the point of reversal invariably died in spite of reinfusion of the shed blood with or without additional volumes of fluid, whereas those which were reinfused before reversal usually survived.

Wiggers designated that state one of irreversible shock, and considered/
considered that it was due to a sudden loss of tone in the peripheral vascular system, with pooling of blood, particularly in the splanchnic circulation: the fall in venous pressure which was observed could readily be explained on this basis. However he also showed that "if normal venous flow and pressure are restored at this time by additional reinfusions, the stroke volume and cardiac output still remain below control values".  

This depression of myocardial contractility Wiggers believed to be an important component of the experimental irreversible shock syndrome, and subsequent work by other groups has led to conflicting verdicts on whether cardiac depression is an important component or merely a terminal event in experimental shock. Crowell and Guyton have favoured the first interpretation, basing their conclusions on repeated determinations of the ventricular function curve during a period of reservoir shock. They observed a steady depression in cardiac contractility which commenced well before the point of reversal, so that progressively higher filling pressures were required to maintain cardiac output. In contrast, Fine has produced good evidence that irreversibility in haemorrhagic shock is due to a breakdown in the intestinal mucosa and a collapse in reticulo-endothelial function, allowing widespread dissemination of intestinal bacteria or their products. He showed that survival could be improved by prior sterilisation of the gut, and claimed that this evidence argued against the importance of myocardial depression in irreversible shock.

Clinical evidence of cardiac failure/
Clinical evidence of cardiac failure

Since the haemodynamic changes in shock in man and in the dog differ considerably, conclusions based on experimental work can only be applied in a clinical context with caution. There is very little evidence from clinical experience that cardiac performance becomes deficient in man purely as a result of oligaeamic shock, and in the absence of coronary disease or pre-existing congestive cardiac failure. However, there is good evidence that in some cases of bacterial shock, probably those more advanced, and particularly in patients with infection due to Gram-negative organisms, a low cardiac output is associated with a high central venous pressure (CVP)\textsuperscript{6,7,8}, a combination which is usually taken to indicate the presence of cardiac failure.

Clinical haemodynamic evidence of cardiac failure

More detailed haemodynamic studies, specifically designed to detect the onset of cardiac failure in seriously ill general surgical patients, have been undertaken by Siegel and his colleagues\textsuperscript{9}, and by this author. Siegel confirmed the association in some patients of a normal or high CVP with low values of stroke volume; his patients were relatively young and were in shock as a result of infection, principally following septic abortion.

Data relating to cardiac performance are at present available for eight patients studied while undergoing intensive therapy (Fig. 1b). The results will be summarised briefly here since they serve/
serve to illustrate some of the clinical problems which the experimental studies - forming the basis of this paper - were designed to clarify. In five of the eight patients (M.C., M.N., A.J., M.H., D.L.) there was unequivocal evidence of cardiac failure at an early stage of resuscitation. Of these five, stroke volume was low and CVP high (12-20 mm Hg) in three elderly patients (M.C., M.N., A.J.): they were considered to be seriously but not critically ill, and all recovered from the acute episode and were discharged from the unit. One patient (A.J.) had signs of established congestive cardiac failure on admission, and another (M.C.) responded well to digitalisation, hypertonic sodium chloride and restriction of fluid intake. For these reasons we believe that the haemodynamic data in these three patients indicate a state of chronic congestive cardiac failure in which right ventricular failure has become established, leading to high central venous pressures and simultaneously protecting the lungs and left ventricle from fluid overload.

The remaining two patients in cardiac failure (M.H., D.L.) resembled one another in several respects. Aged 64 and 54 respectively, they were below the age where congestive cardiac failure might be considered common, and in neither patient was there any previous history to suggest this condition. Both had been pedestrians involved in road traffic accidents, sustaining multiple fractures and intra-abdominal injuries confirmed at laparotomy. Both/
Both patients were critically ill; one died 24 hours after admission. The haemodynamic data were similar in both patients, comprising a combination of low stroke work with a CVP towards the upper range of normal (6-12 mm Hg), values which resemble those reported by Siegel in his younger patients with bacterial shock. We have designated this situation one of secondary failure since cardiac performance is apparently impaired solely as a result of the shock episode. It should be emphasized that the combination of low stroke work and normal CVP was observed at an early stage of treatment, suggesting that cardiac contractility was impaired before resuscitation was commenced. It is therefore unlikely that failure developed in these patients as a result of the overloading of a normal heart, but rather that cardiac performance was impaired as a result of shock in such a way that an intravenous load which might be considered normal for a relatively healthy patient was somehow rendered excessive.

**Methods of treatment**

Cardiac failure in acutely ill surgical patients has been treated with cardiac glycosides, isoprenaline, and most recently with glucagon. Although there is evidence of clinical and haemodynamic improvement with these agents their effects have frequently proved transient and evidence is lacking - although admittedly difficult to obtain - that survival is improved as a result of their use.

The measurement of cardiac performance/
The measurement of cardiac performance

The measurement of cardiac contractility in terms of the length-tension relationship for the myocardial muscle fibre extrapolated to zero initial tension is widely recognised as the most accurate method available. However, for the purposes of routine clinical assessment the most specific parameters currently available are central venous pressure (CVP), and stroke work index (SWI), the latter being a measure of stroke volume which in addition takes account of body surface area and of external work performed by the left ventricle against the arterial pressure load. A graph of SWI plotted against a range of cardiac filling pressures yields the curve illustrating Starling's Law, and Sarnoff has pointed out that a potential range of such ventricular function curves exists for any individual. Each curve represents a steady state of contractility and implies a predictable response to intravenous infusion. Mathematical expressions for contractility based on an entire curve have been developed, although in clinical practice the volumes of reinfusion required to inscribe the entire curve are rarely indicated. For these reasons the change in SWI per unit change in filling pressure elicited by infusion, \( \frac{\Delta \text{SWI}}{\Delta \text{CVP}} \), or the gradient of the function curve, has been adopted as a measure of contractility in these studies. Over short segments of the curve, involving smaller infusions, this gradient will approximate to the configuration of the function curve (Fig. 2a). We believe that the gradient of the correlated responses of SWI and CVP to infusion is/
is a measure of cardiac performance which might be of value in the early detection of clinical cases of cardiac failure, since it is the directly measured response of the heart to a specified increase in venous return.

The present studies

The experiments reported in this paper were designed for four purposes:

1. To determine the validity of the gradient of the correlated responses of SWI and CVP to infusion as a measure of cardiac performance in the dog.

2. To reproduce experimentally, by means of a period of induced haemorrhagic shock, a state of impaired cardiac performance similar to that encountered clinically.

3. To assess the reliability of central venous pressure and stroke work measurements - the methods at present available to the clinician - in the early detection of cardiac failure.

4. To measure the effects of inotropic agents on the response of the heart to infusion after shock.

The choice of agent for inotropic support of the heart in the clinical management of surgical shock is discussed in the light of the results obtained and existing knowledge of the pathophysiology of shock.
EXPERIMENT I

The first group of experiments was designed (1), to compare in dogs the response of the heart to infusion - expressed as the gradient of the ventricular function curve - before and after reservoir shock carried beyond the point of irreversibility and, (2), to examine the effect of rapid digitalisation (ouabain) on the response to infusion after shock.

METHODS

Eleven acute experiments were performed using healthy adult collie/mongrel dogs (mean body weight 12.97 kg, range 8.86-17.47). Anaesthesia was induced with pentobarbital, 30 mg/kg given intravenously, and was maintained with intermittent intravenous doses of 60 mg pentobarbital. An endotracheal tube was inserted and the animal allowed to breathe room air spontaneously. In advanced shock ventilation was assisted in two animals with a Cyclator respirator. The right femoral and right external jugular veins and the right common carotid artery were exposed and catheters introduced for infusion and measurement of central venous and aortic pressures respectively. Pressures were recorded with Sanborn 267BC transducers calibrated against a mercury manometer, with reference levels 8 cm above the surface of the operating table. The central venous catheter was manipulated until respiratory pulsations could be observed and satisfactory dye curves were obtained. Cardiac output was/
was measured by the dye dilution method using indocyanine green injected through the central venous catheter. Arterial blood was sampled through a Waters densitometer cuvette at a rate of 15 ml/min. Dye curves were recorded in duplicate on 20 cm paper, separated by an interval of approximately 90 seconds. The curve areas were measured by the method of Williams et al 17, which has been shown to correlate closely with that of Stewart and Hamilton 18. The electrocardiogram was recorded and a continuous trace of pulse rate obtained from the R wave using a Sanborn cardiotachometer.

