Effects of Hydralazine and High Molecular Weight Dextran upon the Circulatory Responses to Severe Thermal Burns

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With the technical assistance of SP-5 Thomas Chapman and PFC John Povalchik

- Hemodynamic and cardiovascular changes following severe thermal injury have been categorized into a niche frequently called "burn shock." Many of these pathophysiological alterations appear to be well-defined, but the mechanisms involved in their production remain obscure.

Investigators in the field have variously ascribed the greatly depressed cardiac output following thermal trauma to a decrease in myocardial contractile force, a decrease in fluid volume, "blood sludging," or an increase in peripheral resistance coupled with a decrease in effective circulating fluid volume. Data presented in this report suggest that it is primarily this latter mechanism which is responsible for the precipitous fall in cardiac output.

The approach used in this study was designed to evaluate the effects of reversing the vasoconstriction and plasma volume deficit individually and in combination. It was expected that correction of either abnormality alone would be insufficient to restore normal cardiovascular function, but that the combination therapy would be effective. This was found to be the case, suggesting that at least these two mechanisms operate to produce the observed effects of a burn.

Methods

The 18 dogs used in this study were mature male and female (not in estrus) mongrels that had been immunized against canine distemper and hepatitis complex, were free of intestinal parasites and apparent infections, and had been on a diet of commercial dog food (Purina Dog Chow) for at least two weeks prior to experimentation.

All animals were anesthetized throughout the entire study. After induction with intravenous thiopental sodium, general anesthesia was maintained with sodium barbital administered intravenously in a single dose of 200 mg/kg body wt.

The animals were subjected to a full skin thickness burn two hours after induction of anesthesia by submerging them, feet first, to the tip of the xyphoid process of the sternum into 20 gallons of boiling water for 12 seconds.

Cardiac output (ml/min), mean circulatory time (seconds), and central blood volume (ml) were measured by the dye dilution technique as previously described. A constant volume and concentration of the indicator (Cardio Green—Hynson, Westcott, and Dunning, Inc.) was injected as a bolus into the right atrium via an indwelling polyethylene cannula (0.035 inch internal diameter). A Gilford constant flow system (Model 105-S) was used to withdraw blood from the sampling site in the aortic arch. Dye dilution curves were recorded with a Waters densitometer (Model X-250) and a Sargent high impedance recorder (Model MR).

Systolic end arterial blood pressure (mm Hg) was recorded from the cannulated right brachial artery with a Statham pressure transducer (Model P23Db) and a Sanborn multichannel recorder (Model 67-1200), and subsequently evaluated as mean arterial blood pressure. Pulse rate (beats/min) was derived from standard limb lead E electrocardiographic (R wave) tracings also recorded on the Sanborn recorder.

Arterial hematocrit (cell volume per cent) were measured by the micro-technic of Guest.

The dogs were divided into three groups of six animals each.

Group I animals received intravenous hydralazine* 0.5 mg/kg body wt immediately post-

*Furnished as Apranolone through the courtesy of Ciba Pharmaceutical Company, Summit, New Jersey.
### TABLE 1

