Factors Concerned in the Early Stages of Thermal Shock

By Ernest L. Dobson, Ph.D. and George F. Warner, M.D.

With the assistance of Caroline R. Finney and Dorothy M. Adamson

The present study is concerned with the early stages of burn injury and demonstrates that the factor of plasma volume reduction does not adequately account for the prompt, precipitous fall in cardiac output.

Among the various well-known shock-producing traumata, such as hemorrhage, crush and burns, most experimental data has been collected from studies on hemorrhage. Although experimental studies after burn injury have been made, the accumulated information is much less for this shock-producing agent. Particularly lacking is an assessment of the factors concerned in the very early stages of thermal burn shock and of the initial changes involving the circulation.

Method

General. A large group of apparently healthy mongrel dogs weighing from about 10 to 25 Kg. were anesthetized with sodium pentobarbital, 30 mg./Kg. Baseline determinations of cardiac output, liver blood flow, plasma volume and arterial pulse-pressure contour were obtained. Thermal trauma was most frequently produced by immersion of the closely shaved animal to the axillae in hot water at temperatures of 80 to 85 C. for 30 sec. However, because of technical difficulties, measurements prior to 7 min. were obtained after pouring about 8 L. of water at 100 C. over the caudal half of the body. The determinations listed above were repeated as soon as possible after the burn and at frequent intervals during the postburn course.

Cardiac Output. Cardiac output was measured by integration of the arterial dilution curve (femoral or carotid artery) following the rapid intravenous injection (jugular vein) of 30 to 150 u. of colloidal chronic phosphate labeled with P32. The principles underlying this method are those described by Hamilton and co-workers for the dye-dilution technic. Values for cardiac output were calculated in liters per minute, but are presented as a percentage of the preburn value for comparative purposes.

Liver Blood Flow. This quantity was determined by the rate of disappearance of colloidal chronic phosphate labeled with P32 from venous blood. This method has been described in detail previously. Values for liver blood flow obtained by this technic are expressed as disappearance rate constants (k) and represent the fraction of the extra-splanchnic blood volume perfusing the liver per minute.

Plasma Volume. Plasma volume was measured by the dilution technic. Iodinated (I131) human serum albumin was usually used because of its commercial availability. The dilution curves of I131-labeled human serum albumin were measured for 1 to 2 hours and the volumes calculated by extrapolation to 0 time. The activity of the dilution-curve samples was measured in whole blood for technical simplicity and the plasma volume was then calculated from the hematocrit.

Other Measurements. Hematocrits were determined by the standard Wintrobe method. Tracings were obtained of arterial pulse contours as well as mean arterial pressures using a Sanborn recorder in combination with a Statham pressure transducer and mercury manometer.

Results

A summary of the changes in cardiac output, plasma volume and liver blood flow (k) with time after thermal injury is presented graphically in figure 1. This figure is constructed from 43 simultaneous or almost simultaneous measurements of these parameters on 24 dogs. Individual experimental data are given in table 1.

Cardiac Output. The most striking among the cardiovascular changes following thermal injury was the almost immediate and precipitous fall in cardiac output. Figure 2 illustrates an individual example in which cardiac output and plasma volume were measured.
FIG. 1. Time course of plasma volume (upper plot), liver blood flow (middle plot) and cardiac output (lower plot) after thermal burn injury in the dog. Vertical lines through the plotted points, standard errors of the mean. Ordinate, per cent of preburn value; abscissa, time after burn, minutes. Within 5 min. after the burn, cardiac output has fallen essentially to a minimum, even though plasma volume reduction has not yet begun. Then, when plasma volume does fall between 5 and 20 min. postburn, no further significant reduction in cardiac output results. Liver blood flow parallels, in general, the cardiac output reduction. After the first 20 min., all parameters stabilized at reduced levels.

simultaneously. At 6 minutes cardiac output has fallen to one third of the preburn level in spite of a 10 per cent increase in plasma volume. At 1 hour the cardiac output reduction remains unchanged although plasma volume has dropped by 20 per cent.

