Body Temperature and the Neonatal Response to Hemorrhage

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Budin, in 1900, recognized that there was a relationship between temperature and neonatal mortality. Premature infants whose rectal temperatures were below 32°C had a 5% survival rate, while 77% of those with a temperature over 37°C survived. More recently Silverman, Ferget and Berger studied two groups of premature infants maintained at different incubator temperatures. Those kept at an ambient temperature of 32°C had a survival rate of 83%, while those in a cooler environment, 29°C, had a 68% survival. Beutow and Klein, in 1964, showed that a similar relationship existed between skin temperature and premature infant survival. Babies maintained at a warm skin temperature, 36°C, had a 58.4% survival while those with a lower temperature, 34°C, had a survival rate of 46.5%.

Brück's clinical investigations helped clarify the relationship of temperature and neonatal survival. He found that in the newborn period an environmental temperature of 34°C could be described as thermal neutrality. When the ambient temperature fell below this level the baby's metabolic activity increased and heat production rose without shivering. This mechanism was termed non-shivering thermogenesis. A brief cold exposure to an ambient temperature of 22°C produced almost a three-fold increase in oxygen consumption and a maintenance of near normal body temperature.

Gandy et al., found that exposure to cold resulted in increased metabolic work and the accumulation of acid metabolites leading to metabolic acidosis. Other investigators have observed that the infant subjected to a cold stress has a fall in blood glucose and a decrease in arterial oxygen tension. It appears that cold exposure in the newborn infant may be detrimental because of the increased metabolic work required to maintain body temperature and that proper regulation of the thermal climate is of clinical significance.

There are, however, apparent contradictions to the above findings. A large body of clinical and experimental information supports the concept that hypothermia reduces metabolic activity and oxygen requirements of the organism. In summarizing the proceedings of the Symposium of the Physiology of Induced Hypothermia convened by the National Academy of Science in 1956, Horvath concluded "there seems to be one point of agreement among all investigators, namely that there is a decrease in oxygen consumption in all systems of the organism in hypothermia..." That the reduced metabolic activity accompanying hypothermia may be protective in certain situations has been repeatedly suggested. Miller and Miller studied survival time of the neonatal puppy asphyxiated at normothermic and profound hypothermic body temperature (15°C). The cooled puppies survived and recovered from a period of oxygen deprivation that was four times longer than the lethal ex-

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posure period for warm litter mates. The hypothermic puppies\textsuperscript{13} showed less reduction in pH and blood glucose, and a slower rise in the lactate-pyruvate ratio. Several clinical reports\textsuperscript{4, 7, 18} have described the use of hypothermia in resuscitation of newborn infants suffering from birth asphyxia. The combined data from four different authors\textsuperscript{7} have shown that the mortality in babies with low Apgar scores treated by rapid induction of hypothermia was 11.9% as compared to 44.7% observed in similarly low Apgar scored babies treated by standard resuscitative measures.

There is evidence to implicate cold on the one hand as being detrimental to the newborn, and on the other hand as being protective in nature. To properly understand this apparent paradox it is important to differentiate between two different conditions: (1) The cold challenge—The newborn with an intact thermoregulatory system exposed to an ambient temperature below thermoneutrality. In this environment metabolic activity increases through non-shivering thermogenesis in order to maintain normal body temperature. Oxygen consumption increases and the increase in metabolic work may prove detrimental to the newborn by depletion of energy stores and accumulation of acid metabolites. (2) The hypothermic state—The newborn has a low body temperature. Hypothermia is rapidly achieved and thermogenesis may be inhibited by any of a variety of methods,\textsuperscript{10, 14} anesthesia, drugs, hypoxia or hypercapnea. Low body temperature is reached without an increase in metabolic activity. Once hypothermic levels are achieved metabolic work and oxygen requirements are reduced. Presumably, in this state, the organism is better able to withstand oxygen deprivation and other life threatening challenges.

During a series of experiments in which newborn puppies were subjected to hemorrhage we repeatedly observed that body temperature fell to 34°–35° C. within 10 minutes of the puppy being removed from the mother. A further reduction in temperature to 32°–33° C. followed hemorrhage. The ambient temperature of the room was 22.8° C. The question arose whether unanesthetized newborn animals maintained at moderate levels of hypothermia (32°–33°) breathing room air would have different hemodynamic and metabolic responses to a life threatening challenge, hemorrhage, than those kept at normothermic body temperatures. We hoped to determine if (1) a body temperature of 32°–33° C. would be either detrimental to the newborn’s response to hemorrhage because of the increased metabolic demands necessitated by the cold exposure, or protective, because of the lower body temperature and reduction in metabolic activity.