**Mean Per Cent Change Within Groups from Immediate Preburn Value**

<table>
<thead>
<tr>
<th>Data source</th>
<th>Immediate</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tr>
<td><strong>Pulse rate</strong></td>
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<tr>
<td>Hydralazine</td>
<td>+6 ± 7*</td>
<td>-11 ± 2</td>
<td>0 ± 7</td>
<td>-4 ± 10</td>
<td>0 ± 10</td>
<td>+10 ± 12</td>
<td>+15 ± 12</td>
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<td>Dextran</td>
<td>+17 ± 9</td>
<td>-5 ± 6</td>
<td>-8 ± 8</td>
<td>0 ± 10</td>
<td>+11 ± 11</td>
<td>+14 ± 12</td>
<td>+21 ± 12</td>
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<tr>
<td>Hydralazine &amp; dextran</td>
<td>-5 ± 6</td>
<td>-11 ± 4</td>
<td>+8 ± 5</td>
<td>+8 ± 6</td>
<td>+19 ± 7</td>
<td>+24 ± 8</td>
<td>+26 ± 7</td>
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<tr>
<td><strong>Mean arterial blood pressure</strong></td>
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<tr>
<td>Hydralazine</td>
<td>+30 ± 16</td>
<td>-28 ± 12</td>
<td>-27 ± 8</td>
<td>-37 ± 10</td>
<td>-39 ± 6</td>
<td>-34 ± 6</td>
<td>-30 ± 6</td>
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<tr>
<td>Dextran</td>
<td>+12 ± 8</td>
<td>-4 ± 11</td>
<td>-11 ± 9</td>
<td>-9 ± 10</td>
<td>-4 ± 8</td>
<td>-3 ± 11</td>
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<td>-16 ± 6</td>
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<td>-17 ± 8</td>
<td>-10 ± 8</td>
<td>-14 ± 9</td>
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<td><strong>Cardiac output</strong></td>
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<td>Hydralazine</td>
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<td>-44 ± 10</td>
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<tr>
<td>Dextran</td>
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<td>-68 ± 4</td>
<td>-52 ± 11</td>
<td>-53 ± 8</td>
<td>-46 ± 8</td>
<td>-62 ± 7</td>
<td>-48 ± 6</td>
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<tr>
<td>Hydralazine &amp; dextran</td>
<td>-35 ± 10</td>
<td>-41 ± 5</td>
<td>-36 ± 6</td>
<td>-17 ± 12</td>
<td>+3 ± 9</td>
<td>-2 ± 9</td>
<td>+14 ± 16</td>
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<tr>
<td><strong>Mean circulatory time</strong></td>
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<td>Hydralazine</td>
<td>+28 ± 13</td>
<td>+52 ± 10</td>
<td>+17 ± 8</td>
<td>+18 ± 8</td>
<td>+20 ± 7</td>
<td>+18 ± 17</td>
<td>+8 ± 12</td>
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<tr>
<td>Dextran</td>
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<td>+38 ± 12</td>
<td>+35 ± 13</td>
<td>+45 ± 14</td>
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<tr>
<td>Hydralazine &amp; dextran</td>
<td>+44 ± 16</td>
<td>+29 ± 9</td>
<td>+20 ± 10</td>
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<td>-2 ± 3</td>
<td>-8 ± 4</td>
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<td><strong>Central blood volume</strong></td>
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<tr>
<td>Hydralazine</td>
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<td>-35 ± 4</td>
<td>-19 ± 13</td>
<td>-36 ± 8</td>
<td>-35 ± 9</td>
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<td>-31 ± 8</td>
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<td>-15 ± 4</td>
<td>-40 ± 6</td>
<td>-35 ± 7</td>
<td>-36 ± 3</td>
<td>-32 ± 5</td>
<td>-27 ± 6</td>
<td>-28 ± 6</td>
</tr>
<tr>
<td>Hydralazine &amp; dextran</td>
<td>-13 ± 6</td>
<td>-26 ± 5</td>
<td>-16 ± 7</td>
<td>-9 ± 10</td>
<td>+2 ± 10</td>
<td>-11 ± 8</td>
<td>0 ± 12</td>
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<tr>
<td><strong>Hematocrit</strong></td>
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<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>+29 ± 4</td>
<td>+40 ± 8</td>
<td>+37 ± 8</td>
<td>+43 ± 13</td>
<td>+62 ± 11</td>
<td>+58 ± 12</td>
<td>+90 ± 10</td>
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<tr>
<td>Dextran</td>
<td>+21 ± 7</td>
<td>+25 ± 9</td>
<td>+16 ± 6</td>
<td>+11 ± 6</td>
<td>+12 ± 10</td>
<td>+16 ± 13</td>
<td>+20 ± 13</td>
</tr>
<tr>
<td>Hydralazine &amp; dextran</td>
<td>+22 ± 6</td>
<td>+12 ± 4</td>
<td>+10 ± 4</td>
<td>+8 ± 5</td>
<td>+22 ± 5</td>
<td>+17 ± 5</td>
<td>+14 ± 6</td>
</tr>
</tbody>
</table>

*Standard error.
burn and the same dosage intramuscularly one hour, three hours, and five hours postburn.

