HEMODILUTION AND WHOLE BODY OXYGEN BALANCE DURING NORMOTHERMIC CARDIOPULMONARY BYPASS IN DOGS

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Objective: The purpose of this study was to determine the minimum hematocrit value that can support whole body oxygen consumption during normothermic cardiopulmonary bypass. The effect of hemodilution on peripheral resistance, whole body oxygen delivery, and oxygen consumption was determined over a range of hematocrit values. **Methods:** Measurements were obtained during 38° C cardiopulmonary bypass with progressive normovolemic hemodilution (hematocrit value 40% to 9%) in nine dogs. Dextran 70 (6%) was used as a diluent. Anesthesia consisted of high-dose fentanyl and midazolam. A mean arterial pressure of 60 mm Hg was maintained throughout cardiopulmonary bypass via increases in pump flow. **Results:** Progressive hemodilution was associated with a decreasing total peripheral resistance. During normothermic cardiopulmonary bypass with a whole blood prime, the whole body oxygen consumption approximated values previously reported in dogs under nonbypass conditions. Oxygen delivery and whole body oxygen uptake were maintained between a hematocrit value of 39% and 25%. Significant decreases for both were seen when the hematocrit value was reduced to 18% and below. **Conclusions:** A hematocrit level greater than 18% was needed to maintain systemic oxygen delivery and consumption during warm cardiopulmonary bypass. The critical hematocrit value may be higher under bypass than nonbypass conditions because the flow increases that are practical during cardiopulmonary bypass do not approximate those seen in response to hemodilution of the intact circulation. Finally, the critical hematocrit value for the body may be higher than that required for the brain during warm cardiopulmonary bypass. (J Thorac Cardiovasc Surg 1998;115:1203-8)

Although hemodilution is standard practice during cardiopulmonary bypass (CPB), the limits of hemodilution at differing extracorporeal temperatures have not yet been systematically determined.¹ The purpose of this study was to define the minimal hematocrit value that supports whole body oxygen consumption during normothermic CPB.

The systemic response to hemodilution under non-CPB conditions is well described. Under normal conditions, systemic and regional oxygen consumption is independent of oxygen delivery. Oxygen delivery and consumption are maintained during moderate hemodilution by increases in cardiac output, increases in tissue blood flow, and later by an increase in tissue oxygen extraction.²⁻⁴ However, for the individual organ and the body as a whole, there is a critical hematocrit value at which oxygen consumption becomes delivery-dependent. In the dog, under non-CPB conditions, systemic oxygen consumption is maintained to a hematocrit value of approximately 10%.⁵ The same physiology is applicable during CPB, during which whole body oxygen balance is actively manipulated by changes in hematocrit value, temperature, and pump flow.

Transfusion practice varies greatly in cardiac surgery and improved transfusion guidelines are needed.^{6,7} These issues are made more pressing

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Fig. 1. Total peripheral resistance (TPR) in dynes · sec · cm⁻⁵ versus hematocrit (Hct) during the five CPB study periods. Values are mean ± standard deviation (*n* = 9). A regression curve was generated from 45 individual values of TPR at individual hematocrit values.

with the shift to normothermic CPB in the past few years.^{8,9} Given the higher oxygen demand associated with “warm” CPB,¹⁰ there is a tendency to transfuse more frequently, but this practice is not based on a systematic evaluation of hemoglobin requirements. In fact, variability in transfusion practice arises in part because the relationship between temperature, hematocrit level, and oxygen balance has not been adequately characterized.

In evaluating the relationships between hematocrit value, systemic oxygen consumption, and oxygen delivery during normothermic CPB, we hope to provide a more physiologic foundation on which to make decisions on perfusion and hematocrit management during CPB.