Left ventricular stroke work index (SWI) was calculated in units of gm-M/kg from the formula:

\[
\text{SWI} = \frac{C_0 \cdot (L/min) \times (\text{MSEP-CVP}) \times (\text{mm Hg}) \times 13.6}{\text{Heart rate/min} \times \text{Body weight} \ (\text{kg})}
\]

where MSEP = mean systolic ejection pressure (mm Hg), measured by manual integration of the systolic phase of the aortic pressure trace.

The gradient of the function curve was obtained from correlations of SWI with CVP before and after infusion, and expressed as

\[
\frac{\text{change in SWI}}{\text{change in CVP}} \text{ in units of gm-M/kg/mm Hg.}
\]

**EXPERIMENTAL PROCEDURE**

Following insertion of the catheters and baseline measurements of cardiac output, dextran 110 (Glaxo) at body temperature was infused in 100 ml stages at a rate of 15 ml/min until the rate of rise of CVP began to increase. Infusion was restricted to a maximum of 400 ml/
400 ml in order to avoid excessive haemodilution. Cardiac output and stroke work index were determined after each 100 ml of the infusion and plotted against CVP, thus providing the initial gradient of the ventricular function curve (Gradient before shock, Figs. 2a, b, Table I). The animal was then bled out from the femoral catheter at the same rate into a reservoir containing heparin (1,000 units) until a mean arterial pressure of 55 mm Hg was reached, and cardiac output was again measured. In accordance with the usual behaviour of the Wiggers' preparation, it was necessary to remove small additional volumes of blood in order to restrict arterial pressure to the same level over approximately the next two hours. Reversal was considered to have occurred at that time at which it became necessary to infuse small volumes of blood in order to maintain arterial pressure. This slow reinfusion was continued for 30 minutes, as it had been established in preliminary studies that reinfusion immediately following reversal was not usually associated with any loss of contractility: approximately 40 ml reservoir blood was required during this period.

Reinfusion was in three stages. In the first phase 200 ml 0.9% sodium chloride was given in experiments 1-5, these animals constituting the control group. In experiments 6-11 the first phase of infusion consisted of 200 ml 0.9% sodium chloride containing 0.02 mg/kg ouabain; these animals were designated the treatment group. In both groups the duration of this infusion lay between 10 and 13 minutes. Saline was infused at this stage of the experiment.
experiment in order to maintain venous return during digitalisation, since the inotropic effect of digoxin may be obscured by its concomitant action in reducing venous return. Stroke work index and central venous pressure were correlated before and after this infusion, and the slope of the resulting segment of the function curve was measured (Gradient during saline: Stage I, Fig. 2; Table I).

The second stage of the reinfusion (II) was identical in both groups: the reservoir blood was returned at 15 ml/min through the femoral cannula, and stroke work index and central venous pressure again correlated before and after this infusion, permitting further calculation of the gradient of the function curve (Gradient during reinfusion of reservoir: Stage II, Fig. 2, Table I). The duration of this infusion lay between 15 and 30 minutes.

When the reservoir had been completely reinfused cardiac output was generally below control levels, and a further infusion of dextran - 110 was therefore given until it appeared that the peak of the function curve had been reached. Correlation of SWI and CVP before and after the first 100 ml of this infusion provided the values for gradient after reinfusion of the reservoir (Stage III, Fig. 2; Table I). The experiment was terminated with an instantaneous dose of 1,000 mg pentobarbital.

Statistical comparisons were made of body weight, initial cardiac index and the gradients in response to infusion at the four stages of the experiment: these parameters were compared within and/
and between groups using Student's T-test and the Mann-Whitney U-test.

RESULTS

(a) Before Shock

Individual and mean values and standard deviation for body weight and haemodynamic parameters, including the gradient of the function curve before and after the period of oligoemia, are shown in Table I. Each value shown for cardiac index is the mean of two determinations. Although the mean values of body weight were comparable in the two groups, body weight was more variable in the treatment group. Mean initial central venous pressures were 1.8 and 0.8 mm Hg in the control and treatment groups respectively. The mean gradients of the function curve in response to initial infusion of dextran (Gradient before shock, Fig. 2) were $1.35 \pm 0.76$ and $1.29 \pm 0.68 \text{ gm-M/kg/mm} \pm 1 \text{ S.D.}$ respectively. In order to assess the reproducibility and normal range of this parameter as an index of myocardial performance, the initial gradients for all eleven experiments were also plotted together as a histogram (Fig. 3): in eight experiments the initial gradient lay between 0.80 and 1.40 gm-M/kg/mm.

(b) Reinfusion I (saline + ouabain)

The gradients of the function curves in response to infusion of saline with or without ouabain were $0.88 \pm 0.24$ and $1.27 \pm 1.20 \text{ gm-M/kg/mm}$.
gm-M/kg/mm in the control and treated groups respectively (Gradient during saline; Stage I, Fig. 2; Table I): this difference between groups was not significant (Mann-Whitney U = 14, \( p > 0.3 \)). The reduction in gradient from 1.35 to 0.88 gm-M/kg/mm in the control group following shock was also not significant. In experiments 9 and 10 there were increases in SWI in response to reinfusion with no accompanying rise in CVP; the gradient measured were therefore theoretically equal to infinity. So that the data could be handled statistically, these gradients were assigned finite values equal to the maximum gradient recorded in any experiment (3.30 gm-M/kg/mm, gradient of response to reinfusion of reservoir, experiment 4).

(c) **Reinfusion II (reservoir)**

The reservoir of shed blood was next reinfused, and the gradients of response of SWI and CVP again compared in the two groups (Gradient during reinfusion of reservoir: Stage II, Fig. 2; Table I). In the control group the mean gradient was 1.09 ± 1.56 and in the treatment group 2.26 ± 0.73 gm-M/kg/mm: these figures are both higher than the respective value for each group during Stage I, but neither increase was statistically significant. The mean gradient of the treated group was however significantly higher than that of the control group during reinfusion of the reservoir (Mann-Whitney U = 14, \( p < 0.03 \)).

(a)/
(d) **Reinfusion III (dextran after reinfusion of the reservoir)**

In the final phase of the experiment the gradients of the infusion responses to 100 ml dextran - 110 were compared within and between groups: this infusion was given over 10-15 minutes and was completed within 45-60 minutes from the commencement of Stage I. In each group there was now a marked fall in gradient (Fig. 2b); this reduction was significant in the group which had received ouabain ($t_5 = 11.38, p < 0.01$). The value of 0.89 gm-H/kg/mm in the control group was higher than that of the treated group (0.28 gm-H/kg/mm) due to the high gradient recorded in experiment 4. This animal required further infusion, evidenced by reduction of central venous pressure and cardiac output, and the gradient response to a further infusion of dextran fell to 0.12 gm-H/kg/mm.

(e) **Cardiac deficit**

The effects of a period of oligaemia and of treatment on cardiac performance were also assessed by comparing the SWI before shock with a value of SWI after reinfusion: the second value of SWI was recorded at a stage of treatment when central venous pressure was equal to that obtaining before the bleedout. In terms of Starling's Law, if central venous pressure is unchanged and length-tension relationships in the myocardium remain unaltered then any change in SWI must reflect a true alteration in contractility. Table II shows values of SWI recorded at identical levels of central venous pressure before and after shock in the two groups. When the value/
value of SWI after shock is expressed as a percentage of that observed at the same level of CVP before shock, it will be seen that there is no significant net change in the control group (91% of SWI before shock) although the variation between individual animals is quite marked. Similarly, in the treated group there is no net change in SWI at comparable levels of venous return (107% of SWI before shock).