Group II dogs received an infusion (5 ml/kg body wt at a rate of 5 ml/min) of 6% high molecular weight dextran (average molecular weight 185,000) in 0.9% saline† beginning one hour postburn and repeated every hour thereafter for the remainder of the study period. This infusion would be the equivalent of 0.8 ml/per cent burn/kg body wt/hr and is therefore less than the total fluids administered by the standard fluid replacement formulas for burned patients,18 but in excess of the usual amount of colloid administered.

Group III animals received both hydralazine and 6% high molecular weight dextran in physiological saline in the previously mentioned dosages and sequences.

All animals were sacrificed at the end of the sixth postburn hour.

Data for each postburn period are presented for each group as the mean per cent change (+ standard error) from the immediate preburn period. The following mathematically independent statistical comparisons have been made by analysis of variance (F test) for each time period: (1) Group I (hydralazine treatment) versus Group II (dextran treatment), and (2) Group III (combined treatment) versus Group I plus Group II.

Results

GROUP I (HYDRAZINE)

Data from each of the three experimental (treated) groups are summarized in table 1. Similar data for untreated, burned animals are shown for comparison in table 2.

The maximum decrease of cardiac output (—56%) occurred during the first postburn hour. After this time, cardiac output (CO) increased; however, it did not reach preburn levels.

Mean circulatory time (MCT) reached its maximum by the first hour after burning. One hour later the MCT returned toward normal and became relatively stable thereafter.

Central blood volume (CBV) decreased markedly following the burn and remained depressed (average decrease 36%). Pulse rate remained relatively stable throughout the six-hour postburn period, whereas arterial

TABLE 2

<table>
<thead>
<tr>
<th>Untreated Burned Dogs—Mean Per Cent Change from the Immediate Preburn Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour postburn</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Immediate</td>
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<td>2</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

*Standard error.

High molecular weight dextran in physiological saline furnished through the courtesy of Baxter Laboratories, Morton Grove, Illinois. (New drug limited by Federal law to investigational use only.)
blood pressure remained depressed (average decrease 32%). The hematocrit became elevated immediately after burning (+29%) and continued to rise.

**GROUP II (DEXTRAN)**

The maximum decrease of cardiac output (−68%) occurred during the first postburn hour. After a slight rise during the next hour, the cardiac output remained constant.

Mean circulatory time increased (+30%) immediately after burning and reached its maximum one hour later. A pronounced decrease in MCT was observed after this point.

A slight fall (−15%) in CBV was noted immediately following the burn. The maximum depression (−40%) was noted at the first postburn hour, followed one hour later by a slight rise.

The pulse rate did not vary greatly during the postburn hours and the arterial blood pressure stabilized at a slightly depressed value by the first postburn hour.

There was a prompt elevation (+21%) in hematocrit immediately after burning. By the second postburn hour, the hematocrit began to decline slowly, continuing this trend until the sixth postburn hour.

**GROUP III (HYDRAZINE + DEXTRAN)**

Cardiac output was decreased 41% by the first postburn hour. Following this, there was a gradual increase in cardiac output culminating at the sixth postburn hour with a mean increase of 14% above the preburn (control) value.

Mean circulatory time increased immediately after burning (+44%), but one hour later it returned toward normal. The MCT appears to have stabilized by the fifth postburn hour at a mean value of 8% less than the control.

The greatest fall in CBV was seen one hour after burning (−13%). It then increased gradually, reaching the control value five hours later.

Following the initial rise of 31%, the mean arterial blood pressure dropped below the control value by 15% and appeared to stabilize around this value.

During the early postburn hours, the pulse rate was relatively unaffected, but a trend towards tachycardia was observed by the fifth postburn hour.

Following the initial elevation of 22%, the hematocrit promptly fell, stabilizing around a mean elevation of 10% for the remainder of the study.

