

## Hemodynamic Consequences of Halothane Anesthesia during Chronic Anemia

Manuel Barrera, M.D.,\* David J. Miletich, Ph.D.,† Ronald F. Albrecht, M.D.,‡ William E. Hoffman, Ph.D.§

The hemodynamic effects of halothane anesthesia in chronically anemic mongrel dogs were evaluated. Control and anemic animals ( $13.7 \pm 0.4$  g/dl hemoglobin mean  $\pm$  SE vs.  $3.4 \pm 0.3$  g/dl) were exposed to 0.75, 1.5, and 2.25% inspired halothane and changes in cardiac output (CO), heart rate (HR), dp/dt, heart work, heart efficiency, myocardial oxygen consumption ( $MVO_2$ ), mean arterial blood pressure (MABP), central venous pressure (CVP), left ventricular end-diastolic pressure (LVDP), left coronary blood flow (CBF), systemic vascular resistance (SVR), and myocardial lactate metabolism were measured and compared. Anemic dogs showed a significantly lower SVR at each halothane dose when compared with controls. In addition, SVR progressively decreased with increasing halothane in anemic dogs, while SVR remained unchanged in controls. CO, CBF,  $MVO_2$ , and heart work all were significantly greater in anemic canines compared with controls with each halothane concentration. Heart efficiency, dp/dt, HR, and MABP were not significantly different in anemic and control dogs. Neither control nor anemic dogs demonstrated myocardial hypoxia as evidenced by a lack of myocardial lactate production. The results from this study suggest that anemic animals appear to tolerate large concentrations of halothane. (Key words: Anesthetics, volatile: halothane. Blood: anemia. Heart: blood flow; cardiac output.)

THE PERCEIVED "critical" hemoglobin value varies among individual anesthesiologists, but the majority accept a minimum of 10 g/dl before proceeding with elective anesthesia.<sup>1</sup> Anything less may result in blood transfusion or case postponement.

There are several reasons for the selection of the 10 g/dl limit, but the primary reason is one of a perceived "safety margin" based on the potential oxygen carrying capacity. It is commonly thought that hemoglobin concentrations above 10 g/dl carry sufficient oxygen reserves to meet the needs of critical organs such as heart and brain. However, hemoglobin concentration is only one factor governing oxygen delivery to tissues. Many studies have shown that hemoglobin levels far less than 10 g/dl

are capable of meeting vital organ requirements for extended periods because of the increase in cardiac output (CO) and decrease in systemic vascular resistance (SVR) normally associated with anemia.<sup>2-19</sup> But despite these hemodynamic studies, the impression persists that hemoglobins below 10 g/dl should be corrected whenever possible. Perhaps, this belief persists because very few studies have been reported concerned with the hemodynamic consequences of anesthesia during anemia, and because of the prevailing attitude that depressant inhalation anesthetics are sometimes bad for the circulatory system, particularly when vascular pathology is present. However, studies have shown that anesthetics that depress the myocardium need not be detrimental in all circumstances.<sup>20,21</sup> Therefore, it was the purpose of this study to examine the effects of halothane anesthesia on myocardial performance and hemodynamics in chronically anemic animals.

### Methods

The study was performed with 25 male, mongrel, pre-conditioned dogs weighing between 24 and 38 kg (pre-conditioning consisted of a negative test for microfilariae, treatment for intestinal parasites, and vaccinations for distemper and hepatitis). Fourteen dogs were rendered anemic by daily bleeding via a permanently implanted jugular catheter. The amount of blood withdrawn (approximately 300-500 ml/day) was replaced with normal saline solution at a ratio of 3 ml of saline for each milliliter of whole blood. The actual volume of blood removed each day was dependent on the progress made in lowering blood hemoglobin concentrations, since dogs varied in their ability to replace removed hemoglobin. When hemoglobin level of 3-5 g/dl was reached (19-24 days) the dog was prepared for study. All anemic dogs were placed on a special diet containing ample nutritional requirements but that was deficient in iron and copper.

On the day of study, anesthesia was induced with thiopental (5 mg/kg iv) followed by halothane (0.75-1.0%) in 100% O<sub>2</sub>. All dogs were ventilated mechanically in order to maintain normal blood gases. After a stable, surgical plane of anesthesia was reached, femoral artery and venous catheters were inserted. The femoral venous catheter was advanced to the right atrium. Following this, a left thoracotomy at the 5th intercostal space was performed. An electromagnetic blood flow probe was placed around the pulmonary artery for the continuous mea-

\* Resident, Michael Reese Hospital and Medical Center.

† Associate Professor, Michael Reese Hospital and Medical Center and Pritzker School of Medicine, University of Chicago.

‡ Clinical Professor and Chairman, Michael Reese Hospital and Medical Center and Pritzker School of Medicine, University of Chicago.

§ Assistant Professor, Michael Reese Hospital and Medical Center and Pritzker School of Medicine, University of Chicago.

