Effect of Moderate Hypothermia in the Treatment of Canine Hemorrhagic Shock

DAN M. MEYER, M.D., and JURETA W. HORTON, PH.D.

This study evaluated a possible protective and therapeutic effect of moderate hypothermia in the treatment of severe hemorrhagic shock. A modified Wiggers shock preparation was used. Normothermic dogs (Group I, N = 6) were maintained at normal body temperature throughout hemorrhagic shock and resuscitation. In Group II, hypothermia was initiated after 15 minutes of hemorrhagic shock (N = 12) and maintained for 60 minutes after fluid resuscitation. Animals were then rewarmed with Group IIA (N = 7) receiving sodium bicarbonate to correct acidosis, while Group IIB (N = 5) did not; all dogs were studied for an additional 120 minutes. During shock heart rate was lower in both hypothermic groups (IIA and IIB) compared to normothermic dogs (85.0 ± 3.9, 77.7 ± 4.6 *vs.* 136.7 ± 4.2, respectively, $p < 0.05$), while +dP/dt (mmHg/s) remained stable in all dogs. Furthermore, pH was lower in the hypothermic (Groups IIA and IIB) compared to normothermic animals at this time period (Group IIA: 7.19 ± 0.02, Group IIB: 7.13 ± 0.02 *vs.* Group I: 7.24 ± 0.02). Arterial pCO_2 was higher in the hypothermic hemorrhagic shock Groups IIA and IIB compared to normothermic group (34.5 ± 2.2, 37.4 ± 2.2 *vs.* 20.3 ± 20, 3 ± 2.0, $p < 0.05$) due to hypothermia-depressed respiration. A higher myocardial O_2 consumption and a negative myocardial lactate balance occurred in the normothermic animals during hemorrhagic shock. After resuscitation and rewarming, stroke volume (mL/beat) and cardiac output (L/min) were lower in hypothermic animals with persistent acid–base derangements (12.6 ± 2.5, 1.3 ± 3.0, respectively) compared to hypothermic dogs with acid–base correction (20.1 ± 3.3, 2.2 ± 0.3) and normothermic dogs (24.6 ± 3.0, 3.0 ± 0.3, $p < 0.05$), while myocardial O_2 extraction and myocardial lactate production were higher. Results suggest hypothermia decreases the metabolic needs and maintains myocardial contractile function in hemorrhagic shock. Hypothermia may have a beneficial effect and, with normalization of acid–base balance, a therapeutic role in hemorrhagic shock.

THE EFFECT of hypothermia in the treatment of hemorrhagic shock is controversial. Hypothermia, which decreases total body oxygen consumption,[1] has been shown to increase survival rate[2] and prolong the period of tolerance to severe hemorrhage.[3] The disciplines of neurologic and cardiovascular surgery have utilized hypothermia during surgical procedures and described a protective effect.[4,5] However, the therapeutic value of hypothermia in the shock state is much less clear, and conflicting data regarding any beneficial effect of hypothermia have been attributed to differences in experimental preparation, type and degree of shock produced, as well as the level of hypothermia achieved.[6–9] The present study was designed to evaluate the effect of moderate hypothermia on cardiovascular function, regional blood flow, and oxygen consumption in hypothermia plus severe hemorrhagic shock.

From the Department of Surgery, University of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas

Reprint requests and correspondence: Jureta W. Horton, Ph.D., Department of Surgery, University of Texas Health Science Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75235-9031.

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Materials and Methods

Hemodynamic Studies

Eighteen mongrel dogs of either sex, weighing between 16 and 28 kg were included in the study. Anesthesia was induced with sodium thiopental (15 mg/kg, I.V.) and maintained with alpha-chloralose in polyethylene glycol 200 (50 mg/kg, I.V.). Dogs were intubated and allowed to breathe room air spontaneously. Polyethylene catheters were placed in the femoral and brachial arteries and advanced into the descending aorta for removal of blood during hemorrhage, blood sampling, and measuring arterial blood pressure. Arterial blood pressure was monitored with a strain gauge transducer (Statham, Model 231D). Polyethylene femoral venous catheters were also placed and advanced into the inferior vena cava for administration of fluids, drugs, and the return of shed blood. Left ventricular pressure was obtained from a Millar catheter (Millar, Inc., Houston,