Materials and Methods

Twenty-four puppies were successfully studied. Only those animals that were healthy and active were chosen. Animals were eliminated from the study if blood in excess of 3 ml. was lost during cannulation, or technical factors prevented the measuring of all variables. Body weight varied between 314 Gm. and 786 Gm. The age range was 1 hour to 7 days. The mothers were all healthy mongrel dogs who delivered spontaneously through the vagina. By matching for litter, weight, and age, the newborn dogs were divided into three study groups.

Measurements. The following hemodynamic variables were measured: Heart rate, arterial pressure, central venous pressure, cardiac output, stroke output and systemic vascular resistance. A modified dye dilution technic using a Holter pump for blood withdrawal and reinfusion was used for cardiac output estimation. This experimental model has been previously described.\textsuperscript{1, 18} Rectal temperature was continuously monitored by a thermistor probe, and arterial blood was sampled at intervals for hema-
tocrit, pH, $P_{CO_2}$ and $P_{O_2}$ determinations. The pH and blood gas values were corrected to body temperature. Base excess was calculated using the Severinghaus blood gas calculator. Body temperature was maintained by an electric thermal pad and a radiant heat lamp. Total blood volume was calculated, using $^{51}$Cr tagged red blood cells. Blood loss from sampling was replaced with an equivalent volume of maternal blood or the puppy's own blood obtained during the hemorrhage.

**Experimental Groups (Table 1):**

I. Normothermic Controls

Body temperature was maintained at 37°C for a period of two hours—there was no hemorrhage.

II. Normothermic Hemorrhage

Rectal temperature was maintained at 37°C. The animals were subjected to a hemorrhage of 30% of the total blood volume.

III. Hypothermic Hemorrhage

The animals in this group were subjected to a hemorrhage of 30% of total blood volume. Rectal temperature was maintained between 32° and 33°C after hemorrhage.

**Experimental Design.** Following vascular cannulations baseline hemodynamic and metabolic observations were made. Graded hemorrhage consisting of 30% of the estimated total blood volume was accomplished over a 10-minute period in puppies belonging to Groups II and III. Immediately following the hemorrhage, the same set of observations were made, and repeated every 15 minutes for a 90-minute period. Similar observations at identical time increments were made in the control group (Group I) where no hemorrhage was induced. At the end of the experiment, each animal was sacrificed by withdrawing all available blood for dye-curve calibration.

Table 1. General Data

<table>
<thead>
<tr>
<th>Group Classification</th>
<th>Temperature*</th>
<th>Age (days)</th>
<th>Weight (Gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Control group</td>
<td>37-38°C</td>
<td>9</td>
<td>467</td>
</tr>
<tr>
<td>II. Normothermia group</td>
<td>37-38°C</td>
<td>8</td>
<td>432</td>
</tr>
<tr>
<td>III. Hypothermia group</td>
<td>32-33°C</td>
<td>7</td>
<td>425</td>
</tr>
</tbody>
</table>

* Maintained rectal temperature during study

** Instrumentation Laboratory blood gas analyzer.

Blood Gas Calculator 984-300, Radiometer A/S, Copenhagen.


Table 2. Paired t-Test for Consecutive Experimental Stages Before and After Hemorrhage#

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normothermia Group (III)</th>
<th>Hypothermia Group (III)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Temperature</td>
<td>-0.492</td>
<td>-1.106</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>0.784*</td>
<td>-0.088</td>
</tr>
<tr>
<td>Arterial pressure</td>
<td>2.888*</td>
<td>-0.830</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>5.800**</td>
<td>-5.826**</td>
</tr>
<tr>
<td>Systemic resistance</td>
<td>-10.080**</td>
<td>4.124**</td>
</tr>
<tr>
<td>$pH$</td>
<td>0.762</td>
<td>4.393**</td>
</tr>
<tr>
<td>Base excess</td>
<td>3.528*</td>
<td>6.927**</td>
</tr>
<tr>
<td>$P_{O_2}$</td>
<td>-1.086</td>
<td>-1.684</td>
</tr>
<tr>
<td>$P_{CO_2}$</td>
<td>0.570</td>
<td>-3.317*</td>
</tr>
</tbody>
</table>