Received from the Department of Anesthesiology, Michael Reese Hospital and Medical Center, Pritzker School of Medicine, University of Chicago, Chicago, Illinois. Accepted for publication December 7, 1983.

Address reprint requests to Dr. Miletich: Department of Anesthesiology, Michael Reese Hospital and Medical Center, 29th Street and Ellis Avenue, Chicago, Illinois 60616.

surement of cardiac output (CO). Catheters were placed in the left ventricle, left atrium, and coronary sinus for the measurement of left ventricular dp/dt, injection of radioactive microspheres, and measurement of sinus blood oxygen levels, and lactate concentrations, respectively.

Once the catheters were implanted, the lungs were expanded and the thorax tightly closed in two layers (the surgical procedure averaged about 2 h to completion). Inspired halothane concentration then was adjusted to 0.75% and the animal was permitted to stabilize for 30 min. At the end of this period, blood samples were drawn from arterial and coronary sinus catheters for determination of blood gas levels and lactate concentrations. Cardiac output, dp/dt, heart rate (HR), mean arterial blood pressure (MABP), central venous pressure (CVP), and myocardial oxygen consumption ( $MVO_2$ ) then were measured. Lead II of the ECG was recorded throughout the entire procedure. Thereafter, radioactive microspheres were injected via the left atrial catheter for the calculation of total left ventricular coronary blood flow (CBF) and epicardial/endocardial blood flows. Approximately  $3 \times 10^6$  microspheres  $15 \pm 3 \mu\text{m}$  in diameter were suspended in 10 ml saline, sonicated for mixing, and injected into the left atrium (the microspheres were labelled with either  $^{57}\text{Co}$ ,  $^{46}\text{Sc}$ , or  $^{85}\text{Sr}$  at 10 mCi/g; Amersham Corp.). This dose of microsphere was selected because it resulted in a microsphere concentration of 400–500 per gram of tissue. Left coronary blood flow and regional flows were calculated as previously described.<sup>22</sup> Briefly, after completion of the study, the heart was removed and weighed. The left ventricular wall then was separated and weighed. Several grams of the outer most portion of left epicardium and inner most portion of the endocardium were removed (approximately 0.5 cm in depth in each case). Care was taken to remove the endocardial and epicardial samples from the same area of each heart (approximately halfway between the base and the apex of the heart). Radioactivity then was determined by gamma scintillation counting. Blood flow values in  $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  were calculated from the formula:

$$\text{CBF} = \text{CO} \times \%iD$$

where: CO = cardiac output in ml/min (as measured with electromagnetic flow probe); %iD = per cent of the total injected dose of microspheres found in the heart (or region).

Following the completion of all measurements at 0.75% halothane, the concentration was increased to 1.5% and subsequently to 2.25%, after which all variables again were determined as described. Thirty minutes were allowed following each dose change to permit hemodynamic stabilization. Randomization of halothane dosages was not attempted because randomizing would have produced both an impractical increase in the length of each ex-

periment and possibly introduce other undesirable time related variables.

Pressure-volume heart work was calculated according to Rothe using the formula:

$$\text{Heart Work} = \text{CO} \times \text{MABP} = \text{joules of work/min}$$

where: CO represents cardiac output in cubic meters per minute and MABP in newtons per square meter (recall that  $1 \text{ l/min} = 1 \times 10^{-3} \text{ m}^3/\text{min}$ , and  $1 \text{ mmHg} = 133.3 \text{ N/m}^2$ ).<sup>23</sup>

Cardiac efficiency in terms of pressure-volume work was derived by dividing heart work in joules/min by the amount of myocardial oxygen consumed per minute.

Myocardial oxygen consumption ( $MVO_2$ ) was determined by multiplying the oxygen difference found between arterial blood and the coronary sinus blood times the total left ventricular CBF. It was assumed that the  $MVO_2$  calculated in this fashion was reflective of left ventricular activity and, therefore, represented most of the oxygen consumed by the entire heart.

Systemic vascular resistance (SVR) was determined from the formula:

$$\text{SVR} = \frac{\text{MAPB} - \text{RAP}}{\text{CO}} \times 80 = \text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$$

where: CO = cardiac output in l/min; MAPB = mean arterial blood pressure in mmHg; RAP (CVP) = right atrial pressure (central venous pressure) in mmHg.

Blood lactate concentrations were determined by the Sigma Chemical Co. Lactate Dehydrogenase Diagnostic Assay kit No. 826-UV. Blood gases were measured with an IL 1303 blood gas analyzer and oxyhemoglobin concentrations by an IL 282 Co-oximeter with special electronic adaptation for dog blood hemoglobin.

Statistical significance of data was evaluated by one-way analysis of variance (ANOVA) of the difference between control and anemic values and anesthetic dose in conjunction with the Bonferroni multiple comparison procedure.<sup>24</sup> Paired data *t* test was used to determine the statistical significance of within group sequential data. Data are reported as means  $\pm$  SEM, with  $P < 0.05$  considered statistically significant.