Texas) inserted through the left internal carotid artery. The Millar transducer was initially zeroed and calibrated in a 37 C water bath (Millar, Inc., Model PC470). A polyethylene catheter was also placed into the coronary sinus through the right internal jugular vein, and a Swan-Ganz catheter was placed into the pulmonary outflow tract, through the left internal jugular vein. These three catheters were placed under the aid of fluoroscopy. A derivative computer (Hewlett-Packard, Model 8814A, Richardson, TX) provided continuous monitoring of maximal rate of left ventricular pressure rise (+dP/dt) and fall (−dP/dt). All hemodynamic parameters were recorded on a Mingograf recorder (Siemens, Model 81, Grand Prairie, TX). Cardiac output was determined in duplicate by the dye dilution technique using indocyanine green. In addition to the vascular catheters, four peritoneal dialysis catheters (Travenol Laboratories, Model 2C4105, Deerfield, IL) were placed in the ventral midline region of the animals. These catheters were introduced intraperitoneally via an open technique. This involved visualization of the parietal peritoneum before placement of the four catheters. All dogs were heparinized (100 units/kg) immediately before insertion of the left ventricular catheter (Fig. 1).

Coronary Blood Flow and Myocardial Oxygen Consumption

Regional blood flow was measured by injection of 1 $\times 10^6$ microspheres (15 ± 3 μm) as a bolus into the left ventricle (3M Company, St. Paul, MN; New England Nuclear, Boston, MA). Immediately before each injection, the vial containing the microsphere (^{113}SN, ^{57}Co, ^{46}SC, ^{95}Nb, ^{125}I, and ^{85}Sr) was mixed by vortex agitation. One milliliter of the microsphere suspension was rapidly injected into the left ventricle and the catheter was immediately flushed with 10 mL of saline solution. This volume of microsphere-containing suspension allowed for an adequate number of microspheres to be administered (at least 400 microspheres/tissue sample) and ensured accurate measurement of blood flow. Simultaneous with the injection of microspheres and continuing for 120 seconds, reference blood samples were obtained from the femoral arteries, each at a rate of 10 mL/min (Holter pump, Model 911, Critikon, Inc., Tampa, FL). At the end of each experiment, the animals were killed by an overdose of barbiturates. The heart was removed and placed into a buffered formalin solution. The myocardial tissue and reference blood samples were counted for 5 minutes in a multichannel gamma scintillation spectrometer (Packard, Model 5320, Legona Hills, CA). The remaining internal organs were treated similarly. For each set of samples, vials containing small aliquots of each microsphere were used to determine the energy level setting on the scintillation counter to be used.

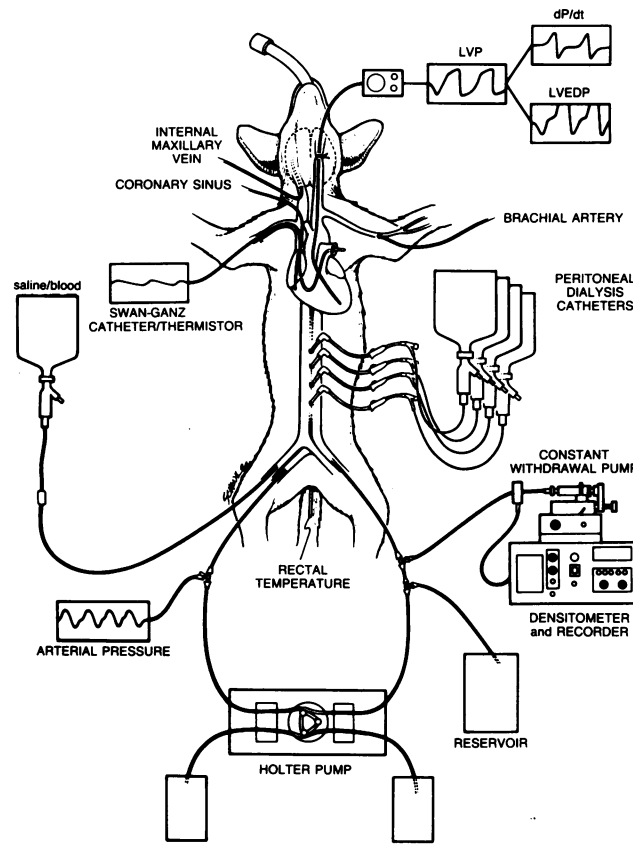

FIG. 1. Experimental model.

From the standards of each microsphere used to set the energy level and the actual sample containing the highest count of microspheres injected, the cross-talk fraction or overlap of gamma energies was calculated for each of the microspheres. The contribution of this overlap of gamma energies of each microsphere was then subtracted and a nuclide reference factor (mL/min/counts) calculated for each microsphere. For each of the samples, the background counts were subtracted and the counts for each isotope were multiplied by the nuclide reference factor in order to obtain a mean blood flow rate.