Materials and methods

After review and approval by the Institutional Animal Care and Use Committee of the Mayo Clinic, nine unmedicated fasting adult mongrel dogs weighing 17 to 20 kg were studied. The dogs were placed in an acrylic plastic box (Plexiglas box, Rohm and Haas Company, Philadelphia, Pa.) and anesthesia was induced with halothane 3% to 4% inspired. After the onset of anesthesia, peripheral intravenous access was secured, muscle relaxation was obtained with pancuronium (0.1 mg · kg⁻¹), and the trachea was intubated. Ventilation was controlled with a Harvard pump (Harvard Apparatus Co., Inc., S. Natick, Mass.) set to maintain arterial carbon dioxide tension (Paco₂) at 35 to 40 mm Hg and an arterial oxygen tension (PaO₂) greater than 150 mm Hg. Anesthesia was maintained with isoflurane 0.5% to 1.5% inspired and fentanyl and midazolam (bolus: 250 μg · kg⁻¹ fentanyl and 350 μg · kg⁻¹ midazolam, followed by infusion: fentanyl 3.0 μg ·

kg⁻¹ · min⁻¹ and midazolam 9.6 μg · kg⁻¹ · min⁻¹). Muscle relaxation was maintained by continuous infusion of pancuronium (0.8 μg · kg⁻¹ · min⁻¹).

A cannula was surgically inserted into a femoral artery for mean arterial blood pressure measurements and blood sampling. Body temperature was measured with a nasopharyngeal thermistor.

For CPB, a left-sided thoracotomy was performed. Venous drainage to the extracorporeal circuit was by a 36F cannula placed in the right atrium via the right atrial appendage. The blood was circulated by centrifugal pump through a combined heat exchanger–oxygenator (Bentley Univox, Irvine, Calif.) and returned via a cannula (4.4 mm inner diameter) into the root of the aorta. Before aortic cannulation, intravenous heparin was given to maintain an activated coagulation time greater than 600 seconds. The bypass machine was primed with blood (approximately 750 ml) from a donor dog and with saline solution (about 250 ml). Mean arterial pressure was maintained between 55 and 70 mm Hg throughout the period of bypass by altering bypass pump flow. No vasoconstrictors or vasodilators were used. Arterial hemoglobin concentration, blood temperature, and blood gas data were continuously monitored by in-line detectors (CDI 100 and CDI 400, Cardiovascular Devices, Inc., Tustin, Calif.). Pump flow was measured with an in-line ultrasonic blood flowmeter (Sarns/3M, Ann Arbor, Mich.).

After establishment of CPB, control measurements and blood samples were obtained after the target nasopharyngeal temperature of 37.5° C to 38.5° C (low normal dog temperature) was achieved. Arterial blood was drawn from the femoral line and mixed venous blood was drawn from the venous return line just proximal to the CPB reservoir. Arterial and venous oxygen and carbon dioxide partial pressures (PO₂, PCO₂) and pH were measured with an IL 1306 pH and blood gas analyzer (Instrumentation Laboratories, Inc., Lexington, Mass.) with the electrodes maintained at 37° C. Hemoglobin concentration and oxygen saturation were measured by an IL 482 Co-Oximeter (Instrumentation Laboratories) with its coefficient setting selected for canine blood. Venous lactate levels were measured with a YSI model 23A analyzer (Yellow Springs Instrumentation, Yellow Springs, Ohio).

Oxygen consumption, oxygen delivery, oxygen extraction ratio, and total peripheral resistance were calculated by means of standard equations.

Oxygen consumption ($\dot{V}O_2$):

$$\dot{V}O_2 = \frac{(\text{Pump flow} \cdot \text{AVDO}_2)}{\text{BSA}} \text{ ml O}_2 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$$

where BSA = body surface area.

Arteriovenous oxygen content difference (AVDO₂):

$$\text{AVDO}_2 = (\text{CaO}_2 - \text{CvO}_2) \text{ ml} \cdot \text{dl}^{-1}$$

Arterial or venous oxygen content (CxO₂):

$$\text{CxO}_2 = 1.34 \text{ Hb}(\text{SxO}_2) + 0.003 (\text{PxO}_2)$$

where Hb = hemoglobin concentration; SvO₂ = oxygen saturation; PxO₂ = partial pressure of oxygen; and x = arterial or venous.

Oxygen delivery (DO_2):

$$DO_2 = \frac{\text{Pump flow} \cdot CaO_2}{BSA} \text{ ml } O_2 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$$

Oxygen extraction ratio (OER):

$$OER = \frac{\dot{V}O_2}{DO_2}$$

Total peripheral resistance (TPR):

$$TPR = \frac{(MAP - CVP) \cdot 80}{\text{Pump flow}} \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$$

where MAP = mean arterial pressure and CVP = central venous pressure.