DISCUSSION

(Experiment I)

The principal aims of the first group of experiments were threefold. First, since any assessment of inherent cardiac performance must take account of the state of venous return, we have attempted to assess the value of the gradient of the infusion response as an estimate of contractility. Second, we have sought confirmation of the experimental demonstrations by earlier workers of diminution in the response of cardiac output to comparable infusions following haemorrhagic shock. By this means it was hoped to create an experimental model resembling as closely as possible the type of acute cardiac failure which is thought to occur under clinical conditions. Third, using this model we have tried to determine whether prophylactic digitalisation improves myocardial performance during reinfusion.

The gradient of the correlated responses of SWI and CVP to infusion was chosen as a measure of contractility for two reasons. First/
First, a similar correlation is available during intravenous therapy in clinical cases of shock, where cardiac output and arterial and central venous pressures are being monitored. A reduction in this gradient during infusion would be expected to provide early evidence that further infusion might lead to congestive failure. Secondly, a simple statement of SWI, at a specified central venous pressure, while theoretically taking account of the state of venous return, is inadequate due to the wide range of normal central venous pressures occurring in different individuals: a measurable change in CVP is of greater significance. The histogram showing the distribution of the initial gradient of response to infusion (Fig. 3) suggests that this parameter is distributed as a normal variable, rather than in a random fashion, and we therefore conclude that the term has physiological significance.

The degree of reproducibility of gradient measurements in individual animals was difficult to assess since it was not possible to repeat similar infusion/withdrawal manoeuvres under identical conditions. However, from the paired measurements of cardiac output under basal conditions we have calculated that 93% of the duplicate cardiac output values are within 10% of the first reading. Central venous pressure measurements under anaesthesia and with spontaneous ventilation were found to be highly reproducible, with a variation of less than $\pm 0.25$ mm Hg. Calculating from these figures, it is likely that any change in gradient of greater than 20%
20% in an individual animal is significant: our conclusions with respect to the occurrence of depression or increased contractility in individual animals are based on this estimate. The reproducibility of clinical measurements of gradient of response is likely to be less satisfactory due to the greater variability of central venous pressure in a conscious and possible restless patient.

The second purpose of this group of experiments - to induce by means of shock a state of impaired cardiac performance - was achieved in the majority of cases. On the basis of our estimate of reproducibility of measurements of the gradient of response to infusion, it appears from our results that myocardial performance is usually altered by haemorrhagic shock carried beyond the point of reversal, although in varying directions. The gradient was significantly reduced in experiments 1, 2, 5, 8, 9 and 11, confirming the earlier demonstrations of depressed ventricular function in haemorrhagic shock. In two experiments (4, 6) there was no change in gradient immediately following the shock period, and in two dogs receiving saline with ouabain (7, 10) the gradient in response to this infusion (Stage I) was greater than before shock. This may possibly have indicated very rapid development of an inotropic response to ouabain, but since the gradient was recorded before infusion of ouabain was complete, we believe that this increased gradient more probably reflects the inotropic effect of increased levels of circulating catecholamines which Walker and his colleagues have demonstrated at this phase of experimental reservoir shock.
No significance is attached to the increase in gradient seen in experiment 3 since the gradient of the response to initial infusion of dextran before shock was abnormally low.

It seems probable that the observed variation in the gradient of the response to reinfusion after shock among individual animals reflects the varying influences of several different biological factors on myocardial performance in shock. However, variation due to technical factors cannot be excluded in the interpretation of these data. These factors are discussed below, and were rectified in the second group of experiments. The biological factors underlying variability in the effects of shock on cardiac performance are discussed on pages 39-41.

With respect to the third purpose of these experiments, we conclude from the between-groups comparison of the gradient during reinfusion of the reservoir (Stage II, Fig. 2b, Table I) that the response to reinfusion of the reservoir blood was greater in the treated than in the control group, and that this was most probably due to digitalisation. The increased response to reinfusion of the reservoir in the treated group was not sustained: there was no significant difference between the two groups in their response to subsequent infusion of dextran after reinfusion of the reservoir (Stage III). This is well illustrated by experiment 10 (Fig. 4); the response to infusion was sufficiently effective for reinfusion of the reservoir to be completed without any increase in central venous pressure. However, the response to infusion then ceased abruptly/
abruptly: there was no further increase in SWI, and this parameter remained at 64% of the level achieved in response to comparable filling pressures before shock.

This finding suggests that a state of depression may supervene, in spite of an initial response to digitalisation. This secondary reduction in performance is probably not attributable to the normal decay of the effect of an instantaneous dose of ouabain: in all experiments the gradient at Stage III of reinfusion was measured within one hour of administration of ouabain. Crowell and Guyton⁴, using similar experimental material, demonstrated an inotropic response to ouabain which they also found to be transitory. For this reason any assessment of digitalis in experimental haemorrhagic shock must also take into consideration effects on mortality, and a beneficial effect on survival must be demonstrable before its use in clinical practice can be advocated. McPherson and Haller²⁰ found that ouabain did not improve survival in dogs subjected to reservoir shock. However, these workers employed a preparation in which mortality in the control group was 100%: in this type of severe, irreversible preparation it is unlikely that any form of treatment will secure a proportion of surviving animals. Our experiments were terminated deliberately and we can therefore contribute no information on survival.

There are three aspects of the experimental technique adopted for the first group of studies which may have contributed to some
of the variability encountered in the effects of shock on myocardial performance, and which might have served to conceal the true magnitude of any inotropic effect under investigation.

The first of these factors, already referred to, is the reproducibility of measurements of the gradient of response to infusion. The wide estimate suggested for the confidence limits (±20%) for the gradient measurements derives from the use of central venous pressure as an index of pulmonary venous return to the left side of the heart. This assumption is open to criticism since the contractilities of the two ventricles may vary independently; left ventricular stroke work index, as measured in these experiments, can therefore only be properly compared with a measure of filling pressure on the left side of the heart.

Second, the use of intermittent doses of barbiturate for anaesthesia may have contributed to some of the variability encountered in the gradient of the response to infusion before shock, and in the effects of shock on cardiac performance. Errors may arise where anaesthesia is either excessive or insufficient. In experiment 3 the gradient of the response to infusion before shock was particularly low (0.35 gm/M/kg/mm), and this we believe may have indicated persisting myocardial depressant effects of a recent injection of pentobarbital for maintenance of anaesthesia: transient depressions of arterial pressure, with a rise in central venous pressure, were regularly associated with maintenance doses of anaesthetic. Conversely, increased contractility is frequently due to/
to the inotropic effect of raised levels of circulating catecholamines; the increased gradients in response to initial infusion seen in experiments 2 and 11 were associated with pulse rates of 195 and 177 respectively, and may therefore have reflected the increased catecholamine activity frequently seen after induction of anaesthesia.

Thirdly, systemic acidosis is a recognised cause of myocardial depression, and the inotropic effect of digitalis may also be reduced by metabolic acidosis. Standard bicarbonate levels before and after the period of oligaemia were compared in six of the present series of experiments, and a reduction confirmed in each case (Table I). It is therefore possible that the effect of digitalis observed in these experiments might have been greater and more prolonged if acid-base status had first been corrected.

However, the greater part of the variability encountered both in the effects of shock on the gradient of the function curve, and in the response to ouabain, probably reflects alterations in a delicate equilibrium between the catecholamine response to shock on the one side, and on the other, depressant affects such as systemic acidosis, mobilisation of free fatty acids, and intracellular damage resulting from underperfusion. These factors are further discussed on page 41. Reductions in haematocrit due to the infusion of dextran in these experiments, with consequent changes in blood viscosity and peripheral resistance, are unlikely to have influenced the results since the calculation of stroke work index takes account of/
of work done against systemic arterial resistance as well as of
stroke volume. Mean reductions of haematocrit during the initial
infusion of dextran were 18.8% in the control group and 17.0% in the
treated group, and the difference in response to treatment in the
two groups is therefore unlikely to be due to this factor.

SUMMARY
(Experiment I)

Ventricular function responses were plotted by infusion of
dextran 110 before and after a period of reservoir shock in 11 acute
experiments using dogs lightly anaesthetised with pentobarbitone.
Six animals received ouabain (0.02 mg/kg) with the first 200 ml
of reinfusion. The initial gradients of the infusion curves were
compared with the gradients during early and subsequent phases of
reinfusion.