Hemorrhage, Hypothermia, and Resuscitation

All dogs were given 10 mL/kg of 0.9% normal saline solution during instrumentation. Animals were then allowed to stabilize for 30 minutes. Baseline blood pressure, mean arterial pressure, heart rate, +dP/dt, −dP/dt, left ventricular pressure, left ventricular end-diastolic pressure, pulmonary capillary wedge pressure, pulmonary artery pressure, respiratory rate, urinary output, core body temperature, and rectal (body) temperature (via the Swan-Ganz [American Edwards Laboratories, Santa Ana, CA] catheter thermistor and a rectal temperature probe, respectively) were measured and a micro-

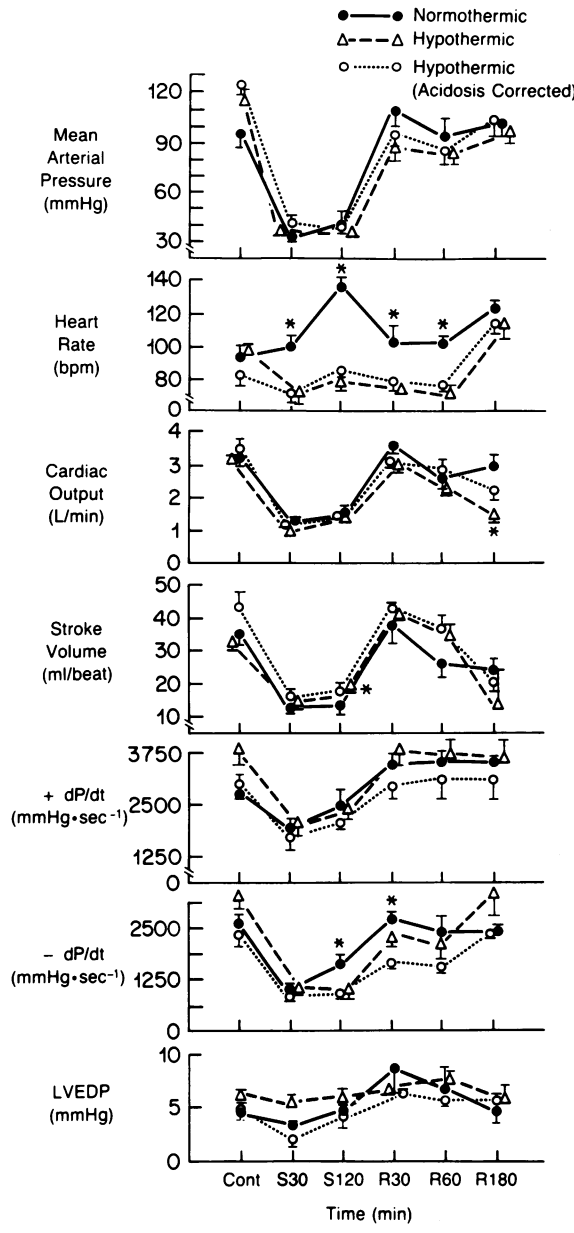

FIG. 2. Hemodynamic and left ventricular contractile response to hemorrhagic shock and hypothermia. All values are given as mean ± SEM. *Significant difference between groups, $p < 0.05$.

sphere was injected for measurement of baseline blood flows. The right femoral artery cannula was then connected to an air-pressure–regulated blood reservoir, and shock was induced, with the end-point being a mean arterial pressure of 35 mmHg. Animals were then divided into three groups. In Group I, six dogs were hemorrhaged over 5 minutes. After 2 hours of controlled hemorrhagic shock, shed blood was returned to all dogs through a micropore filter (Fenwal Laboratories, Model 4C2423, Division of Travenal, Deerfield, IL) via the femoral vein cannula and lactated Ringer's solution was infused (50 mL/kg), with no hypothermic intervention. In Group II shock was established as described for Group I. Hypothermia was achieved after 5 minutes of hemorrhagic shock by instilling iced normal saline at 4 C into the peritoneal cavity via the peritoneal dialysis catheters. The iced saline was then circulated using a siphon exchange effect to remove the fluid, until a target temperature of 33 C was reached. All measurements, including microsphere flow determinations, were recorded after 30 and 120 minutes of hemorrhagic shock. Two hours after the onset of shock, dogs were resuscitated as described for Group I, and hypothermia was maintained. All measurements were again recorded at 30, 60, and 180 minutes after resuscitation. The animals in Group II were rewarmed 60 minutes after resuscitation, using warmed normal saline solution at 44 C infused through the peritoneal dialysis catheters; then the animals were divided into two subgroups for assessment of hypothermia on acid–base derangements. In Group IIA (N = 7) acidosis was corrected during rewarming using IV sodium bicarbonate titrated to an arterial pH of greater than 7.25. In Group IIB (N = 5) acidosis remained uncorrected. During rewarming animals were given lactated Ringer's solution at a rate of 10 mL/kg/h to keep mean arterial pressure and heart rate at approximate baseline levels.