**Discussion**

The major hemodynamic alterations observed in untreated, burned dogs (table 2) were a precipitous fall in cardiac output and central blood volume and an increase in mean circulation time and hematocrit. These data suggested to us that at least two major factors were responsible for these profound alterations: (1) a decrease in venous return to the heart associated with a decrease in effective circulating fluid volume, and (2) an increase in peripheral resistance.

The early loss of large amounts of fluid from the vascular into the extravascular space have been reported and probably explains the progressively increasing hematocrit (table 2). Since dextran therapy alone fails to restore the cardiac output and central blood volume to preburn levels (table 1), we do not believe that hypovolemia alone is entirely responsible for the observed hemodynamic changes. However, attempts have been made to treat "burn shock" solely by administration of enormous amounts of water, saline, and colloid.

The great decrease in central blood volume during the early postburn hours suggested to us the possibility that peripheral venous pooling might be a major factor in reducing venous return to the heart. Furthermore, this might explain the precipitous fall in cardiac output, since venous return is one of the most important factors regulating cardiac output. It has been reported also that, following severe trauma, the reservoir function of the pulmonary circuit is depleted, so that blood entering the left atrium is a direct function of the systemic venous return.

By definition, the ratio of arterial blood pressure to cardiac output is an index of
peripheral resistance. Therefore, the unchanged arterial blood pressure and decreased cardiac output observed in the burned untreated animals indicate an increase in peripheral resistance. This resistance, however, may be due to vascular components, viscosity effects, or a combination of the two factors. Although no satisfactory methods have been developed for measuring the viscosity of flowing blood in vivo, it is possible that the hemoconcentration is responsible for at least some increase in viscosity. The vascular component is likewise difficult to evaluate, but is perhaps studied best by attempting to reduce vasoconstriction through the administration of a vasodilating agent.

Thus, it was decided to evaluate this dual hypothesis by assessing the two suspected factors individually and in combination. A colloid (high molecular weight dextran) was employed to provide volume expansion and hemodilution, and hydralazine was used to produce vasodilatation. It was hoped that the increased venous return and decreased peripheral resistance might permit a reversal of the hemodynamic abnormalities observed in the untreated burned animals.

Administration of dextran or hydralazine increased cardiac output and central blood volume, while decreasing mean circulatory time (table 1). Quantitatively, however, dextran was slightly less effective than hydralazine in producing these effects. In contrast, dextran had a significant effect in reducing hematocrit, while hydralazine had virtually no effect. The mean arterial blood pressure was somewhat depressed following hydralazine administration, but remained relatively unchanged with dextran. Thus, despite some overlapping effects, these two agents appear to act via different mechanisms.

When dextran and hydralazine were administered together, the reversal of the altered hemodynamics was striking. Whereas the difference in cardiac output following either of the two agents alone was not significant ($P > 0.05$), a highly significant ($P < 0.001$) effect was produced by their combination. Likewise, the effect of the combination treatment upon central blood volume was statistically significant by the third postburn hour ($P < 0.05$). By inspection of the data, it appears that the effect is more than a simple additive one and undoubtedly involves considerable interaction.

The high degree of effectiveness of the combination therapy suggests that reduction of peripheral resistance combined with minimal fluid volume augmentation produces increased venous return to the heart, in turn increasing the central blood volume and permitting an increased cardiac output. That the heart is able to respond to this increased return by increasing cardiac output implies that there is no significant interference with myocardial contractility.

Although we believe that these data support our initial hypothesis, we cannot exclude the possibility that additional unrecognized factors are operative and may be influenced by the mode of therapy.

**Summary**

The greatly depressed cardiac output observed in untreated burned dogs appears to be due to a combination of two factors: (1) a decrease in venous return to the heart associated with a decrease in effective circulating fluid volume and (2) an increase in peripheral resistance. This hypothesis is supported by the observations that administration of a peripheral vasodilator (hydralazine) and minimal fluid volume replacement (high molecular weight dextran in isotonic saline) restore the cardiac output to preburn levels by the fourth postburn hour.

**References**

CIRCULATORY RESPONSES TO THERMAL INJURY

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