In six dogs there was evidence of a deficient myocardial response
to the early phase of reinfusion, whereas in two others there was an
increase in contractility. In four of the six dogs which received
ouabain there was an improvement in the myocardial response to
reinfusion, whereas only in one of the five dogs which received
identical reinfusion without ouabain was there an improvement in
contractility. This difference was significant \( p < 0.03 \), but was
not sustained. The various factors which may introduce variability
in these results are discussed.

EXPERIMENT II/
EXPERIMENT II

INTRODUCTION

From analysis of the first group of experiments there emerged three technical factors which it was felt might have a significant bearing on the results. A second series of experiments was therefore performed, again studying haemorrhagic shock in dogs, with the following alterations in procedure. First, following induction with thiopentone, anaesthesia was maintained with an inhalational agent in an attempt to maintain a steady plane of anaesthesia: nitrous oxide supplemented with a small concentration of halothane was selected for this purpose. Second, systemic metabolic acidosis was corrected with sodium bicarbonate prior to the administration of any inotropic agent. Third, cardiac performance was assessed with respect specifically to the left ventricle, by comparing left ventricular contractility with a left-sided filling pressure. These parameters were derived in real time from continuous analysis of the left ventricular pressure trace, using a parallel hybrid computer on line.

METHODS

Ten acute experiments were performed on healthy adult collie/mongrel dogs (mean body weight 12.5 kg, range 10.6-14.8): five animals survived for the full duration of the experiment (Table III). Following overnight starvation, with water available ad libitum, anaesthesia was induced with sodium thiopentone 250 mg (2.5% solution) given/
given intravenously over 30 sec. The trachea was intubated, and
anaesthesia was then maintained with nitrous oxide 5 l/min, oxygen
1.5 l/min, and halothane 0.5% (Flutec vaporizer) delivered through
a Magill circuit. Respiration remained spontaneous throughout the
majority of the experiments. Some animals required brief periods of
artificial ventilation if arterial pressure was allowed to fall below
50 mm Hg; with restoration of arterial pressure spontaneous
respiration returned in all experiments.

Aortic and central venous pressures, and the electrocardiogram
and heart rate were measured and recorded by the methods previously
described. Core temperature was recorded on a rectal thermometer
and maintained at 37°C (± 1.5°C) by means of a variable heat source
beneath the operating table. Cardiac output was measured by the
dye dilution technique. Left ventricular stroke work index was
calculated in this group of experiments as follows:

\[
L_v S.W.I. \ (gm\cdot m/kg) = \frac{C_0 \cdot (l/min) \times (MAP-CVP) \ (mm\ Hg) \times 13.6}{Heart\ rate/min \times Body\ weight\ (kg)}
\]

Left ventricular pressure was recorded by means of a Kifa-pattern
catheter (Eschmann, FG 6, 50 cm) inserted by exposure of the left
common carotid artery (Fig. 6). The catheter was connected to a
Sanborn 267BC pressure transducer by means of a rubber connector
5 cm in length. A gate clamp was mounted on this connector and
tightened until excessive overshoot on the waveform was abolished.
Identical waveforms were secured for each experiment (Fig. 5). At
the conclusion of the final experiment the catheter was withdrawn
from/
from the animal and without altering the gate clamp the frequency response of the system was examined by the method of Fry$^{21}$. Frequency response was flat up to 16.7 Hz. (mean of four values, range = 15.4 - 18.5).

The crude pressure trace was displayed and recorded in the laboratory and simultaneously conveyed through a multichannel data link to an EAL TR 48 analogue computer (Fig. 7). The trace was processed in real time using a parallel hybrid configuration previously described$^{22}$. The resulting beat-by-beat values for maximum rate of rise of left ventricular systolic pressure (dp/dt max, mm Hg. sec$^{-1}$) and for left ventricular end-diastolic pressure (L.V.E.D.Po, mm Hg) were converted to time-loaded means by derivation in the computer of the exponentially mapped past (E.M.P.) function. The outputs of the computer were two d.c. voltages which were returned to the experimental laboratory and displayed on an X-Y recorder with dp/dt max on the vertical and L.V.E.D.Po on the horizontal axes respectively. A continuous and permanent plot of ventricular function in terms of standard coordinates was therefore available as each experiment proceeded.

**EXPERIMENTAL PROCEDURE**

Following introduction of the catheters there was frequently a short period of persistent tachycardia which settled spontaneously: baseline recordings were then taken. In this group of experiments no initial infusion was given and the experimental procedure commenced with the induction of oligaemia by bleeding from the femoral cannula/
cannula into a heparinized reservoir. Correlations of the reduction of dp/dt with EDP, and of LVSWI with EDP during the bleedout generated function curves which established the initial values of cardiac performance (Fig. 8). The bleedout was terminated when mean arterial pressure had fallen to 55 mm Hg. As the vasoconstrictor response to oligaemia developed it became necessary to withdraw additional small volumes of blood in order to restrict arterial pressure to the selected level. Using on-line analysis of the left ventricular pressure trace supplementary function curves were plotted where the additional withdrawals of blood were sufficiently large to generate a function curve (Fig. 9).

Following reversal a period of 30 minutes was allowed to elapse during which some reinfusion of reservoir blood was required in order to maintain arterial pressure. Prior to reinfusion of the greater part of the reservoir the correlation of dp/dt and EDP was recorded, and if the condition of the animal permitted dye curves were taken, allowing correlation of LVSWI with EDP. (Fig. 10).

Reinfusion of each animal was in three stages. The reservoir blood was first reinfused, while responses of dp/dt and EDP were recorded and correlated continuously. At an intermediate point and at the end of this infusion, cardiac output was recorded, allowing calculation and construction of an approximate function curve for LVSWI against EDP.

An infusion of sodium bicarbonate (60 mEq/100 ml) was next given/
given. Approximately 5 minutes after completion of the reinfusion of the reservoir, the base deficit (mEq/l) was measured, using the equilibration method of Sigaard-Andersen. The volume of the infusion given was calculated by assuming arbitrarily that the volume of the extracellular fluid space requiring correction of acidosis was 40% of the total body weight (kg). Continuous correlations of dp/dt and EDP were again made during this infusion and L.V.S.W.I. and EDP were compared before and after infusion (Fig. 8).

The third infusion consisted in each animal of 100 ml dextran - 110 (Glaxo) again correlating SWI and dp/dt with E.D.P. Ouabain or saline was given in this series of experiments as a single injection of 0.5 ml volume over 90 seconds: the animals were allocated randomly into control or treatment groups and the code withheld from the observer until assessment of results was complete. Fifteen minutes after this injection a fourth infusion was given to both groups of animals, again consisting of 100 ml dextran - 110, with correlations of SWI and dp/dt with EDP.

Following this infusion each animal was observed for one hour. In two experiments (4,5) there were marked reductions of L.V.E.D.P., dp/dt, cardiac output and arterial pressures during this period. These changes were taken to indicate progressive loss of effective circulating blood volume, perhaps due to loss of tone in capacitance vessels, and additional dextran - 110 was therefore infused at a rate sufficient/
sufficient to maintain L.V.E.D.P. constant; in both experiments 200 ml of infusion was required. Where an animal survived to the end of this period the probable outcome of the experiment in terms of further maintenance of cardiac performance was judged by reference to two criteria:-

1. Preservation of the correlations of L.V.S.W.I., dp/dt and EDP on the ventricular function curve obtaining at the time of the second infusion of dextran.

2. Absence of arrhythmia.

RESULTS

(a) Control study

The tenth experiment performed in this series served as a control animal for assessment of the effects of the catheterisation procedure and of prolonged anaesthesia on myocardial performance (Table IV). Initial L.V.S.W.I. was 1.67 gm-M/kg, with L.V.E.D.P. 9.8 mm Hg; pulse rate was 120/min. No significant changes occurred in haemodynamics during the initial eight hours of observation. Over the subsequent hour there was a fall in L.V.S.W.I. to 1.12 gm-M/kg; mean L.V.E.D.P. fell simultaneously to 5.4 mm Hg, a combination of changes suggesting loss of blood volume. Some slow venous haemorrhage from the catheter sites was observed and an infusion of 100 ml dextran = 110 therefore given over one hour. L.V.S.W.I. returned to/
to 1.56 gm-N/kg, a value within the limits of reproducibility of
the initial value: L.V.E.D.P. rose to 9.9 mm Hg, essentially
identical with the initial level. An unsatisfactory feature of this
experiment was a progressive metabolic acidosis, standard
bicarbonate falling to 12.6 mEq/l.