An oversized (36F) venous cannula (for a 20 kg dog) was placed in the right atrium to ensure complete right heart drainage such that the central venous pressure could be assumed to be negligible.

Hemodilution was achieved by removing blood from the CPB circuit and replacing it with 6% dextran 70. After each reduction in hematocrit value, a period of hemodynamic stabilization of at least 15 minutes was allowed before blood samples were withdrawn and measurements recorded. Mixed venous oxygen saturation was also monitored for stability before measurement recording and blood sampling.

Statistical analysis. All physiologic and metabolic data collected at the five levels of hemodilution during CPB were analyzed by means of repeated-measures analysis of variance. Differences between the five periods (with period 1 designated as control) were determined by the Student-Newman-Keuls test when necessary. All values are expressed as mean $\pm$ standard deviation. Regression curves for oxygen delivery, oxygen consumption, and total peripheral resistance were generated from the 45 individual data points for each variable at each measured hematocrit value. The data were fit to a logarithmic curve by means of the formula $y = a + b (\ln x)$. The figures present these curves, as well as mean values and standard deviations for each variable.

Results

As hematocrit value was reduced from 40% to 9%, systemic physiologic variables remained stable (Table I). Throughout CPB, temperature, mean arterial pressure, PaO_2 , $Paco_2$, and pH remained unchanged. The pH tended to decrease in the final hemodilution step, but this decrease did not reach statistical significance (Table I).

Progressive hemodilution resulted in a progressive reduction in total peripheral resistance (Fig. 1, Table II). However, mean arterial pressure was maintained at approximately 62 mm Hg throughout the study by increases in pump flow. A 50% increase in pump flow was required to maintain mean arterial pressure as hematocrit value was reduced from 39% to 18% (Table II). The oxygen delivery at a hemat-

Fig. 2. Whole body oxygen consumption ($\dot{V}O_2$) ($\square$) in $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ and oxygen delivery (DO_2) ($\blacksquare$) in $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ versus hematocrit (Hct) during the five CPB study periods. Values are mean $\pm$ standard deviation ($n = 9$). Each regression curve was generated from 45 individual values of oxygen consumption and oxygen delivery at individual hematocrit levels.

ocrit value of 23% was 274 $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ (11.5 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and did not differ from the oxygen delivery at a hematocrit value of 39%. Only when hematocrit concentration was reduced to $18\% \pm 2\%$ was there a significant decrease in systemic oxygen delivery to 238 $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ (10 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Similarly, systemic oxygen consumption was stable between hematocrit values of 39% and 25% and showed a significant reduction at a hematocrit value of 18% and below (Table II, Fig. 2).

During normothermic CPB with a hematocrit value of 39%, the venous oxygen saturation was 57%. This tended to decrease with progressive hemodilution and was 50% or less when the hematocrit value was 18% or below. The oxygen extraction ratio also tended to rise throughout CPB and increased from 41% to approximately 55% as hemoglobin concentration was progressively reduced. Changes in venous lactate parallel changes in the oxygen extraction ratio (Table II).

Discussion

The beneficial effects of hemodilution during CPB are well recognized. CPB hemodilution reduces the demand for blood therapy and may reduce the incidence of transfusion-related complications. Under both CPB and non-CPB conditions, hemodilution increases blood flow in a variety of organ beds.^{2, 4, 11, 12} This effect may be particularly advan-

Table I. Systemic physiologic variables with progressive hemodilution during normothermic CPB

CPB period	Hct (%)	Temp (°C)	MAP (mm Hg)	Pao ₂ (mm Hg)	Paco ₂ (mm Hg)	pH
1	39 ± 6	38 ± 0.9	62 ± 10	253 ± 93	36 ± 3	7.35 ± 0.06
2	25 ± 2	38.5 ± 0.8	62 ± 4	302 ± 105	37 ± 4	7.33 ± 0.07
3	18 ± 2*	38.0 ± 0.3	62 ± 3	260 ± 83	34 ± 3	7.35 ± 0.04
4	14 ± 1*	38.1 ± 0.5	62 ± 5	279 ± 93	37 ± 3	7.33 ± 0.06
5	9 ± 1*	38.1 ± 0.5	62 ± 5	290 ± 63	37 ± 6	7.31 ± 0.04

Data are mean ± standard deviation ($n = 9$). CPB, Cardiopulmonary bypass; Hct, hematocrit value; Temp, temperature; MAP, mean arterial pressure.