## Results

Periodic bleeding over a 3-week span resulted in a mean Hb of  $3.4 \pm 0.3 \text{ g/dl}$  (table 1). Arterial and coronary sinus blood pH and  $\text{PO}_2$  levels remained unchanged at each dose of halothane.  $\text{PaO}_2$  levels were significantly greater in anemic dogs at all three doses of inspired halothane. Arterial lactate concentrations in anemic dogs were not significantly different from controls at 0.75 and 1.5% inspired halothane concentrations. However, arterial lactates increased significantly in anemic dogs at

TABLE 1. Effects of Anemia and Halothane Anesthesia on Blood Chemistries

Halothane Concentration	Hb g/dl	PaO <sub>2</sub> mmHg	Coronary Sinus P <sub>O<sub>2</sub></sub> mmHg	pH	Art. Bld. Lactate μM	Coronary Sinus Lactate μM	Myocardial Uptake μmol/min	% Lactate* Extraction
Control								
0.75	13.7 ± 0.4	368 ± 21	40 ± 5	7.38 ± 0.07	1.3 ± 0.4	0.8 ± 0.3	78 ± 21	6 ± 2.4
1.5	—	353 ± 23	38 ± 6	7.37 ± 0.07	1.4 ± 0.6	1.0 ± 0.5	29 ± 9	2 ± 1.1
2.25	—	337 ± 25	39 ± 5	7.34 ± 0.04	1.4 ± 0.4	0.8 ± 0.3	30 ± 11	1 ± 0.9
Anemic								
0.75	3.4 ± 0.3†	414 ± 20†	35 ± 6	7.34 ± 0.07	0.9 ± 0.4	0.8 ± 0.4	36 ± 15	4 ± 1.6
1.5	—	408 ± 26†	36 ± 7	7.34 ± 0.06	1.0 ± 0.4	0.9 ± 0.5	27 ± 13	2 ± 1.1
2.25	—	394 ± 22†	37 ± 4	7.33 ± 0.08	2.1 ± 0.6†	1.6 ± 0.6	148 ± 37†	7 ± 1.7†

Values represent mean ± SE.

\* Myocardial lactate uptake as a per cent of arterial lactate con-

centration.

† Significantly different from control values; *P* < 0.05 (*n* = 25)

2.25% halothane. Likewise, myocardial uptake of lactate and lactate extraction also increased at 2.25%.

Cardiac output was increased significantly in anemic dogs compared with controls at all dose levels of halothane as was MVO<sub>2</sub> and CBF (figs. 1A, B, and C). Increasing

concentrations of inspired halothane resulted in a significant and progressive decrease in control CO. Anemic dogs showed a similar dose related decrease in CO. Both control and anemic dogs showed a significant decrease in MVO<sub>2</sub> and CBF as inspired halothane concentrations