(b) Changes in myocardial performance after shock

In the five animals subjected to haemorrhage, and which survived
beyond reinfusion of the reservoir, myocardial performance was
assessed by comparison of L.V.S.W.I. after reinfusion of the reservoir
with a value of L.V.S.W.I. recorded at an equal level of L.V.E.D.P.
before shock. The value of L.V.S.W.I. after shock was expressed
as a percentage of the initial value (Table IV). In three animals
(1,3,4) there was a marked reduction in performance; in one animal
(2) there was no change; in the fifth animal performance was
increased above control levels, and remained elevated during
subsequent infusions given to counteract progressive loss of
intravascular volume in the late stages of this experiment.

(c) Response to sodium bicarbonate

Five of the nine animals subjected to shock in these experiments
(1-5) survived to that stage of the study at which acid-base status was
corrected. Measurements of arterial pH, pCO₂ and standard
bicarbonate were made before and after infusion of sodium
bicarbonate in three of these animals (Table V) and of pH alone in a
fourth. Of the animals which were substantially acidotic and in
which acid-base status appeared significantly improved with bicarbonate (1,3,5), only the fifth animal showed a positive inotropic response in addition to the vascular expanding effect of the infusion. In one animal (4) respiration ceased for 5 minutes following infusion of bicarbonate; artificial ventilation was applied during this period and spontaneous respiration then returned.

(d) The effect of ouabain on left ventricular performance

Values of left ventricular stroke work index, $\frac{dp}{dt}$ max and end-diastolic pressure before and after ouabain are shown in Table VI for the four animals (2-5) receiving this agent. In experiments 1 and 2 either saline 0.5 ml or ouabain 0.02 mg/kg was given, the selection being randomised. In neither animal was an inotropic response recorded, and both animals survived for the observation period of one hour following treatment. After confirmation that one animal had received ouabain, the treatment option was changed for experiments 3-9 to 1.0 ml saline vs. 0.04 mg/kg ouabain.

For experiments 3 and 5 ouabain was the treatment option selected. In the first of these animals, there was no response of $\frac{dp}{dt}$ max to the first 100 ml infusion of dextran, whereas after ouabain there was a marked response to dextran (Table VI); however, complete heart block associated with progressive left ventricular failure developed after nine minutes, and the animal died thirty minutes later. The second of these animals (5) showed a small positive inotropic response to ouabain, but subsequently developed ventricular extrasystoles/
extrasystoles and failure, and died.

In experiment 4 there was no response to the inotropic agent: left ventricular failure developed shortly afterwards and the result was therefore immediately judged unsuccessful, and a further injection given, ouabain (0.04 mg/kg) now being selected deliberately. After eight minutes a marked positive inotropic response had developed, reflected in increased stroke work and dp/dt, with reduced E.D.P: however, complete heart block occurred after ten minutes, with progressive and irreversible bradycardia. After analysis of the results it was confirmed that the first injection in this experiment had been saline.

DISCUSSION (EXPERIMENT II)

The first objective of this group of experiments was to assess the value of an analogue computing technique in the assessment of myocardial performance. A parallel hybrid programme similar to that employed in these experiments was described by Smith and Schwede, but to our knowledge the present studies represent the first attempt to employ these techniques on a routine basis for analysis of experimental data.

Several substantial advantages of this technique emerged in these studies. First, the time required for manual measurements of dp/dt and L.V.E.D.P. from the crude trace is considerable, and usually precludes the sampling of more than a small proportion of beats/
beats: the programme employed here analyses all beats, thus avoiding sampling errors. Second, whereas the criteria adopted by the observer for visual measurement of $\frac{dp}{dt}$ and of $L.V.E.D.P.$ require an element of arbitrary selection, identical criteria are applied by the logic network to the analysis of each beat. Third, the choice of varying time constants for simulation of the exponentially mapped past (averaging) function allows the display of mean values of the parameters over intervals selected by the observer. Thus slow phasic changes due for example to respiration can be damped. Under these conditions the mean recorded values remain stable within narrow limits ($\frac{dp}{dt} \pm 3\%, L.V.E.D.P. \pm 0.25 \text{ mm Hg}$), and a change of 1 mm observed in $E.D.P.$ is significant, changes of this order of magnitude occurring for example during withdrawal of 30 ml blood for a dye dilution curve. A final and highly valuable advantage of this technique was the ability to assess accurately the state not only of myocardial contractility but also of venous return as the experiment proceeded, by comparison of the position of the recording pen with the control ventricular function curve generated by the bleedout (Figs. 8, 9).

As these studies proceeded certain disadvantages of this system emerged. First, at the low values of $\frac{dp}{dt}$ encountered during initial bleedout, some readjustment of the relay threshold voltages was sometimes necessary in order to allow the $\frac{dp}{dt}$ gating circuits to operate (Fig. 7). Such readjustments did not however affect the final/
final values of \( \frac{dp}{dt} \) recorded. Second, the frequency response characteristics of the left ventricular catheter system introduce some attenuation of \( \frac{dp}{dt} \) values above 2000 mm Hg sec \(^{-1} \); measurements of \( \frac{dp}{dt} \) are therefore of limited value for purposes of comparison of separate experiments, although we consider comparisons of \( \frac{dp}{dt} \) values within a single experiment to be valid. Thirdly, \( \frac{dp}{dt} \) max is partially rate-dependent, and to this extent is not a specific measure of cardiac performance: however, changes in \( \frac{dp}{dt} \) must indicate true changes in contractility where no simultaneous change in heart rate occurs. For these reasons we attach greater significance to L.V.S.W.I. as a measure of the capacity of the heart to perform external and therefore "useful" work.

The application of a computing technique such as this to clinical measurements of left ventricular performance has considerable potential value, not only for processing of diagnostic catheterization data, but for monitoring of patients requiring fluid therapy and at risk of developing left ventricular failure. Such patients include those recovering from open-heart surgery, those with acute myocardial infarction, and perhaps those with haemodynamic evidence of cardiac failure secondary to bacterial or traumatic shock (Fig. 1b).

The second aim of these experiments was to establish the relative incidences of increased and decreased myocardial contractility following oligaemia. In the first group of experiments, depression, enhancement and no significant change were observed in six, two and two animals respectively: however these results/
results were open to criticism on the grounds that a specific measure of left ventricular filling pressure had not been employed. In the second group of studies depression, enhancement and no significant change were observed respectively in three, one and one animals surviving to completion of reinfusion: this ratio closely resembles that seen in the earlier studies. It is concluded that this experimental model provides an effective means of inducing cardiac failure secondary to shock, and that the inferences drawn from the earlier studies are correct.

Third, we have attempted to determine the effect of correction of extracellular acidosis on myocardial performance, and on the response of the heart to digitalis. The depressant effect of acidosis on the heart has long been recognised, and has been most recently confirmed by Wildenthal and his colleagues using infusions of lactic acid. The results of the present studies were disappointing: of five animals receiving bicarbonate, three responded with changes in $\frac{dp}{dt}$, $S.W.I.$ and $E.D.P.$ to a higher point on the same ventricular function curve, indicating purely a vascular expanding effect. In one animal (4) there was a marked but transient improvement in performance which coincided with administration of bicarbonate: however since the increase in standard bicarbonate was no greater than 4.1 mEq/l it seems unlikely that the observed changes indicated a direct effect of the bicarbonate infusion on the heart. Only in one animal (5) was a sustained inotropic response to bicarbonate infusion observed in addition/
addition to vascular expansion.

It seems unlikely from these results that extracellular acidosis is the principal factor contributing to cardiac depression in oligaemic shock: more probably systemic acidosis reflects the development of intracellular damage which is more directly responsible for disturbances of function in a number of tissues, one of these being the myocardium.