After the burn a considerable delay in the time required for the injected activity to make the transit from the injection site, through the heart and lungs to the sampling site, is reflected by a lag in both the initiation and the peak of the postburn as compared to the preburn arterial dilution curves of figure 2.

**Plasma Volume.** As shown in figure 1 the marked reduction in cardiac output was not associated in its initial stages with a significant reduction in plasma volume. In fact, reduction in plasma volume lagged behind cardiac output reduction by 10 to 15 min. Furthermore, contrary to the visual observation of progressive edema at the burn site, plasma volume did not appear to decrease in a progressive manner after the first half-hour, but remained relatively constant at a reduced level.

In the calculation of plasma volume, a correction for plasma hold-up in the cell fraction was not made for either the preburn or the postburn values of the hematocrit, because the possibility of poor packing with a high hematocrit makes the value for such a correction uncertain. Since the thesis of this paper is concerned with the demonstration that plasma volumes are not sufficiently reduced to account for the initial changes in cardiac output, it seemed prudent to use the uncorrected hematocrits because these yield calculated plasma volume reductions that are probably greater than those which actually occurred.

**Plasma Protein Disappearance.** In spite of the failure of plasma volume to decrease progressively with time after thermal injury, the postburn iodinated albumin curves show a marked increase in the rate of disappearance amounting to about a five-fold increase in the preburn rate. Disappearance rates as great as 100 per cent per hour (half-time = 40 min.) have been observed. Such a rapid outpouring of plasma protein in these animals is incompatible with the observed survival time of 12-24 hours unless there is an active compensating source of plasma protein. In this regard, a few dogs were given I'31-labeled human serum albumin prior to the burn and pre- and postburn determinations of total plasma proteins as well as I'31 albumin concentrations were made. From these data a value for the specific activity of plasma protein, I'31 albumin concentration, could be calculated. This specific activity begins to decline immediately after the burn and continues to fall for many hours. Simple plasma protein loss of itself will not change the specific activity. This observation means, therefore, that an increased protein turnover in the plasma must exist. However, the postburn plasma protein composition was not fractionated and may have included proteins not normally found in the plasma.

**Liver Blood Flow.** Liver blood flow, as measured by the colloid disappearance rate constant (k), paralleled the cardiac output in its precipitous decline. Figure 3 shows a series of pre- and postburn disappearance curves of colloidal chromic phosphate. The disappearance
**Table 1.—Changes Produced by Experimental Thermal Burn Injury, per cent of Preburn Value**

<table>
<thead>
<tr>
<th>Experiment number</th>
<th>Cardiac output (time after burn)</th>
<th>Plasma volume (time after burn)</th>
<th>Liver blood flow (k) (time after burn)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-10 min.</td>
<td>11-30 min.</td>
<td>1-3 hr.</td>
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<tr>
<td>12-16-53</td>
<td>10.7</td>
<td>90</td>
<td>27</td>
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<tr>
<td>3-17-54</td>
<td>19.1</td>
<td>52</td>
<td>45</td>
</tr>
<tr>
<td>3-25-54</td>
<td>13.6</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>3-30-54</td>
<td>18.4</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>4-13-54</td>
<td>15.4</td>
<td>16</td>
<td>12</td>
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<tr>
<td>4-20-54</td>
<td>14.6</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>5-26-54</td>
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<td>68</td>
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<td>10-26-54</td>
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<td>66</td>
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<td>12-20-55</td>
<td>15.9</td>
<td>47</td>
<td>115</td>
</tr>
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</table>

* Experiment numbers 12-16-53 through 8-4-55: burn injury produced by immersion to the axillae in water of 80 to 85 C. for 30 sec.

Experiment numbers 10-25-55 through 1-24-56: burn injury produced by pouring 8 L. of water at 100 C. over the caudal half of the body.

† Previously splenectomized.