Statistical Analysis

Results were expressed as mean ± SE. Statistical analysis included an ANOVA and repeated measure procedure (Newman-Keuls). All values were considered significant at $p < 0.05$. All hemodynamic and flow parameters changed significantly from baseline with shock ($p < 0.05$).

Results

Cardiovascular Response

Before shock cardiocirculatory function and metabolic status were similar in all dogs. Hemorrhage to a mean arterial blood pressure of 30 mmHg reduced cardiac output, stroke volume, ±dP/dt, stroke work, and regional blood flows to a similar extent in all animals. Early shock (S15) was characterized by acid–base derangements that included a fall in arterial pH and bicarbonate as well as a rise in circulating lactate levels. Throughout shock, heart rate and respiratory rate were significantly lower in all hypothermic compared to normothermic dogs while mean arterial blood pressure, cardiac output, and left ventricular end-diastolic pressure were similar in the three groups (Fig. 2). Baseline peripheral vascular resistance (mean arterial blood pressure divided by cardiac output and multiplied by 80 to convert units to dyne × s × cm^{-5}) was similar in all dogs (normothermic: 2480 ± 280; hypothermic Group IIA: 2640 ± 244; hypothermic Group IIB: 2880 ± 480). After

120 minutes of shock, the rate of left ventricular relaxation (−dP/dt) was significantly lower in hypothermic Groups IIA and IIB compared to the normothermic shock groups (875 ± 150, 975 ± 200 *vs.* 1550 ± 275 mmHg/s, $p < 0.05$), while the rate of left ventricular pressure rise (+dP/dt), cardiac output, LVEDP, and stroke work were comparable in the three groups at this time. After 2 hours shock, stroke volume was significantly higher ($p < 0.05$) and heart rate lower ($p < 0.05$) in hypothermic compared to normothermic shock dogs.

After fluid resuscitation, but before rewarming, the heart rate remained lower in hypothermic dogs (Group IIA: 75.7 ± 3.8; Group IIB: 70.0 ± 5.4) compared to normothermic dogs (100 ± 4.5 beats/min, $p < 0.05$), while mean arterial blood pressure, peripheral vascular resistance, left ventricular pressure, left ventricular end-diastolic pressure, +dP/dt, and −dP/dt were similar in all dogs during this time. Thirty minutes after fluid resuscitation, cardiac output returned to baseline values but was significantly lower in hypothermic than in the normothermic dogs ($p < 0.05$). Rewarming the hypothermic animals after volume replacement increased cardiac output to a level comparable to that observed in the normothermic animals. Peripheral vascular resistance was higher in all hypothermic compared to normothermic dogs after volume replacement (Group IIA: 3224 ± 240; Group IIB: 3664 ± 280; Normothermic: 2768 ± 300 dyne × s × cm^{-5}; $p < 0.05$). Peripheral blood flows were comparable in all dogs throughout the experimental period, regardless of body temperature (Fig. 3). Adrenal blood flow tended to be lower in both hypothermic groups compared to normothermic dogs after resuscitation, but this difference did not achieve statistical significance.

Myocardial Blood Flow and Oxygen Metabolism

Baseline myocardial blood flow, myocardial oxygen extraction, myocardial oxygen delivery, and circulating lactate levels were similar in all dogs (Fig. 4). In addition, endocardial-epicardial ratios were similar in all dogs before hemorrhage (normothermic: 1.12 ± 0.06; hypothermic Group IIA: 1.16 ± 0.04, hypothermic Group IIB: 1.09 ± 0.06). There was, however, a tendency toward a higher myocardial oxygen consumption in the normothermic compared to hypothermic shock dogs before shock, but these differences did not achieve statistical difference. Total body oxygen consumption and myocardial oxygen extraction fell during hemorrhagic shock but to a significantly greater extent in the hypothermic dogs, $p < 0.05$. In early shock, myocardial oxygen delivery and myocardial oxygen consumption decreased to a similar extent in all dogs, regardless of body temperature. In late shock endocardial-epicardial flow ratios in normothermic dogs fell significantly from