The effects of digitalisation observed here confirm the earlier findings: in both experiments an immediate inotropic response was observed, but in neither series was this effect sustained. Of the present nine animals subjected to oligaemia five survived to the stage of the experiment at which saline/ouabain was given. In the first of these animals (1, Fig. 9) left ventricular insufficiency secondary to shock persisted throughout reinfusion and subsequently; nevertheless the animal survived the full period of observation following reinfusion and represents successful management of cardiac failure without the use of inotropic agents. The second animal did not respond to ouabain (0.02 mg/kg); there were no side effects of the drug in this dosage, and the animal again survived the period of observation. The increased dosage of 0.04 mg/kg was adopted in order first to ensure an inotropic effect in all animals, and secondly to exclude the possibility that the late cardiac failure seen in the earlier studies was due to an inadequate dose of ouabain. The remaining three animals all responded to this dosage, but in each case this effect remained temporary, failure returning, usually accompanied/
accompanied by arrhythmia: two animals died within the prescribed observation period and the third must also be considered a failure of treatment. Although slightly delayed in this animal the mode of death was similar to that of the other two animals, and does not indicate any relative advantage of ouabain in this animal, but rather that the observation period chosen was too short. The behaviour of these three animals closely resembles that of the treatment group in the first series of experiments in respect of their development of failure following an initial response to ouabain. Moreover, in the present case the infusion was monitored by constant reference during the experiment to L.V.E.D.F., which was maintained by these means within ± 2 mm Hg of the value before bleed out; indeed additional volumes of dextran were often necessary in order to maintain venous return, due probably to capacitance vessel failure and haemorrhagic necrosis of bowel mucosa, the latter feature being peculiar to advanced shock in the dog. Excessive infusion can therefore be entirely excluded as a cause of late cardiac deterioration in these experiments.

CONCLUSIONS (EXPERIMENT II)

1. It would appear from both groups of studies that the incidence of overt cardiac depression in the present experimental preparation is approximately 60%: in a further 20% of animals cardiac performance is increased, while in the remainder no change is observed.
2. It is considered that adequate correction of extracellular acidosis was achieved in three animals: only in one of these did cardiac performance improve, although temporary non-specific increases of cardiac output due to vascular expansion usually occurred.

3. Even with the more closely controlled and favourable conditions of the present experiments, a case for the use of ouabain, either on a prophylactic or a therapeutic basis, remains to be proved. The margin between a dose whose inotropic effect can be relied upon, and one producing unacceptable side effects, is so narrow as to render its use impracticable and perhaps dangerous. Possible explanations for the transient effects of ouabain are suggested in the following section.
Enhancement or impairment of cardiac performance?

A striking feature of the results presented has been the variability of the changes observed in contractility following shock. In the present preparation depression occurred in 60% of experiments and enhanced performance in 20%, the remainder showing no change. The findings of other workers are also conflicting: Wiggers and Crowell and Guyton considered that cardiac performance was invariably depressed if filling pressure was maintained at the initial value. In contrast Desai, Kim and Showmaker found that the ventricular function curve was elevated at a comparable phase of their experiments.

Enhanced cardiac performance in shock

A progressive increase in contractility was regularly observed during the intermediate and advanced stages of oligaemia in the second group of experiments: this is most probably the effect of increased concentrations of circulating catecholamines, demonstrated in experimental haemorrhagic shock by Walker and his colleagues.

Catecholamine activity is capable of neutralising the depressant effects of a substantial accumulating acidosis (pH 6.8): with B-adrenergic blockade this protective influence is removed and the full depressant effects of acidosis and other factors (see below) are/
are then observed. We would suggest that the myocardial depression observed later in these experiments represents a gradual shift in the relative preponderance of positive and negative inotropic influences as acidosis and intracellular damage progressively increase (Fig. 11). The apparent conflict in the results from individual experiments and from other laboratories may perhaps be resolved on this basis.

**Causes of myocardial depression**

The myocardial depressant effect of systemic acidosis in an otherwise normal animal is well recognised. Henderson and his colleagues have shown that under anoxic conditions free fatty acids (F.F.A.) can cause loss of contractility in vitro: F.F.A. are elevated in patients with infection, particularly that due to Gram-negative organisms, and after burns. Levels of plasma F.F.A. are reduced in advanced shock in the present model, and this factor is therefore unlikely to be significant under these particular conditions. Some anaesthetic agents are recognised to cause myocardial depression: halothane is one such agent, but in the concentration employed in these experiments (0.5%) this effect has been shown to be minimal.

Brand and his colleagues have detected in the plasma of cats subjected to haemorrhagic shock a substance capable of causing depression of cardiac contractility in vitro. Further work by Lefer suggests that this substance is a peptide (m.w. approximately 1000), perhaps liberated by the action of proteases on plasma proteins.
proteins. The source of proteolytic enzyme is believed to be ischaemic pancreatic tissue, and it was shown that myocardial depression could be prevented by prior administration of TrasyloI\(^{34}\).

A direct effect of endotoxin on the heart may prove to be of importance in the aetiology of acute cardiac failure in bacterial shock. Schumer and his colleagues\(^{35}\) have shown that if E. coli endotoxin is given in vivo and cardiac muscle mitochondria subsequently extracted, their oxidative metabolism is impaired; similar effects on skeletal muscle and on liver mitochondria have been demonstrated\(^{36}\).

**Intracellular damage**

Whatever the relative importance of these factors, it seems likely that the principal cause of depressed myocardial performance is the direct effects of cardiac underperfusion on intracellular metabolism, the mitochondria again being principally affected. Ledingham\(^{37}\) has shown that myocardial blood flow is reduced in experimental oligaemia: the secondary effects of oligaemia on skeletal muscle include reductions in surface pH\(^{38}\), membrane potential\(^{39}\), and loss of potassium\(^{40}\), the "sick cell syndrome". There is also loss of potassium from acutely ischaemic myocardium\(^{41}\), and more chronic depletion of potassium from the heart is associated with loss of contractility\(^{42}\). Cardiac mitochondria are extensively damaged following oligaemia\(^{43}\), and it is therefore reasonable to postulate that impaired cardiac performance arises as a result of a vicious/
vicious circle in which impaired perfusion, abnormal distribution of cations across cellular and mitochondrial membranes, and impaired oxidative metabolism are inseparably linked. While the specific nature of this disturbance remains unclear, a similar mechanism is probably common to the effects of underperfusion throughout the body. It seems likely that the early effects of underperfusion are reversible, whereas if this is sustained an increasing proportion of cells is irreparably damaged. The failure of peripheral oxygen utilization which has been observed in refractory septic shock following adequate restoration of oxygen delivery may occur on this basis. In the light of this argument the potential harm which may arise from the use of digitalis in this situation may be more readily appreciated, especially if the intracellular effects of the cardiac glycosides are taken into consideration. There is inhibition of the membrane exchange mechanism for sodium and potassium, together with increased oxygen uptake due to enhanced contractile activity. Demand for high energy intermediate groups such as adenosine triphosphate is therefore likely to increase following digitalisation. If this requirement cannot be met owing to mitochondrial damage as a result of earlier oligaemia, then the effect of digitalis must inevitably be to accelerate not only the depletion of these intermediates but also the derangement of ion distribution across membranes: cellular damage may therefore be increased in direct proportion to the scale of the inotropic response obtained. The occurrence/
occurrence of left ventricular failure and ventricular arrhythmias following administration of digitalis may perhaps be explained on this basis.

Experimental evidence compatible with this hypothesis has recently been presented: the area of ischaemic damage following myocardial vascular occlusion is increased in the presence of digitalis.
METABOLIC AGENTS IN THE TREATMENT OF CARDIAC FAILURE IN SHOCK

In view of the present unsatisfactory results of conventional inotropic treatment an alternative approach is required, in which an attempt might be made to correct one of the abnormalities of metabolism which develops in low perfusion states, namely depletion of intracellular potassium.

Solutions of glucose, insulin and potassium given in high concentration are believed to facilitate entry of glucose and potassium into cells. This treatment has been extensively investigated as a means of stabilizing the myocardial cell membrane following infarction, with variable results: it has, however, been successful in the treatment of acute cardiac failure following bypass surgery. In general surgical patients with electrolyte abnormalities following severe trauma, glucose and insulin have been effective in restoring normal serum concentrations and excretion of sodium; these changes were interpreted as indicating extrusion of excess sodium from cells, with reaccumulation of potassium within them. There may therefore be a place for these agents in the management of several acute situations complicating surgical lesions; these include cardiac arrhythmia, acute left ventricular failure, disturbances of sodium distribution, and impaired renal function. Furthermore, in view of the widespread cellular effects of underperfusion and perhaps of circulating bacteria or their components, the use of these agents in a greater range of acute surgical conditions should be evaluated.