Rates are expressed as half-times and can be converted to disappearance rate constants (k) by division into 0.693. Eight minutes after thermal trauma of 85 C. for 30 sec., the disappearance half-time has become prolonged to 2.5 min. With increasing time after injury there is a progressive decrease in colloid disappearance rate. As noted in figure 1, reduction in liver blood flow (k) is smaller than the reduction in cardiac output; however, when (k) is multiplied by the plasma volume to obtain the liver blood (plasma) flow, the magnitude of liver blood (plasma) flow and cardiac output reduction becomes identical. The value for the colloid disappearance constant (k) at 270 min., although shown in figure 3, is omitted from figure 1 because a decrease in phagocytic efficiency of the reticulo-endothelial cells of the liver occurs 2 to 4 hours after thermal injury. Therefore, this measurement does not accurately reflect liver blood flow beyond this time.

**Arterial Pressure Changes.** Throughout the experiments cited above, mean arterial pressures, arterial pulse pressure contours and pulse rates were measured. Simultaneous electrocardiograms were also obtained; these data have been described elsewhere. Mean arterial pressure, after an initial rise, showed an average reduction of about 15 per cent after the first 5 min., which remained fairly constant throughout the first 5 postburn hours. In some individual cases, a sustained increase in pressure was observed and in others marked reductions occurred; however, it was not unusual to see little or no change...
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in mean arterial pressure in spite of severe cardiac output reduction.

Although mean arterial pressure did not parallel the reduction in cardiac output, pulse pressures for the most part showed a high degree of correlation with output. Pulsus alternans appeared often but not universally; sometimes it was persistent but more frequently it was transient. A rise in mean arterial pressure, in spite of the presence of pulsus alternans and a severely reduced cardiac output, was also observed. Detailed examples of these changes have been illustrated elsewhere.19

Sequence of Events Following Burn Injury. Although individual variations occur (table 1), the average experience indicates that the sequence of events is as follows:

Beginning within the first few minutes after burn injury, cardiac output, liver blood flow and probably blood flow to all other regions, are markedly reduced. Mean arterial blood pressure, however, shows a definite transient rise occurring simultaneously with the fall in cardiac output. The rising arterial pressure in the face of a marked fall in cardiac output indicates extreme peripheral vasoconstriction. Plasma volume at this stage, however, is not reduced and therefore cannot be the factor responsible for either the vasoconstriction or the impaired cardiac output.

By 5 to 10 min. after burn injury, plasma volume begins to decrease. At this time, however, cardiac output and liver blood flow have already reached their minimum levels and show no further decrease in spite of a subsequent progressive reduction in the plasma volume.

By 20 min. after the injury, cardiac output, liver blood flow, mean arterial pressure and plasma volume have all become stabilized at reduced levels. The simple measurement of these parameters after such stabilization will no longer yield information as to the cause and effect relationship between them.

Theory of Local Fluid Loss. In general, there can be little doubt that fluid loss into an area of injury can and does occur. A number of investigators during the past 30 years have concluded from their experiments that this local loss of fluid at the site of injury is the responsible mechanism in the evolution of the shock syndrome and the cardiovascular abnormalities which accompany it. Blalock, one of the leading proponents of the fluid loss theory, concluded from his studies of trauma to muscle and to the intestines that sufficient

Fig. 2. Serial arterial dilution curves before and after thermal burn injury (dog number 11-S-55). Area under curves, inversely proportional to the cardiac output. Simultaneous plasma volumes: pre-burn, 0.89 L.; 6 min. postburn, 0.97 L.; 1 hr. postburn, 0.72 L. Ordinate, blood activity; abscissa, seconds.

Fig. 3. Serial disappearance curves of colloidal chromic phosphate before and after thermal burn injury. Ordinates, blood activity; abscissa, minutes. Half-times of the curves, are inversely proportional to fraction of blood volume perfusing the liver per minute. After 3 hours, disappearance slopes represent a combination of altered liver blood flow and depressed phagocytic removal efficiency.
loss of blood volume into the areas of trauma occurred to account for the subsequent hypotension. Harkins, in his experimental burn studies, reiterated the local fluid loss theory in relation to the development of cardiovascular changes, and showed that the shift of fluid into the burn site was rapid, with 40 to 75 per cent of the ultimate shift occurring within the first hour.