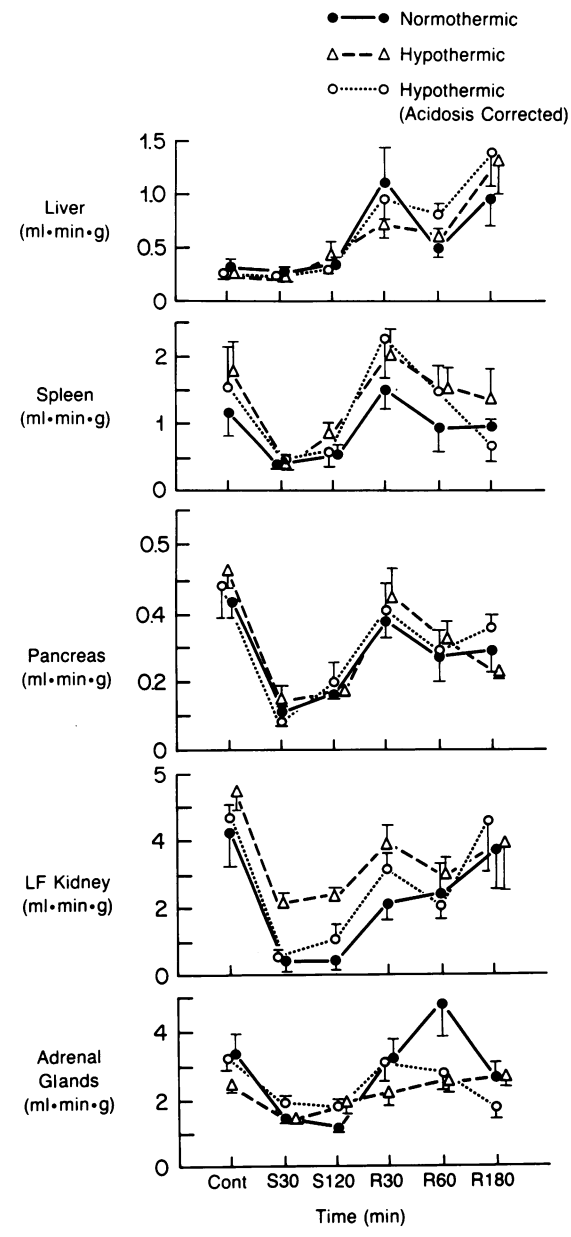

FIG. 3. Changes in regional blood flow during hemorrhagic shock and hypothermia.

baseline values of 1.12 ± 0.06 to 0.87 ± 0.03, $p < 0.05$. After 2 hours sustained shock, subendocardial perfusion in the hypothermic dogs was unchanged from baseline values and significantly higher in the hypothermic (Group IIA: 1.07 ± 0.05; Group IIB: 0.98 ± 0.04) compared to normothermic dogs (0.87 ± 0.03, $p < 0.05$). In late shock (S120), myocardial blood flow and myocardial oxygen delivery increased to 87% of baseline values in the normothermic shock group but remained significantly lower in hypothermic dogs ($p < 0.05$). After fluid resuscitation, myocardial blood flow and myocardial oxygen delivery increased and myocardial oxygen extraction fell to a similar extent in all dogs. After re-