#—values of calculated t-statistic; significance at 5 and 1 per cent level are indicated by * and **, respectively.
respectively, the group lines Table variables, was tested each Table 2nd stages not.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (I)</th>
<th>Experimental Groups</th>
<th>Hypothermia Group (III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate</td>
<td>0.380</td>
<td>0.954</td>
<td>-5.725**</td>
</tr>
<tr>
<td>Arterial pressure</td>
<td>0.743</td>
<td>-5.039**</td>
<td>-4.237**</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>-1.165</td>
<td>-3.043*</td>
<td>-2.707*</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>-1.100</td>
<td>-2.655*</td>
<td>-0.846</td>
</tr>
<tr>
<td>Systemic resistance</td>
<td>-0.740</td>
<td>-1.672</td>
<td>-0.139</td>
</tr>
<tr>
<td>pH</td>
<td>-0.501</td>
<td>-2.790**</td>
<td>-3.920**</td>
</tr>
<tr>
<td>Base excess</td>
<td>-1.120</td>
<td>-4.334**</td>
<td>-6.244**</td>
</tr>
<tr>
<td>P_{O_2}</td>
<td>0.056</td>
<td>3.315*</td>
<td>3.549*</td>
</tr>
<tr>
<td>P_{CO_2}</td>
<td>1.234</td>
<td>1.146</td>
<td>-0.220</td>
</tr>
</tbody>
</table>

# —values of calculated t-statistic; significance at 5 and 1 per cent level are indicated by * and **, respectively.

**Statistical Analysis.** Paired t-test was used to check whether the observations on each variable at any two consecutive stages of the experiment differed significantly or not. The calculated t-values for the 1st (baseline) and 2nd (immediate post-hemorrhage) stages designated as “A,” and for the 2nd and 3rd (15 minutes post-hemorrhage) stages designated as “B,” are given in Table 2.

A straight line was fitted to the data, by the method of least squares, for each of the 24 subjects and for each of the 11 variables. The average shape of the regression lines for each of the three experimental groups was tested for the null hypothesis that the slope was zero. This was done for each of the variables, and the t-values are given in Table 3. In addition, assuming B₁, B₂ and B₃ to represent the average slopes of the regression lines for the control group, normothermic group and hypothermic group, respectively, the null hypothesis that B₁ — B₂ = 0, B₁ — B₃ = 0, and B₂ — B₃ = 0 was tested (Table 4). The respective average intercepts of the regression lines for the 3 groups were tested in a similar manner.

**Results**

(1) **Temperature.** By immediately placing the normothermic controls and normothermic hemorrhaged puppies on an electric thermal pad and under a radiant heater, body temperature was maintained between 37° and 38° C. during the experimental period. High temperature outputs of both heating units were required to maintain stable body temperature after hemorrhage. Body temperature was initially not controlled in the hypothermic hemorrhage group. After 10–20 minutes of exposure to an average ambient temperature of 22.8° C., rectal temperature fell to 35.4° C. Immediately after hemorrhage the level was 34° C. and by 15 minutes post-hemorrhage the temperature had fallen to 32.8° C. To

**Table 3. Null-hypothesis Test for Slope of Regression**

<table>
<thead>
<tr>
<th>Variable</th>
<th>B₁ — B₂ = 0</th>
<th>B₁ — B₃ = 0</th>
<th>B₂ — B₃ = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate</td>
<td>0.918</td>
<td>3.020*</td>
<td>2.170*</td>
</tr>
<tr>
<td>Arterial pressure</td>
<td>0.727</td>
<td>0.280</td>
<td>-1.220</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>0.930</td>
<td>0.970</td>
<td>0.126</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>0.700</td>
<td>-0.240</td>
<td>-1.230</td>
</tr>
<tr>
<td>Systemic resistance</td>
<td>-1.000</td>
<td>-0.420</td>
<td>-1.040</td>
</tr>
<tr>
<td>pH</td>
<td>0.270</td>
<td>0.150</td>
<td>0.173</td>
</tr>
<tr>
<td>Base excess</td>
<td>3.570**</td>
<td>5.310**</td>
<td>1.410</td>
</tr>
<tr>
<td>P_{O_2}</td>
<td>-1.960</td>
<td>-2.110</td>
<td>-0.187</td>
</tr>
<tr>
<td>P_{CO_2}</td>
<td>0.008</td>
<td>1.140</td>
<td>1.090</td>
</tr>
</tbody>
</table>

# —values of calculated t-statistic; significance at 5 and 1 per cent level are indicated by * and **, respectively.
maintain body temperature at this level the
external heating units then had to be con-
tinually utilized.

(2) Mortality. All animals survived the
2-hour period of the experiment.

(3) Pulse Rate (Fig. 1). There was an
immediate fall in the pulse rate after hem-
orrhage in the hypothermic group. The de-
crease was progressive, and significantly
lower than in the normothermic animals
subjected to hemorrhage and highly sig-
ificantly lower than in the control group.
There was a slight reduction in the pulse
rate following hemorrhage in the normo-
thermic animals (Group II).