The results reported herein present no factual contradictions to these earlier observations, but do disagree as regards the interrelationship of the events. From the very early measurements obtained in this study it has been shown that cardiac output falls before plasma volume reduction begins and that, therefore, local fluid loss is symptomatic of burn injury rather than etiologic in the initiation of the circulatory depression which immediately follows experimental burns.

Further evidence against the etiologic role of local fluid loss can be derived from the time course of plasma volume change in the present experiments. When plasma volume loss does begin after 5 to 10 min., it occurs rapidly, in agreement with the observations of Harkins yet no significant additional depression of cardiac output follows. Thus another discrepancy in the time sequence of these 2 parameters is seen.

Other Possible Factors. The concept that plasma volume reduction following burn injury cannot always explain the shock syndrome which follows has been put forth by a number of authors. A number of toxic substances have also been implicated in the development of various postburn phenomena, but as yet definitive proof of their etiologic importance has not been obtained. Printzmetal and co-workers have shown that some mechanism other than fluid loss is capable of producing shock in severely burned animals and have suggested that a circulating toxic factor produces capillary atony. Page, in a study of the cardiovascular changes resulting from experimental scalds, has suggested that the changes are an indirect rather than a direct effect of reduced blood volume, and tentatively postulates the presence of vasotropic substances which exert an effect on vascular and cardiac musculature. In this connection, Alrich has observed evidence of a vasoconstrictor substance in the lymph draining an experimentally burned area, and Rosenthal and colleagues have shown that diffusates obtained from the skin of burned rats are lethal within a few hours after subcutaneous injection into normal rats. Furthermore, Gilmore and Handford, in a study of the hemodynamic response of the dog to thermal burn injury, have confirmed the preliminary findings of the present authors and have concluded that the main initiating factor causing a decrease in cardiac output is something other than a decrease in plasma volume.

Finally, in connection with the prompt initiation of the circulatory derangements and the implication of possible toxic factors, recent preliminary experiments by the present authors indicate that blood draining the burn site contains an extremely toxic substance or is altered in such a manner that it develops toxic characteristics. Specifically, infusions of this blood into normal recipients may cause a marked fall in cardiac output, a severe depression of liver blood flow, and electrocardiographic abnormalities, all of which were so characteristically seen in the burned animals described above.

SUMMARY

Cardiac output, plasma volume, liver blood flow and certain other circulatory parameters were measured before and after experimental thermal burn injury in anaesthetized dogs. The results show an immediate, very marked, and sustained depression in cardiac output and liver blood flow, occurring with little change in mean arterial pressure. Plasma volume reduction, which heretofore has been widely considered to be responsible for the fall in cardiac output, has been shown to follow rather than to precede the circulatory depression. Indications of increased turnover of proteins in the circulating plasma have been observed following experimental thermal burn injury.

SUMMARIO IN INTERLINGUA

Rendimento cardiac, volumine plasmatic, fluxo sanguinee hepatic, e certe altere expres-
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siones circulatori esseva mesurate ante e post thermic lesiones experimental in canes anesthesiati. Le resultatos revela un immediate, multo marcate, e perdurante depression del rendimento cardiac e del fluxo sanguineo hepatic occurrente con pauc alteration del pression arterial medi. Esseva monstrate que le reduction del volume plasmatic—le qual usque nunc esseva extensemente considerate como responsabile pro le reduction del rendimento cardiac—sequ le depression circulatori in loco de preceder lo. Esseva observate indicios de un augmentate transition de proteinas in le plasma circulante post thermic lesiones experimental.

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Circ Res. 1957;5:69-74
doi: 10.1161/01.RES.5.1.69

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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