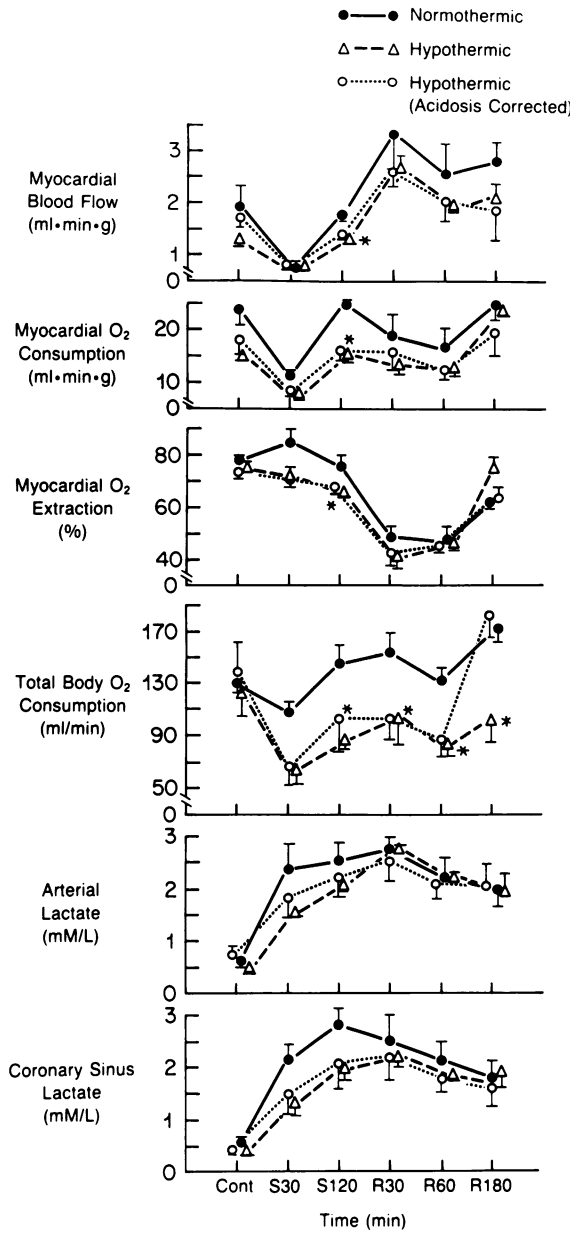

FIG. 4. Coronary blood flow, myocardial oxygen consumption and extraction, total body oxygen consumption, and arterial and coronary sinus lactate levels.

warming (R180) all indices of myocardial perfusion and myocardial oxygen metabolism were similar in the three groups, regardless of body temperature. However, total body oxygen consumption remained significantly lower in those dogs with persistent acid–based derangements ($p < 0.05$).

Acid–Base Status

Baseline measurements of acid–base balance as well as respiratory rate were similar in all dogs (Fig. 5). Hemorrhagic shock caused significant acidosis, as indicated by a progressive rise in circulating lactate levels and a progressive fall in arterial pH and bicarbonate level. While there was considerable variability in arterial pO_2 within groups, the changes from baseline values did not

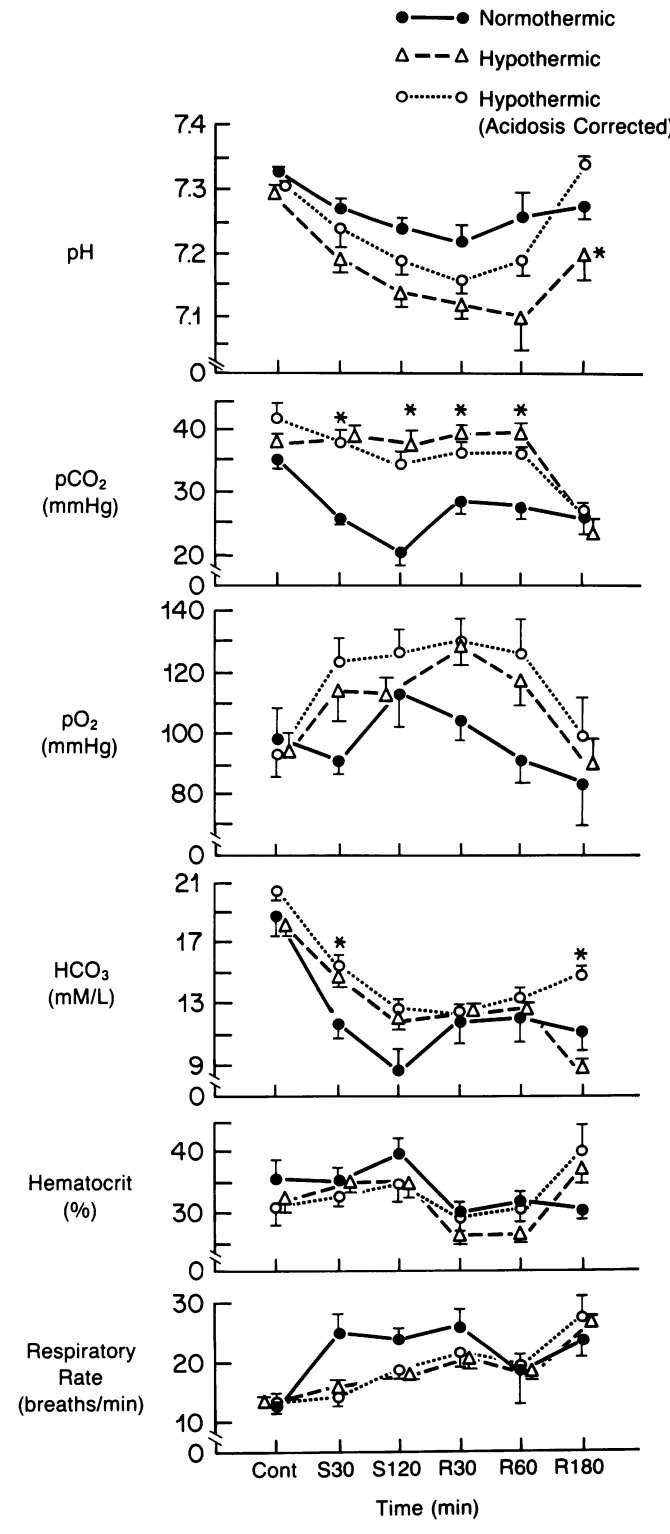

FIG. 5. Acid–base status in hemorrhagic shock and hypothermia.