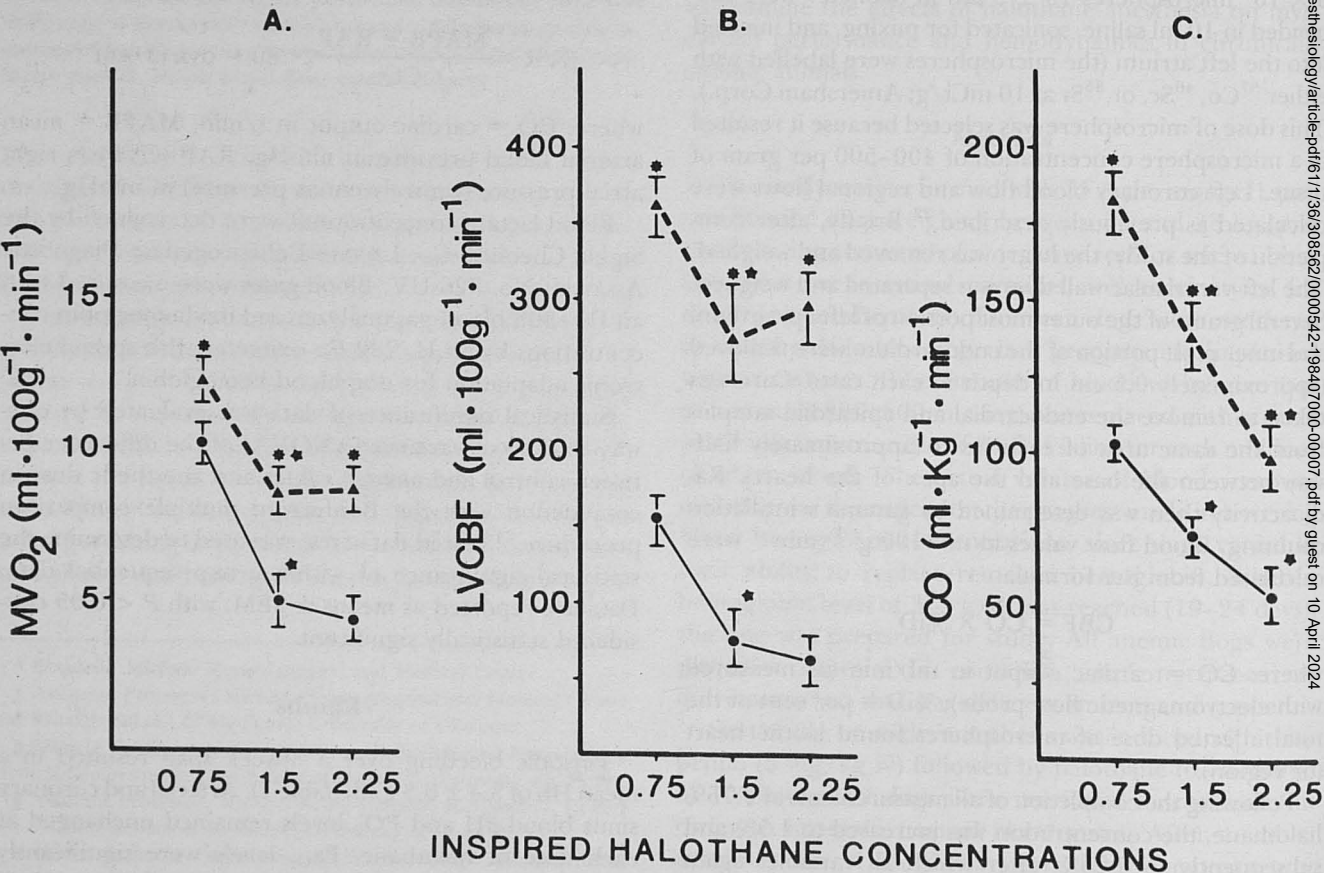


FIG. 1. Effects of inspired halothane concentrations (0.75, 1.5, and 2.25%) and anemia on MVO<sub>2</sub> and cardiovascular hemodynamics; dotted lines represent anemic dogs (*n* = 14), solid lines represent controls (*n* = 11). A. Myocardial oxygen consumption. \*All anemic values are significantly greater than controls *P* < 0.02. ★Values lower than preceding value, *P* < 0.001. B. Left ventricular blood flow. \*All anemic values greater than controls, *P* < 0.001. ★Value less than preceding value, *P* < 0.05. C. Cardiac output. \*All anemic values greater than controls, *P* < 0.001. ★Values less than preceding value, *P* < 0.001.