(4) Arterial Blood Pressure (Fig. 1).
The initial decrease in blood pressure fol-
lowing hemorrhage was greater in the hy-
pothemic animals. Then the fall in the ar-
terial blood pressure was progressive and
similar in both the normothermic and hy-
pothermic animals subjected to hemor-
rhage.

(5) Cardiac Output (Fig. 2). There was
no difference between the pattern of the
response of cardiac output in either of the
groups subjected to hemorrhage. However,
the increase in cardiac output 15 minutes
after the profound post-hemorrhage fall
was greater in the normothermic than in
the hypothermic animals. For this brief pe-
riod of time cardiac output in the normo-
thermic animals was higher but thereafter
a similar gradual decrease in output was
noted in both groups.

(6) Stroke Volume. The response of
stroke volume in the normothermic and hy-
pothermic animals subjected to hemorrhage was identical to the cardiac output response.

(7) **Systemic Resistance** (Fig. 2). There was a highly significant immediate rise in systemic resistance in both groups of animals subjected to hemorrhage. After the initial sharp rise there was a moderate fall. This pattern of the response of systemic resistance was the same in both groups. The decrease in resistance was of greater magnitude in the normothermic animals, and they maintained a lower systemic resistance throughout the experiment.

(8) **Arterial Blood pH** (Fig. 3). The trend of a steady fall in pH after hemorrhage was the same in both groups of animals subjected to hemorrhage. Fifteen minutes after hemorrhage the magnitude of the fall in pH was greater in the normothermic than in the hypothermic animals.

(9) **Base Excess**. There was an equal and progressive fall in base excess in both groups of animals subjected to hemorrhage.

(10) **Arterial P sub CO2**. The response of the normothermic and hypothermic animals subjected to hemorrhage differed. The normothermic animals had a sharp and highly significant rise in P sub CO2 after hemorrhage. The hypothermic puppies had an initially highly significant drop in P sub CO2 after hemorrhage.

(11) **Arterial P sub O2** (Fig. 3). Both hypothermic and normothermic animals responded to hemorrhage with an equal and steady rise in P sub O2 that was highly significant as compared to the control group.

**Discussion**

The pattern of hemodynamic and metabolic responses of newborn puppies subjected to hemorrhage was the same whether body temperature was 33°C or 37°C except for arterial P sub CO2, which rose in the normothermic and fell in the hypothermic animals. There were, however, differences in the magnitude of responses between the two groups after hemorrhage. The hypothermic puppies responded with a slower pulse rate, a lower blood P sub CO2 and a higher systemic resistance. For a short period the hypothermic group had lower cardiac output, stroke volume and blood pressure. Although pH was briefly higher in the hypothermic hemorrhage group, base excess was the same in both groups. There were no deaths in either group. The results suggest that the newborn puppy's tolerance to hemorrhage is neither markedly improved nor reduced by lowering body temperature to moderately hypothermic levels. Body temperature fell to a moderate degree on cold exposure with a rapid reduction following hemorrhage. Hypoxia is known to prevent increased heat production. It is possible that hemorrhage in a similar manner inhibited thermogenesis al-
lowing the animals to quickly reach a lower body temperature.

One may speculate from the quoted literature and the results of this study that the significance of low body temperature to the neonate appears dependent on the manner in which this condition is reached. A rapid fall in body temperature, particularly if thermogenesis is inhibited, produces hypothermia without a large energy expenditure. Low body temperature achieved in this way may be protective by reducing oxygen and energy requirements. On the other hand, with an intact thermoregulatory system prolonged exposure to a cool environment can result in a great increase in heat production. After a period of time body temperature may fall in spite of this maximum response. The neonate now has a marked reduction in energy stores and metabolic acidosis. In this condition he is poorly prepared to meet a life challenging situation. Low body temperature may not be detrimental to the newborn but the process of reaching this temperature may be.

Summary

Newborn puppies were maintained at two different body temperatures, 33° C. and 37° C., and subjected to a hemorrhage of 30% of their total blood volume. The pattern of responses to the hemorrhage was the same in both groups except for arterial PCO2, but the magnitude of the responses differed. The hypothermic puppies had a lower pulse rate and blood PCO2, but a higher systemic resistance. For a short period the hypothermic group had a lower cardiac output, stroke volume, and blood pressure. Although arterial pH was briefly higher in the hypothermic hemorrhage group, base excess was the same in both. There were no deaths.

References