achieve statistical significance. Hematocrit remained unchanged during hemorrhagic shock in all dogs, and there was similar hemodilution in all groups after fluid resuscitation. Normothermic shock caused a significant tachypnea ($p < 0.05$), producing a fall in arterial pCO_2. In contrast, respiratory rate remained unchanged from baseline values in hypothermic animals, causing arterial pCO_2 to be significantly higher in these dogs throughout hypothermic shock. Immediately after fluid resuscitation (R30), respiratory rate remained significantly lower and arterial pCO_2 higher in all hypothermic compared to normothermic dogs ($p < 0.05$). Sixty minutes after resuscitation, respiratory rates were similar in all groups, and this similarity persisted throughout the experimental study. Acid–base derangements persisted in the hypothermic dogs not given bicarbonate as indicated by a lower arterial pH and serum bicarbonate.

Discussion

Our data showed that moderate hypothermia in severe hemorrhagic shock reduced the metabolic requirements of the heart while maintaining cardiovascular function and myocardial perfusion. The cardiovascular responses to normothermic shock in this study were consistent with those reported previously by this laboratory and by other investigators.[10] These changes included tachycardia, a fall in preload and afterload, impaired left ventricular function, reduced peripheral perfusion, and increased respiratory rate. With crystalloid resuscitation, all cardiocirculatory parameters returned toward baseline values. The induction of hypothermia during hemorrhagic shock produced a significant bradycardia and prevented the tachypnea that is typical of normothermic shock. In addition, hypothermia enhanced left ventricular performance in late shock as indicated by a stable cardiac output and a higher stroke volume despite an unchanged LVEDP and a significant bradycardia. Increased left ventricular ejection, accompanied by no change in cardiac filling or fiber length indicates a positive inotropic response to hypothermia. Our data support the findings of Templeton et al. who showed that hypothermia prolonged the time course of cardiac contraction and increased total tension development.[11] Our data are consistent with studies by Monroe who reported increased ventricular work at a constant LVEDP.[12] Furthermore, Monroe showed no change in left ventricular pressure volume relationships when body temperature was below normal. These data contradict studies by Templeton et al. who described marked alterations in myocardial mechanical properties with changes in temperature, showing that stiffness was inversely proportional to temperature.[11]

Resuscitation improved hemodynamic function in all dogs, but bradycardia and a lower respiratory rate persisted in the hypothermic animals. Thirty minutes after rewarming, cardiovascular function was not significantly different from baseline values, regardless of a previous episode of hypothermia.

The finding of a higher peripheral vascular resistance in the hypothermic dogs 180 minutes after volume replacement and 2 hours after rewarming was an interesting and unexpected finding. Hypothermia may have a prolonged constrictive effect on the peripheral arterial sphincters, an effect not evident earlier in the experiment because of the inherent inaccuracy of peripheral vascular resistance determination during the use of the pressure-controlled hemorrhage reservoir. The authors considered the possibility that a primary fluid deficit may have existed, but this proved unlikely in light of a normal cardiac filling pressure or normal left ventricular end-diastolic pressure. Finally, rewarming likely promoted a massive vasodilatation of the peripheral vascular beds, followed by a vasoconstrictive effort in order to maintain central blood pressure. However, these explanations are purely speculative, and the specific effects of hypothermia on the peripheral vasculature warrants further study.

Myocardial blood flow and oxygen metabolism were comparable in all dogs during early shock, regardless of body temperature. In late hemorrhagic shock, coronary blood flow increased in normothermic dogs, likely due to sympathoadrenal activation, tachycardia, and increased metabolic needs of the myocardium. The lower coronary blood flow in late hemorrhagic shock in the hypothermic dogs supports previous reports that hypothermia decreased myocardial oxygen metabolism and reduced myocardial blood flow.[13,14] Other studies of severe hypothermia (body temperature at 21 C) showed a decrease in cardiac output while subendocardial perfusion was preserved.[15] Studies of normovolemic hypothermia with cardiac output held steady showed a fall in cardiac oxygen consumption and heart rate, an unchanged blood pressure, and a significant increase in the per cent of cardiac output to the heart.[16] Similarly, Sabiston et al. reported that the per cent of cardiac output delivered to the heart increased significantly in hypothermic dogs, attributing the selective increase in coronary flow to a direct effect of temperature on the myocardial smooth muscle and active vasodilitation of the coronary vasculature.[17]