SUMMARY/
SUMMARY

1. Evidence is presented from haemodynamic studies of patients in surgical shock, with the conclusion from these and other published data that the contractile performance of the heart may sometimes be impaired as a result of shock. This situation arises at an early stage in reinfusion; it is therefore not the consequence of overinfusion, but does however render the patient particularly susceptible to overinfusion.

2. The incidence of increased and depressed cardiac performance secondary to oligaemia was studied in two groups of dogs subjected to reservoir shock. Stroke work index was correlated first with central venous and later with left ventricular end-diastolic pressures. In both cases there was an initial increase of contractility; subsequently, during reinfusion of the reservoir, performance remained elevated only in 20%, whereas it became depressed in 60% of animals, and returned towards initial values in the remainder.

3. The inotropic effects of rapid digitalisation with ouabain were studied. A significant improvement was demonstrated in both groups of animals, but this was not sustained. The margin between an effective dose and one associated with ventricular arrhythmias was found to be unacceptably small.
4. The haemodynamic effects of correction of extracellular acidosis with sodium bicarbonate solution were studied. The principal effect observed could be attributed solely to a vascular-expanding action: of three animals in which good correction of acidosis was achieved, only one showed a positive inotropic response. Prior correction of acidosis did not improve the response to digitalisation.

5. Aspects of the pathophysiological response to oligaemia which may affect cardiac performance are discussed. It is concluded that in advanced shock the increasing influence of depressant agents progressively neutralizes the positive inotropic effects of catecholamines.

6. It is suggested that the principal cause of myocardial depression is depletion of intracellular potassium, a feature of the effects of oligaemia on other tissues. Reasons are given for believing that this situation may be made worse by cardiac glycosides.

7. In the light of these considerations a "metabolic" treatment regime employing glucose and insulin is proposed: such a regime may have more general potential advantages in the management of acute surgical conditions, in addition to any effect on the heart.

ACKNOWLEDGEMENTS
ACKNOWLEDGEMENTS

These studies were undertaken in the Department of Clinical Surgery, University of Edinburgh; I am grateful to Professor Sir John Bruce for provision of experimental facilities.

I thank Mr. I.B. Macleod for his encouragement and advice in the planning and reporting of these studies.

The computer was provided for the Faculty of Medicine, University of Edinburgh, by the Wellcome Trust: I am grateful to Mr. D.E.M. Taylor, Department of Physiology, for development of the computer logic.

I thank Miss P. Dugard, Department of Statistics, for analysis of the data, Messrs. M. Walker and V. McCallum for technical assistance, and Miss S. Dawson for secretarial assistance.
REFERENCES


31. Strong, A.J. and Oliver, M.F. Unpublished data.


A group of ventricular function curves, demonstrating that the response of stroke volume or stroke work to a change in filling pressure is predictable for any given level of contractility. In the absence of changes in contractility, intravenous infusion or loss of venous return are associated with movements along a single curve.

Fig. 1b

Simultaneous correlations of stroke work index with filling pressure in eight surgical patients in shock, illustrating (a) changes in contractility and filling pressure in individual patients, and (b) marked variations in contractility between individuals. Those with high central venous pressures are considered to have chronic congestive failure while the patients (M.H., D.L.) with multiple trauma may have developed acute failure secondary to traumatic shock (Patients of Professor Sir John Bruce).
Diagram showing general configurations of ventricular function curves before shock and at three stages of reinfusion. Contractility is expressed as the gradient of the straight line between points recorded during the initial phase of each infusion.

Sequence of changes in the gradient of response to infusion in control (mean of 5) and treated (mean of 6) groups. Contractility during reinfusion of the reservoir blood (Stage II) was significantly higher in the treatment group than in the control group.
Number of Experiments

Histogram showing the distribution of the correlated responses of stroke work index and central venous pressure to the initial infusion of dextran (all experiments).

Fig. 3
Responses of stroke work index and central venous pressure to infusion before (●) and after (X) shock in experiment 10, showing an increase in stroke work index with no net increase in C.V.Po during infusion of saline with ouabain (Stage I) and of the reservoir (Stage II). The gradient of the function curve then falls, and there is no further increase in stroke work index in response to infusion of dextran (Stage III). The values of stroke work index attained in response to this infusion remains at 64% of the values of stroke work index at comparable levels of C.V.Po during the infusion of dextran before shock.
Specimen of left ventricular pressure trace after adjustment of damping conditions, yielding a frequency response uniform up to 16.7 HZ.
**Fig. 6**

Diagram of laboratory apparatus for real-time measurement of left ventricular function.

**Fig. 7**

Diagram illustrating computer logic for derivation of maximum rate of rise of systolic pressure and end-diastolic pressure.
Example of simultaneous correlation of mean maximum dp/dt with mean L.V.E.D.P. by computer processing of the left ventricular pressure trace (Experiment II.5). Curve 1-2 shows the correlation of reductions in dp/dt max and end-diastolic pressure in response to withdrawal of 250 ml of blood. This manoeuvre generates a Starling curve which serves as a baseline measurement of contractility. Point 3 demonstrates increased contractility, due probably to the positive inotropic effect of increased levels of circulating catecholamines. Following reversal (4) contractility has fallen markedly; the initial response to reinfusion confirms diminished contractility (4–5) but this recovers (6) with further reinfusion. Between (6) and (7) the remainder of the reservoir is reinfused and acidosis is corrected with sodium bicarbonate; the gradient between 6 and 7 is parallel to that of the baseline curve, demonstrating that the effect of bicarbonate is simply due to volume expansion in this experiment, with no improvement in contractility. At 7 there is a small increase in contractility in response to ouabain in 15 ml of dextran, and the response to further reinfusion (8) now follows an elevated Starling curve, indicating increased contractility. However, acute left ventricular failure develops 100 minutes after digitalisation (9).
Simultaneous correlation of $\frac{dp}{dt}$ max and L.V.E.D.P. in experiment II. 1 (re-drawn from plotting table). The irregularity on the control function curve obtained during initial blood withdrawal is due to temporary malfunction of the computer, controlled by readjustment of relay threshold voltages. The development of increased contractility is reflected in the displacement of further function curves to the left. From the commencement of reinfusion the gradient of the correlated responses of $\frac{dp}{dt}$ max and L.V.E.D.P. remains low; the only response to sodium bicarbonate was due to the volume-expanding effect demonstrated by the persistent low gradient of the resulting function curve.
Simultaneous function plots of (a) stroke work index and (b) $dp/dt_{max}$ against end-diastolic pressure in experiment II.4.

Continuous lines are not function curves, but illustrate the sequence in which observations were made. In Fig. 10b, there is an increase in contractility during the shock period (-200 ml → 100'). At 200 minutes reversal occurs, with 550 ml blood in the reservoir, and there is a loss of contractility. This deteriorates further as a work load is imposed during the first 250 ml of reinfusion; with the remaining 300 ml of reinfusion function recovers. There is a marked increase in contractility following infusion of sodium bicarbonate (Table V), but following maintenance infusions of dextran function again deteriorates, improving only temporarily in response to ouabain.
Diagram summarizing the effects of loss of venous return, reinfusion, and altered myocardial performance on the correlation of contractile power with diastolic filling of the ventricle.
| No. | Weight (kg) | Cardiac L.V.S.W.I. (l/min/kg) | Gradient of Fall in Pressure (mm Hg) | Cardiac Gradient (gmM/kg) | Oliguria (ml/kg/hr) | Response to Dextran Infusion | Response to Initial Infusion (Stage I) | Response to Initial Infusion (Stage II) | Response to Initial Infusion (Stage III) | No. of Patients | Weight Cardiac Gradient Oliguria Response to Initial Infusion
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.73</td>
<td>0.10</td>
<td>0.07</td>
<td>0.9</td>
<td>0.2</td>
<td>-0.03</td>
<td>I*</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10.75</td>
<td>0.11</td>
<td>0.03</td>
<td>1.2</td>
<td>0.2</td>
<td>0.50</td>
<td>X</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12.17</td>
<td>0.08</td>
<td>0.08</td>
<td>0.8</td>
<td>0.4</td>
<td>0.35</td>
<td>X</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12.40</td>
<td>0.12</td>
<td>0.04</td>
<td>1.6</td>
<td>0.2</td>
<td>1.30</td>
<td>X</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>13.79</td>
<td>0.06</td>
<td>0.03</td>
<td>0.7</td>
<td>0.1</td>
<td>1.30</td>
<td>X</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>12.17</td>
<td>0.09</td>
<td>0.05</td>
<td>1.0</td>
<td>0.2</td>
<td>1.35</td>
<td>X</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>12.37</td>
<td>0.08</td>
<td>0.04</td>
<td>0.9</td>
<td>0.2</td>
<td>1.20</td>
<td>X</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>8.86</td>
<td>0.12</td>
<td>0.02</td>
<td>2.0</td>
<td>0.1</td>
<td>1.00</td>
<td>X</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>14.12</td>
<td>0.11</td>
<td>0.05</td>
<td>1.6</td>
<td>0.3</td>
<td>1.34</td>
<td>X</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>16.58</td>
<td>0.20</td>
<td>0.05</td>
<td>2.5</td>
<td>0.2</td>
<td>0.80</td>
<td>X</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>17.47</td>
<td>0.16</td>
<td>0.06</td>
<td>1.5</td>
<td>0.4</td>
<td>2.60</td>
<td>X</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stage I