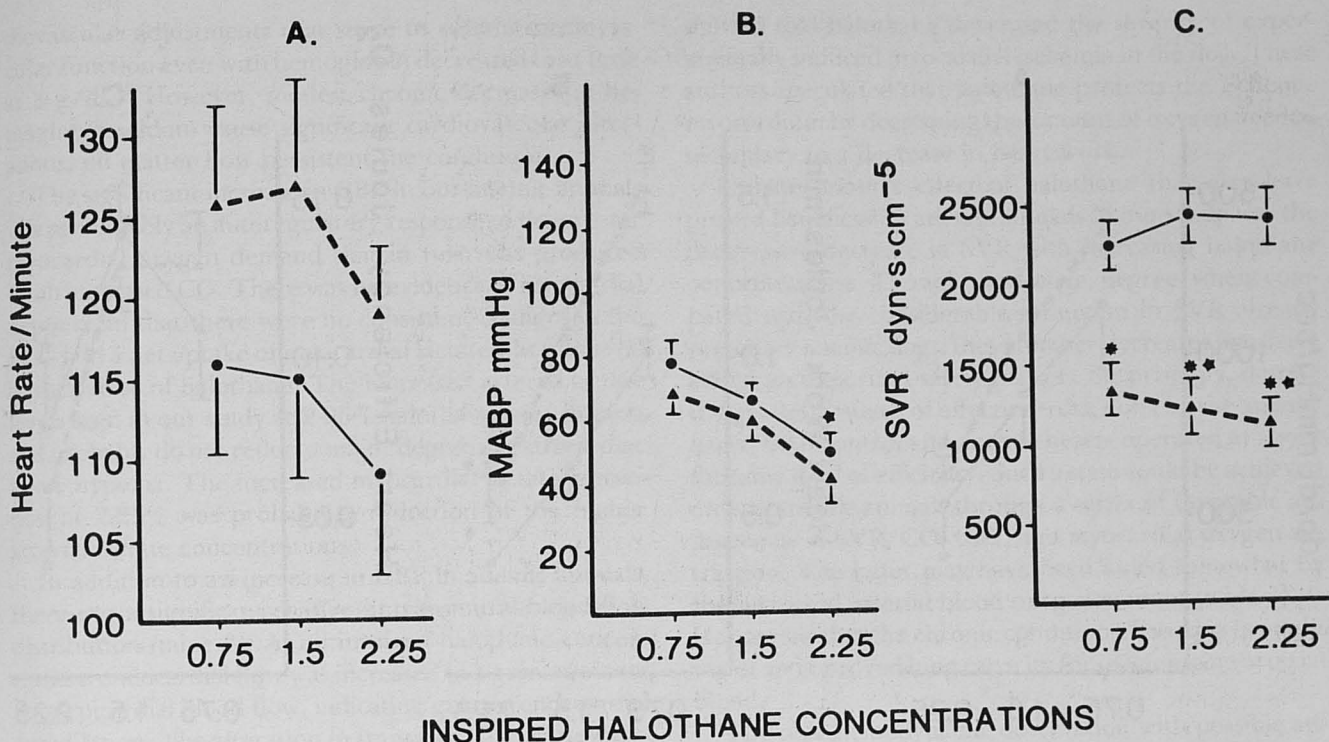


FIG. 2. Effects of inspired halothane concentrations (0.75, 1.5, and 2.25%) and anemia on cardiovascular hemodynamics. Dotted lines represent anemic dogs ( $n = 14$ ); solid line represents controls ( $n = 11$ ). A. Heart rate. No significant difference was noted between anemic and control animals at any of the halothane concentrations examined. B. Mean arterial blood pressure; no significant difference was seen between anemic and control values. ★Values lower than 0.75% values,  $P < 0.01$ . C. Systemic vascular resistance. \*All anemic values significantly less than control values,  $P < 0.001$ . ★Values less than preceding value,  $P < 0.02$ .

were increased to 1.5% and 2.25%. Heart rate, and  $dp/dt$  were not significantly different in control and anemic animals (figs. 2A and 3A). LVED pressures were not significantly different in anemic dogs and were unaffected by increasing halothane (table 2). However, CVP increased significantly in anemic animals with 2.25% halothane (table 2).

Mean arterial blood pressure was unchanged in anemic dogs compared with control animals (fig. 2B). Although MABP decreased in both experimental and control groups with increasing halothane, SVR was significantly less in anemic dogs (figs. 2B and 2C). Anemic animals showed a small but statistically significant decrease in SVR as the concentration of anesthetic was increased (fig. 2C).

Heart work was significantly greater in anemic dogs compared with control animals at all dose levels of halothane (fig. 3B). However, the hearts of both anemic and nonanemic animals maintained approximately equal efficiency at each concentration of anesthetic studied (fig. 3C).

Left ventricular endocardial blood flow was significantly greater than epicardial blood flow in anemic dogs (table 3). It is evident from anemic flow ratios that endocardial vascular vasodilatation was increased signifi-

cantly relative to epicardial vascular tone in anemic animals.

No consistent changes were seen in the S-T segment of the ECG of anemic and control animals during any dose of halothane anesthesia. Both anemic and control dogs displayed occasional, moderate S-T segment elevation at 2.25% halothane concentrations, but there was no difference between the two groups with regard to severity of S-T elevation or frequency of occurrence.

TABLE 2. Effects of Anemia and Halothane Anesthesia on Left Ventricular End Diastolic Pressure and Central Venous Pressure

	LVED mmHg	CVP mmHg
Control		
0.75*	5.2 ± 0.9	1.6 ± 0.5
1.5	5.3 ± 1.2	1.4 ± 0.5
2.25	6.6 ± 1.4	2.8 ± 0.9
Anemia		
0.75*	5.3 ± 0.9	2.6 ± 0.9
1.5	5.3 ± 0.9	2.9 ± 0.7
2.25	6.5 ± 0.8	5.3 ± 1.5†

Values represent mean ± SE.

\* Inspired halothane concentration.

† Significantly increased compared with 0.75 value;  $P < 0.01$ ,  $n = 14$ .