Our data indicate that hypothermia in hemorrhagic shock reduced myocardial oxygen metabolism as indicated by a bradycardia and a lower myocardial oxygen extraction in hypothermic compared to normothermic shock. It was of interest that myocardial oxygen extraction was lower during shock in the hypothermic dogs,

despite a higher stroke volume in this group. The metabolic needs of the myocardium are dictated by both contractile function as well as heart rate. However, the pronounced bradycardia in the hypothermic shock apparently overwhelmed the moderate increases in contractile function, decreasing myocardial oxygen requirements. While total myocardial blood flow was lower in late hypothermic shock, there was no evidence of subendocardial ischemia since endocardial epicardial flow ratios remained unchanged from baseline measurements. Our data support the concept that myocardial oxygen requirements are the primary regulator of coronary blood flow, overwhelming any direct effects of temperature on the coronary vasculature.

The acid–base changes observed in normothermic shock are consistent with those previously reported by our laboratory and others. In shock, progressive metabolic acidosis was accompanied by a respiratory alkalosis, preventing excess arterial pH changes despite severe hemorrhagic shock. A metabolic acidosis without respiratory compensation occurred in the hypothermic groups as indicated by the higher pCO_2 and unchanged serum bicarbonate, lower respiratory rate, and higher circulating lactate levels. Our finding of lower coronary sinus and arterial lactate levels in the hypothermic dogs supports a previous study by Shipp et al. who demonstrated that hypothermia reduced lactate formation in the perfused heart.[18] To our knowledge, while no studies have specifically focused on the acid–base status in our model of hemorrhagic shock followed by hypothermia, a large body of literature describes the effect of pH on the hypothermic heart. These previous studies have shown that moderate variations of the extracellular acid–base environment during hypothermia do not impair myocardial function or oxygen demand ratios.[19] While coronary blood flow and myocardial oxygen delivery were lower in late hypothermic compared to late normothermic shock, it is likely that the leftward shift of the oxygen disassociation curve preserved myocardial oxygen consumption and protected cardiac function under conditions of decreased oxygen supply.[20] These data are consistent with previous reports that hypothermia modifies all determinants of oxygen supply but tissue hypoxia does not occur.[19] Several investigators have proposed that intracellular buffering mechanisms compensate for moderate variations in the extracellular pH and that the depressive effects of acid–base disorders on myocardial contractility are related to severe changes in intracellular pH which overwhelm intracellular buffering mechanisms.[20,21] Studies by Poole-Wilson and Langer,[21] using a hypothermic isolated perfused papillary muscle preparation, observed that acidosis was associated with the rapid fall in myocardial tension development while alkaline pH preserved contractile function in a hypothermic preparation. Becker et al.[22] also showed improved cardiac function in hypothermia if pH was adjusted to an alkaline range, attributing enhanced cardiac performance during hypothermia with pH correction to a more ideal biochemical environment for continued aerobic metabolism. It is likely that the inotropic effect of hypothermia in our study would have been significantly enhanced if acid–based correction and ventilatory support had been instituted during the shock period. This hypothesis is supported by the significant increase in cardiac output with acid–base correction in the hypothermic dogs.

Intracellular acidosis may explain the elevated hematocrit at the end of the experimental period. An appropriate pH is necessary to stabilize the Gibbs-Donnan ratio and red blood cell volume while intracellular acidosis leads to cellular swelling.[23] Other possibilities include fluid deficits, increased viscosity, or decreased blood volume secondary to hypothermia itself.[16] Furthermore, an increased circulating catecholamine level secondary to hypothermia may promote splenic contraction and, therefore, hemoconcentration as seen in our experiment.[24] The cause is likely multifactorial.

While the authors acknowledge several problems inherent in studying hemorrhagic shock complicated by hypothermia, this situation is a difficult clinical issue that needs to be addressed. First, it is difficult to separate the physiologic response to hypothermia from the responses to hemorrhagic shock. Moreover, it is likely the hypothermia-mediated increases in ventricular stiffness[11] impair accurate measurement of contractile changes that relate stroke volume to left ventricular filling pressures. Also, in our model difficulties arose in distinguishing the effects of shock-induced acidosis from the effects of hypothermia-induced acidosis. Are these additive detriments or mutually exclusive insults? Could the combination of increased contractile function and decreased peripheral metabolic rate present in the hypothermic shock portend a lesser degree of coagulopathy than that which occurs in normothermic shock? In summary, our data suggest that hypothermia reduces metabolic requirements during hemorrhagic shock while maintaining cardiovascular function and adequate myocardial oxygen delivery. The application of these findings combined with critical attention to the optimal acid–base balance may suggest a potential role of hypothermia in the treatment of severe hemorrhagic shock.

Acknowledgment

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