Stage II

Stage III

Note: *Denotes significant changes.
<table>
<thead>
<tr>
<th>Experiment</th>
<th>CVP (mm Hg)</th>
<th>S.W.I. before shock (gmM/kg)</th>
<th>S.W.I. after shock (gmM/kg)</th>
<th>( \frac{S.W.I. \text{ after}}{S.W.I. \text{ before}} \times 100 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>4.9</td>
<td>2.7</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
<td>4.4</td>
<td>2.2</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>1.1</td>
<td>1.9</td>
<td>173</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
<td>2.4</td>
<td>1.9</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>7.5</td>
<td>1.4</td>
<td>1.4</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>1.75</td>
<td>1.9</td>
<td>3.6</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>1.0</td>
<td>1.5</td>
<td>2.4</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>-2.0</td>
<td>2.0</td>
<td>3.0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>5.0</td>
<td>5.3</td>
<td>1.2</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>2.0</td>
<td>5.3</td>
<td>3.4</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>3.0</td>
<td>2.5</td>
<td>1.4</td>
<td>-</td>
</tr>
</tbody>
</table>

Mean 91% 

Mean 107%
<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Body weight (kg)</th>
<th>Treatment</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.9</td>
<td>Saline injection 0.5 ml</td>
<td>Depressed cardiac performance after shock: no recovery in contractility but survived full procedure</td>
</tr>
<tr>
<td>2</td>
<td>10.6</td>
<td>Ouabain 0.02 mg/kg</td>
<td>Contractility unchanged after shock: no response to ouabain. Survived full procedure</td>
</tr>
<tr>
<td>3</td>
<td>14.7</td>
<td>Ouabain 0.04 mg/kg</td>
<td>Performance reduced following shock: inotropic response to ouabain but died in complete heart block and L.V. failure after 30 minutes</td>
</tr>
<tr>
<td>4</td>
<td>12.1</td>
<td>(a) Saline injection 1 ml. (b) Ouabain 0.04 mg/kg</td>
<td>Developed L.V. failure: temporary response to ouabain but died in failure, with complete heart block</td>
</tr>
<tr>
<td>5</td>
<td>12.0</td>
<td>Ouabain 0.04 mg/kg</td>
<td>Contractility increased following shock: small response to ouabain: survived 60 minutes' observation period but developed ventricular extrasystoles 40 minutes later and died</td>
</tr>
<tr>
<td>6</td>
<td>12.0</td>
<td>-</td>
<td>Died before reinfusion: bradycardia → asystole</td>
</tr>
<tr>
<td>7</td>
<td>12.2</td>
<td>-</td>
<td>Died before reinfusion? congestive failure</td>
</tr>
<tr>
<td>8</td>
<td>14.8</td>
<td>-</td>
<td>Rapid reversal: bradycardia → ventricular fibrillation during reinfusion</td>
</tr>
<tr>
<td>9</td>
<td>12.3</td>
<td>-</td>
<td>Respiratory arrest during reinfusion</td>
</tr>
<tr>
<td>10</td>
<td>13.2</td>
<td>Control for preparation (no haemorrhage induced)</td>
<td>Myocardial performance sustained over 9 hours</td>
</tr>
</tbody>
</table>

**TABLE III**

Experimental material (second series)
**BEFORE BLEEDOUT**

**AFTER BLEEDOUT**

**SW/I: gradient**

**AFTER REINFUSION. CP RESERVOIR**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Initial value</th>
<th>After 9 hours.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.36</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>105</td>
<td>1520</td>
</tr>
<tr>
<td></td>
<td>6.7</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>6.7</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>610</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>0.7</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>2</td>
<td>1.38</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>1520</td>
<td>1095</td>
</tr>
<tr>
<td></td>
<td>8.2</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>0.27</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>610</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>0.21</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>3</td>
<td>1.31</td>
<td>-2.5</td>
</tr>
<tr>
<td></td>
<td>2190</td>
<td>1655</td>
</tr>
<tr>
<td></td>
<td>-2.5</td>
<td>-2.0</td>
</tr>
<tr>
<td></td>
<td>-1.78</td>
<td>-1.0</td>
</tr>
<tr>
<td>4</td>
<td>1.38</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>1715</td>
<td>1095</td>
</tr>
<tr>
<td></td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>2.7</td>
</tr>
<tr>
<td>5</td>
<td>1.60</td>
<td>12.0</td>
</tr>
<tr>
<td></td>
<td>2060</td>
<td>715</td>
</tr>
<tr>
<td></td>
<td>-0.5</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>0.23</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>-1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**TABLE IV**

<table>
<thead>
<tr>
<th>Left ventricular performance before and after shock, and in a control animal following a slow maintenance infusion (100 ml dextran - 110)</th>
<th>Control</th>
<th>Normotensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse/min</td>
<td>129</td>
<td>163</td>
</tr>
<tr>
<td>PHA</td>
<td>7.26</td>
<td>7.15</td>
</tr>
<tr>
<td>Standard bicarbonate mEq/L</td>
<td>18.4</td>
<td>12.6</td>
</tr>
<tr>
<td>Pinal left ventricular performance (%) of initial value</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>93</td>
</tr>
</tbody>
</table>
### Effects of reduction of extracellular acidosis on left ventricular performance

#### TABLE V

<table>
<thead>
<tr>
<th>Volume effect alone (P&lt;0.01)</th>
<th>Volume effect alone (P&lt;0.01)</th>
<th>Before</th>
<th>Before</th>
<th>After</th>
<th>After</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6.0</td>
<td>0.7</td>
<td></td>
<td></td>
<td>Poor response to volume: no intense inotropic effect in spite of excellent acid-base correction.</td>
</tr>
</tbody>
</table>
### TABLE VI
Effects of ouabain on left ventricular performance.

> indicates the response of each parameter to infusions of 100 ml dextran before and after digitalisation.

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Dose of ouabain (mg/kg)</th>
<th>L.V.S.W.I. (gm M/kg)</th>
<th>dp/dt max (mm Hg sec⁻¹)</th>
<th>L.V.E.D.P. (mm Hg)</th>
<th>Interpretation</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.02</td>
<td>1.11</td>
<td>1.14</td>
<td>1480</td>
<td>1480</td>
<td>6.0</td>
</tr>
<tr>
<td>3</td>
<td>0.04</td>
<td>Not recorded</td>
<td></td>
<td>2015</td>
<td>2015</td>
<td>-0.9</td>
</tr>
<tr>
<td>4</td>
<td>0.04</td>
<td>0.36</td>
<td>0.61</td>
<td>1000</td>
<td>1510</td>
<td>8.8</td>
</tr>
<tr>
<td>5</td>
<td>0.04</td>
<td>0.32</td>
<td>0.55</td>
<td>1650</td>
<td>1755</td>
<td>0.1</td>
</tr>
</tbody>
</table>