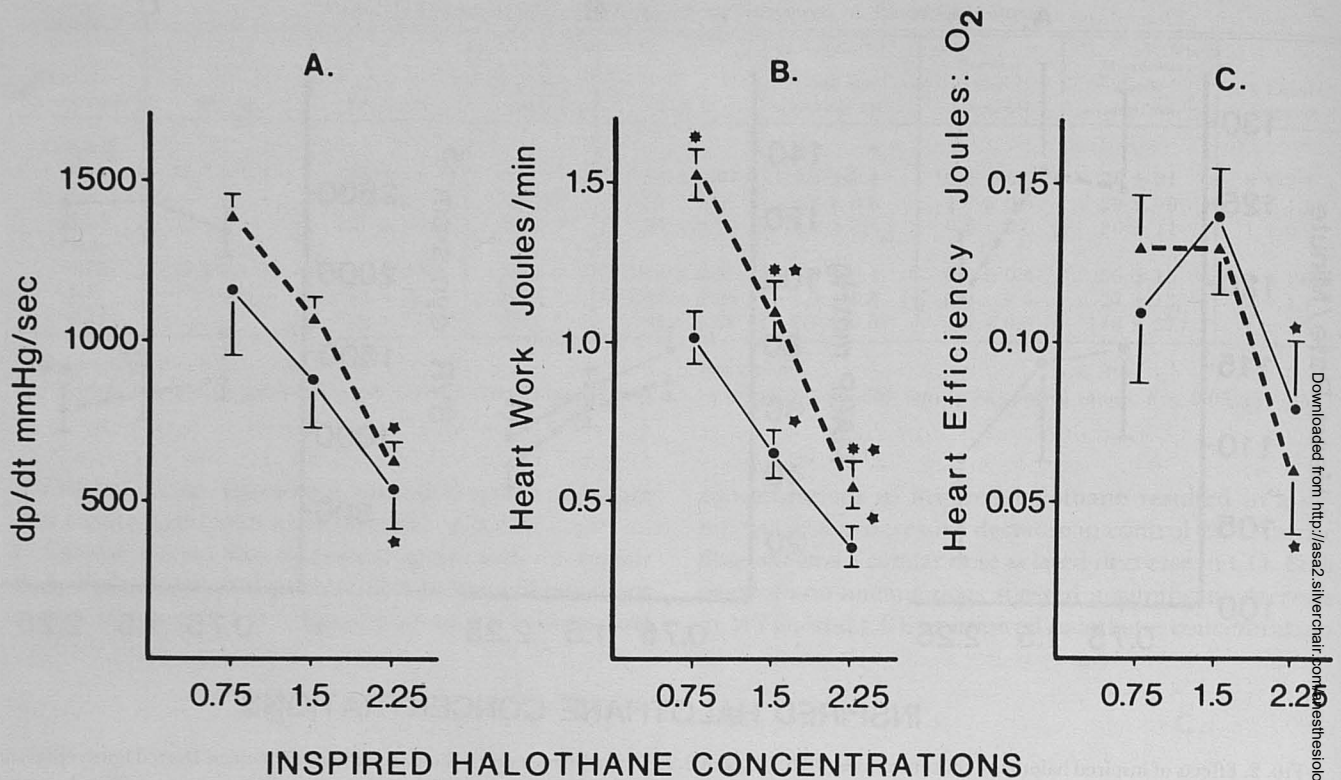


FIG. 3. Effects of inspired halothane concentrations (0.75, 1.5, and 2.25%) and anemia on myocardial function. Dotted line represents anemic dogs ( $n = 14$ ); solid line represents control dogs ( $n = 11$ ). A.  $dp/dt$ ; no significant difference was seen between anemic and controls at any of the dosages of halothane examined. ★Values significantly less than preceding value,  $P < 0.01$ . B. Heart work. \*All anemic values were significantly greater than control values,  $P < 0.01$ . ★Values less than preceding values,  $P < 0.001$ . C. Heart efficiency; no significant difference was seen between anemic and control dogs. ★Values significantly less than preceding value.

### Discussion

Previous investigations concerned with anemia can be categorized into two types: acute, isovolemic, hemodilution studies, and chronic, isovolemic, anemia studies.

TABLE 3. Effects of Anemia and Halothane Anesthesia on Endocardial/Epicardial Blood Flow and Flow Ratios

	Endocardial Blood Flow ( $\text{ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$ )	Epicardial Blood Flow ( $\text{ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$ )	Ratio
Control			
0.75*	$1.57 \pm 0.17$	$1.66 \pm 0.14$	$0.95 \pm 0.08$
1.5	$0.76 \pm 0.09$	$0.87 \pm 0.12$	$0.87 \pm 0.11$
2.25	$0.64 \pm 0.14$	$0.68 \pm 0.13$	$0.94 \pm 0.08$
Anemic			
0.75*	$3.61 \pm 0.18^\dagger$	$3.08 \pm 0.21$	$1.19 \pm 0.05^\ddagger$
1.5	$2.83 \pm 0.16^\dagger$	$2.44 \pm 0.15$	$1.16 \pm 0.04^\ddagger$
2.25	$2.96 \pm 0.26^\dagger$	$2.62 \pm 0.19$	$1.13 \pm 0.07^\ddagger$

Values represent mean  $\pm$  SE.

\* Inspired halothane concentrations.

† Endocardial flow significantly greater than epicardial flow;  $P < 0.01$ ,  $n = 12$ .

‡ Ratio significantly greater than control ratio;  $P < 0.05$ ,  $n = 22$  (Significance determined by  $t$  test).

In general, the chief hemodynamic responses to severe acute hemodilution ( $<7$  g/dl) are increased  $\text{CO}$ ,<sup>1-4</sup>  $dp/dt$ ,<sup>2,10,16</sup> heart rate,<sup>2,4,12,15</sup>  $\text{CBF}$ ,<sup>4,11,12</sup>  $\text{MVO}_2$ ,<sup>4,11,12</sup> along with a significantly reduced  $\text{SVR}$ .<sup>4,11,12,15</sup> In general,  $\text{CO}$  and  $\text{CBF}$  increase linearly with the severity of anemia and inversely with the decrease in  $\text{SVR}$ . Blood pressure may be increased,<sup>3</sup> decreased,<sup>15</sup> or remain unchanged under these conditions.<sup>4</sup> Hemoglobin concentrations above 7 g/dl often result in few serious hemodynamic changes provided the hemoglobin levels are not decreased too rapidly.<sup>6,9</sup> It should be emphasized that, depending on the anesthetic used, the chronicity of anemia, and severity of anemia, exceptions to the preceding observations have been noted.