* $p < 0.05$ versus CPB period 1.

tageous during hypothermic CPB when the reduction in blood viscosity with hemodilution¹³ counteracts the effect of cold-induced vasoconstriction and the increased blood viscosity associated with reduced body temperature.¹⁴

As a result of the reports of the Toronto investigators in 1991,^{8,9} there has been a shift toward normothermic CPB across North America. With this shift, there was a tendency at our institution and others to require higher hematocrit values during CPB, but this practice change was not based on systematic physiologic data on oxygen balance. Generally, guidelines as to "temperature appropriate hematocrit" would be of practical relevance but are largely lacking. Even for institutions not practicing warm CPB, patients approximate normothermia in the initial and late phases of CPB. During these periods hematocrit may be of particular relevance.

Typically, hemodilution during normothermic CPB results in hypotension, and it is common practice to support mean arterial pressure with a vasoconstrictor. In this investigation, we chose to increase pump flow to maintain mean arterial pressure rather than use an alpha agonist, for two reasons. First, supporting arterial pressure with pump flow allowed us to characterize the relationship between hematocrit value and peripheral resistance during CPB. Second, under non-CPB conditions the response to hemodilution is an increase in cardiac output rather than systemic vasoconstriction; as such, an increase in pump flow more closely mimics the physiologic response in the intact circulation. During CPB at equivalent blood pressures, tissue perfusion should be better maintained with increases in flow than with addition of a vasoconstrictor.¹⁵

Our study was designed to identify the minimal hematocrit level that supports whole body oxygen consumption during normothermic CPB. We found that systemic oxygen consumption is maintained at a hematocrit value of 25% but was reduced at 18%.

Interestingly, this range was higher than the reported "critical" hematocrit level of approximately 10% under non-CPB conditions.⁵ However, we found that during warm CPB, the critical oxygen delivery was approximately $10 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$. This is essentially the same as the value reported by Cain⁵ ($9.8 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$) under non-CPB conditions. From this observation, two conclusions may be drawn: First, CPB per se does not alter the critical level of oxygen transport; second, and more important, a higher hematocrit value may be indicated under CPB than non-CPB conditions. In the intact dog, the same critical oxygen delivery is obtained at a much lower hematocrit value (10%) because the intact animal is better able to increase its cardiac output than we are able to increase CPB pump flow. In our study, at a hematocrit value of 18%, the mean pump flow was 2.9 (or $122 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Cain's dogs reached the same critical oxygen delivery when the hematocrit value was approximately 10% because the cardiac output was $300 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, a cardiac index of about $6 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Because there are technical limitations to increasing CPB flows much above 2.6 or $2.8 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, oxygen delivery may be compromised by the limited "cardiac output" response to reduced hematocrit during clinical CPB.

We also found that the critical hematocrit value for the body during warm CPB is higher than that reported for the brain under the same conditions.¹⁶ In a different study, we determined that cerebral oxygen demand in dogs is met with a hematocrit value as low as 15%. We anticipated that the body would be more tolerant of hemodilution than the brain because of its lower oxygen demand per unit weight and higher oxidative reserve. However, the brain is very effective in increasing its flow at low hematocrit values such that cerebral perfusion is maintained by shunting flow from other organ beds.^{17,18} In this way, systemic oxygenation is compromised before cerebral oxygenation.

Table II. Effect of hemodilution on total peripheral resistance, pump flow, and whole body oxygen balance during normothermic CPB

CPB period	TPR (dynes · s · cm ⁻⁵)	Pump flow (L · min ⁻¹ · m ⁻²)	Do ₂ (ml · min ⁻¹ · m ⁻²)	$\dot{V}O_2$ (ml · min ⁻¹ · m ⁻²)	OER (%)	SV _{O₂} (%)	Lactate (mmol · ml ⁻¹)
1	3390 ± 900	1.9 ± 0.5	327 ± 69	131 ± 31	41 ± 7	57 ± 7	3.3 ± 0.8
2	2760 ± 640*	2.3 ± 0.4	274 ± 54	134 ± 21	50 ± 7	52 ± 5	3.1 ± 0.8
3	2370 ± 840*	2.9 ± 0.9*	238 ± 69*	108 ± 17*	49 ± 16	49 ± 12	3.4 ± 1.5
4	1990 ± 570*	3.4 ± 0.9*	217 ± 61*	106 ± 13*	52 ± 13	50 ± 13	3.9 ± 1.9
5	1740 ± 570*	3.8 ± 1.1*	182 ± 48*	93 ± 30*	54 ± 18	47 ± 13	4.6 ± 2.1*