Hemodynamically, severe chronic anemia differs from severe acute hemodilution in that heart rate and blood pressure seldom are increased.<sup>12,14,19</sup> Increased  $\text{CO}$  during chronic anemia is accomplished largely through an increase in stroke volume.<sup>12,19</sup> The lack of heart rate increase with chronic anemia may have special adaptive significance. Since myocardial oxygen consumption is tied more closely to heart rate than stroke volume, it may be that chronically low hemoglobin levels induce subtle car-

diovascular adjustments that serve to sustain cardiovascular function even with hemoglobin decreased to as little as 3 g/dl.<sup>12</sup> However, modest chronic decreases in hemoglobin seldom cause significant cardiovascular alterations, no matter how persistent the condition.

The significant increase in CBF in our anemic animals was presumably an autoregulatory response to the greater myocardial oxygen demand that in turn was produced by an increased CO. There was no evidence of myocardial hypoxia, in that there were no consistent changes in the ECG and a net uptake of myocardial lactate was observed at each dose of halothane. The increased arterial lactate levels seen in our study at 2.25% halothane were modest and probably do not reflect a major degree of extracardiac tissue hypoxia. The increased myocardial lactate extraction at 2.25% was probably a reflection of the higher arterial lactate concentrations.

In addition to an increase in CBF in anemic animals, there was a significant change in transmural blood flow distribution (table 3). At all inspired halothane concentrations endocardial flow was increased to a greater extent than epicardial blood flow, indicating greater endocardial vasodilation. The alteration in transmural blood flow distribution in anemic dogs was likely an adaptive mechanism to insure adequate myocardial muscle oxygenation. Such blood flow changes might be expected, since it is thought that endocardial vasodilatory reserve exceeds epicardial reserve and endocardial oxygen consumption is greater than in the epicardium.<sup>25</sup> But caution must be used in the interpretation of microsphere measurements of blood flow in anemic subjects. Even under ordinary circumstances it is known that microspheres do not behave exactly as red blood cells. Because microspheres are denser they have a tendency to stream more centrally in blood vessels than red blood cells.<sup>24</sup> A recent study by Rosenberg *et al.* has presented evidence suggesting that anemia might increase the tendency for microspheres to lie in the axial portion of the arterial stream.<sup>26</sup> Therefore, it is possible in our study that blood flowing from the epicardium to the endocardium may have contained an inordinately large number of "skimmed" microspheres, thus producing large endocardial flows.

The study by Tarnow *et al.* showed that agents that decrease myocardial oxygen need have considerable impact on the coronary vascular response to anemia.<sup>5</sup> Anemic dogs anesthetized with a narcotic had a 224% increase in total CBF, while dogs anesthetized with halothane without and with propranolol had only a 179% and 143% increase, respectively. Likewise, left ventricular oxygen consumption was decreased significantly in both halothane-anesthetized groups, suggesting that myocardial depressant anesthetics may provide an additional safety margin with regard to myocardial ischemia. This was substantiated further by Bland and Lowenstein.<sup>20</sup> They

showed that halothane decreased the severity of experimentally induced myocardial ischemia in the dog. These authors speculated that halothane protects the ischemic myocardium by decreasing the amount of oxygen needed secondary to a decrease in heart work.

Perhaps another effect of halothane that may have proved beneficial to anemic animals in our study was the progressive decrease in SVR with increasing halothane concentrations. Though modest in degree when compared with the considerable reduction in SVR already present in anemic dogs, these further decreases may have added an important safety margin. Surprisingly, despite the greater amount of effective work done by the anemic heart, both control and anemic hearts operated at about the same level of efficiency. Such a state could be achieved only in anemic animals through a series of favorable adjustments in SVR, CO, CBF, and myocardial oxygen extraction. The latter may have been aided somewhat by the increased arterial blood oxygen content (table 1). It is apparent that the chronic condition of anemia brought about an improved lung capacity for oxygenating arterial blood.

The only hemodynamic observation with possible adverse implications seen in the anemic dogs from our study was the increase in CVP that occurred at 2.25%. Although the increase was modest, it is suggestive of possible myocardial failure. Perhaps if more time were allowed at 2.25% the increase in CVP may have been greater and the implications more evident. However, further study would be necessary in order to determine the importance of this observation.

In conclusion, chronic anemia does not necessarily impart a serious hemodynamic handicap in the otherwise healthy subject nor was there any evidence of myocardial ischemia even at the deepest level of anesthesia.