Data are mean ± standard deviation (n = 9). CPB, Cardiopulmonary bypass; TPR, total peripheral resistance; Do₂, total oxygen delivery; $\dot{V}O_2$, whole body oxygen consumption; OER, oxygen extraction ratio; SV_{O₂}, mixed venous oxygen saturation.

*p < 0.05 versus CPB period 1.

Our study might be criticized for several reasons. First, a pre-CPB systemic oxygen consumption was not reported. However, our pre-hemodilution value is consistent with previously reported values in dogs under non-CPB conditions. In the foundation work by Starr¹⁹ in 1959, the same value was documented before CPB. Our systemic oxygen consumption during CPB period 1 also falls between the values reported by Gutierrez and associates²⁰ and Cain⁵ under non-CPB conditions. Therefore the systemic oxygen consumption of the initial CPB period can be expected to closely approximate the animal's oxygen consumption before CPB.

Second, the oxygen extraction ratio was higher (41%) and oxygen saturation lower (57%) than might be expected during CPB with a whole blood prime. Although in the normal range, the values during the initial period of CPB (hematocrit value 39%) suggest that either the mean arterial pressure or pump flow may have been somewhat low relative to systemic oxygen consumption. We targeted a mean arterial pressure of 60 mm Hg to reflect clinical perfusion practice. However, a dog, like the adult patient with cardiac disease, typically has a mean arterial pressure closer to 80 mm Hg under non-CPB conditions. As such, higher mean arterial pressures or pump flows may be appropriate under normothermic conditions, particularly as hematocrit is reduced.

Most studies of this type also face a methodologic limitation. As in our study, the determination of systemic oxygen consumption and oxygen delivery may be linked mathematically as well as physiologically. This is of particular importance when correlations are performed, and this potential problem can be minimized by determination of linked or coupled variables using independent techniques.²¹ Our laboratory, like most others reporting similar studies, is unable to provide calorimetric studies or

direct measurements of systemic oxygen consumption and so is compelled to rely on the Fick method. However, we do realize the inherent limitation of the technique.

Finally, we provide an assessment of systemic oxygen balance at five levels of hematocrit but cannot clearly identify the single lowest acceptable hematocrit level for warm CPB. Our data indicate that a hematocrit value of 18% is too low with conventional CPB but that 25% is adequate. Ideally, oxygen balance at a hematocrit level between these values would have been determined. However, on the basis of non-CPB studies, we expected that the "critical" hematocrit value would be lower than 18% and we were surprised by the finding that critical oxygen delivery is reached at a higher hematocrit value under CPB than non-CPB conditions. This finding suggests that the minimal acceptable hematocrit value is not a fixed number but will vary within a range, in large part a function of the CPB flow. At a fixed flow, a critical hematocrit value might be more rigidly defined, but if flow adjustments are made, a lower (or higher) hematocrit level will be critical. Nonetheless, until certain practical limitations in CPB circuitry are overcome, the critical hematocrit value closely approximates 18% to 20% at normothermia with conventional flow rates.

In conclusion, we found that CPB does not appear to alter whole body consumption or critical oxygen delivery values. We found that whole body oxygen consumption is not maintained when the hematocrit value is reduced to 18% during normothermic CPB. The reason is probably that the increases in pump flow that are practical during CPB do not approximate what would be seen under non-CPB conditions at equivalent hematocrit levels. It is important to emphasize that we do not define what is a "safe" hematocrit value under normothermic conditions; many physiologic aberrations can be tolerated for

brief periods of time, but it must also be kept in mind that normal dogs will tolerate a lower hematocrit value than today's older adult patient undergoing cardiac surgery. Nonetheless, we hope these findings begin to provide a better physiologic framework for our clinical practice.

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