The authors thank D. Visintine, R. Ripper, G. Dominquez, A. Holland, and C. Seals for their considerable help in order to complete this study.

## References

1. Kowalyszyn FJ, Prager D, Young J: A review of the present status of preoperative hemoglobin requirements. *Anesth Analg* 51:75-77, 1972
2. Biro GP, Beresford-Kroeger D: Myocardial blood flow and O<sub>2</sub>-supply following dextran-haemodilution and methaemoglobinemia. *Cardiovasc Res* 13:459-468, 1979
3. Loarie DJ, Wilkinson P, Tyberg J, White A: The hemodynamic effects of halothane in anemic dogs. *Anesth Analg* 58:195-200, 1979
4. Tarnow J, Eberlein HJ, Hess W, Schneider E, Schweichel E, Zimmermann G: Hemodynamic interactions of hemodilution, anesthesia, propranolol pretreatments and hypovolaemia. I. Systemic circulation. *Basic Res Cardiol* 74:109-122, 1979
5. Tarnow J, Eberlein HJ, Hess W, Schneider E, Schweichel E, Zim-

- mermann G: Hemodynamic interactions of hemodilution, anesthesia, propranolol pretreatments and hypovolaemia. II. Coronary circulation. *Basic Res Cardiol* 74:123-130, 1979
6. Geha AS: Coronary and cardiovascular dynamics and oxygen availability during acute normovolemic anemia. *Surgery* 80:47-53, 1976
7. Fowler NO, Holmes JC: Blood viscosity and cardiac output in acute experimental anemia. *J Appl Physiol* 39:453-456, 1975
8. Brazier J, Cooper N, Maloney JV, Buckberg G: The adequacy of myocardial oxygen delivery in acute normovolemic anemia. *Surgery* 75:508-516, 1974
9. Pavak K, Carey JS: Hemodynamics and oxygen availability during isovolemic hemodilution. *Am J Physiol* 226:1172-1177, 1974
10. Rodriguez JA, Chamorro G, Rapaport E: Effect of isovolemic anemia on ventricular performance at rest and during exercise. *J Appl Physiol* 36:28-33, 1974
11. Murry JF, Rapaport E: Coronary blood flow and myocardial metabolism in acute experimental anaemia. *Cardiovasc Res* 6:360-367, 1972
12. Varat MA, Adolf RJ, Fowler NO: Cardiovascular effects of anemia. *Am Heart J* 83:415-426, 1972
13. Vatner SF, Higgins CB, Franklin D: Regional circulatory adjustments to moderate and severe chronic anemia in conscious dogs at rest and during exercise. *Circ Res* 30:731-740, 1972
14. Bhatia ML, Manchanda SC, Roy SB: Coronary haemodynamic studies in chronic severe anemia. *Br Heart J* 31:365-374, 1969
15. Michalski AH, Lowenstein E, Austen WG, Buckley MJ, Laver MB: Patterns of oxygenation and cardiovascular adjustment to acute transient normovolemic anemia. *Ann Surg* 168:946-956, 1968
16. Horstman DH, Gleser M, Wolfe D, Tryon T, Delehunt J: Effects of hemoglobin reduction of  $\text{VO}_2$  max and related hemodynamics in exercising dogs. *J Appl Physiol* 37:97-102, 1974
17. Cain SM: Appearance of excess lactate in anesthetized dogs during anemic hypoxic hypoxia. *Am J Physiol* 209:604-610, 1965
18. Fowler NO, Holmes JC: Dextran-exchange anemia and reduction in blood viscosity in the heart-lung preparation. *Am Heart J* 68:204-213, 1964
19. Roy SB, Bhatia ML, Mathur VS, Virmani S: Hemodynamic effects of chronic severe anemia. *Circulation* 28:346-356, 1963
20. Bland JH, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. *ANESTHESIOLOGY* 45:287-293, 1976
21. Roizen MF, Hamilton WK, Sohn YJ: Treatment of stress-induced increases in pulmonary capillary wedge pressure using volatile anesthetics. *ANESTHESIOLOGY* 55:446-450, 1981
22. Miletich DJ, Gil KSL, Albrecht RF, Zahed B: Intracerebral blood flow distribution during hypotensive anesthesia in the goat. *ANESTHESIOLOGY* 53:210-214, 1980
23. Rothe CF: *Cardiodynamics, Physiology*. Edited by Selkurt EA. Boston, Little Brown and Co, 1976, pp 337-360
24. Glantz SA: *Primer of Biostatistics*. New York, McGraw-Hill, 1981, pp 245-261
25. Feigl EO: Coronary physiology. *Physiol Rev* 63:1-205, 1983
26. Rosenberg Aa, Jones MD, Koehler RC, Traystman RJ, Lister: Precautions for measuring blood flow during anemia with the microsphere technique. *Am J Physiol* 244:H308-H311, 1983