Acute Hemodilution:

Its Effect on Hemodynamics and Oxygen Transport in Anesthetized Man

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The effects of acute normovolemic hemodilution on hemodynamics, oxygen transport, tissue perfusion and blood volume were studied. The subjects were four patients undergoing total hip replacement with prebleeding and hemodilution under fluoroxene and nitrous oxide anesthesia. The hematocrit was reduced to 29% and 21% by bleeding in two steps with simultaneous infusion of plasmanate and lactated Ringer's solution. The major compensation was a rise in CO to 123% and 136%. Systemic oxygen transport (COX arterial O_2 content) was only slightly reduced and the arteriovenous oxygen difference decreased. Tissue perfusion remained excellent. Blood volume was slightly expanded. The procedure was well tolerated by this group of selected patients, and homologous blood utilization was markedly reduced.

INTRAOPERATIVE HOMODILUTION has been practiced both in cardiac[14,16,25] and general surgery.[29] Advantages include avoidance of homologous blood transfusion with its attendant hazards including serum hepatitis, and conservation of blood. At the Peter Bent Brigham Hospital, prebleeding with hemodilution is used for patients undergoing major operations and cardiopulmonary bypass. Although the effects of chronic anemia have been well studied there are no detailed hemodynamic studies on acute normovolemic hemodilution in man. Safe limits of blood replacement with erythrocyte free solutions have not been well defined. Studies of the effects of acute normovolemic hemodilution in experimental animals[8,19,23] have shown an increase in cardiac output, with no increase in oxygen extraction ratio. In a study of normal volunteers in whom anemia was induced by gradual hemorrhage, there was no increase in cardiac output and a compensatory rise in oxygen extraction ratio was found.[34] The present study was undertaken to discover the effects of acute normovolemic hemodilution on hemodynamics and oxygen transport in anesthesized man, undergoing elective operation.

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Methods

Four patients aged from 29 to 56 years undergoing total hip replacements with hemodilution were studied. Patients with cardiovascular, pulmonary and renal disease were excluded. The study was approved by the human studies committee of the hospital. After thorough explanation, informed consent was obtained from each patient.

On the day prior to operation, blood volume (BV) was measured with ^{51}Cr tagged autologous red cells for red cell mass (RV) and the Evans' blue dye method to measure plasma volume (PV).[3,22] The patients were anesthetized with thiopental (Pentothal) for induction and fluoroxene and nitrous oxide for maintenance. The patients were intubated and spontaneous respiration was permitted with 5% fluoroxene, nitrous oxide, and oxygen. Measured FiO_2 was in the range of 50%. Arterial $PaCO_2$ was kept constant (Table 1).

Blood vessel cannulations were done after induction: a radial artery line percutaneously; a four channel ther-

TABLE 1. *Effects of Hemodilution on Oxygen Transport*

Measurements			Baseline	Hemodilution I	Hemodilution II	End Operation
Systemic O_2 Transport ml/min		ML	462	466	446	484
		SM	992	859	794	709
		RH	659	559	495	589
		SP	913	740	733	529
	Mean	±SEM	756 121	656 88	617 85	578 48
Arterial O_2 Sat. Vol. %		ML	98.4	98.6	98.6	96.4
		SM	95.8	98.4	98.6	98.3
		RH	97.7	98.3	97.7	98.8
		SP	99.1	98.1	97.1	97.3
	Mean	±SEM	97.8 0.7	98.4 0.1	98 0.4	97.7 0.5
Venous O_2 Sat. Vol. %		ML	96.8	96.9	96.3	78.6
		SM	91.0	91.5	89.9	61.2
		RH	73.3	70.1	64.0	58.9
		SP	93.7	91.1	92.4	87.3
	Mean	±SEM	88.7 5.3	87.4 5.9	85.7 7.3	71.5 5.9
Arterial pO_2 mmHg		ML	198	218	213	114
		SM	250	263	278	117
		RH	238	234	251	209
		SP	322	332	333	298
	Mean	±SEM	250 26	262 25	269 25	185 44
Venous pO_2 mmHg		ML	80	84.9	73	43
		SM	64	69.2	64.8	38
		RH	42	36.8	33.8	33.5
		SP	75.3	68.8	72.8	60.3
	Mean	±SEM	65 9	65.0 10	61 9	44 6
A-V O_2 Content Difference Vol. %		ML	0.63	0.62	0.66	2.8
		SM	1.53	1.57	1.56	3.8
		RH	5.56	4.30	4.12	5.2
		SP	1.67	1.65	1.25	1.72
	Mean	±SEM	2.35 1.1	2.04 0.79	1.89 0.76	3.38 0.74
Arterial pCO_2 mmHg		ML	40	38	38.3	36.6
		SM	43	43	43.7	39.7
		RH	37	31.1	27.7	35.6
		SP	45.8	42.7	42.1	44.8
	Mean	±SEM	40.9 2.3	38.7 2.8	38.0 3.6	39.2 2.1

modilution Swann Ganz catheter was directed into the pulmonary artery via an antecubital venous cutdown, so that one channel could be used to measure wedge pressures; two 14 gauge venous cannulae were placed percutaneously. An Instrumentation Laboratory (IL) right angle muscle surface pH electrode was inserted via a cutdown on the biceps muscle and pH measured using a Corning pH meter. Esoghageal temperature was monitored.

After a period of stabilization under anesthesia, baseline measurements were made. This was followed by two bleeds, designated Hemodilutions I and II. After each bleed there was a five minute stabilization period followed by measurement. Measurements were repeated at the midpoint and at the end of operation.

Hemodilutions I and II were conducted as follows. The patients were bled from venous and the arterial cannulae approximately 25% of their blood volume over a period of 20 minutes. Simultaneously a volume of Plasmanate* equal to that of the shed blood and an equal volume of lactated Ringer's solution was infused. Mean hematocrit after Hemodilution I was 29.3%, after Hemodilution II 21.5%. During operation blood loss was replaced with Plasmanate and lactated Ringer's solution, then by reinfusing the patient's own blood toward the end of the procedure.

Large vessel hematocrit (LVH) was measured in triplicate by centrifuging a heparinized sample of blood in Wintrobe tubes at 3,000 rpm for 55 minutes. Paired arterial and venous blood gases were determined with the Radiometer Acid Base Analyzer (Copenhagen PHM 71) and oxygen saturation using an Instrumentation Laboratory cooximeter Model 182. Pyruvate and lactate levels were measured.[10,15] Arterial samples were used to plot three points on the oxyhemoglobin dissociation curve and to calculate the P50.[32] 2–3 DPG,[17,18] total protein, albumen (modified Biuret method) and serum phosphorus by the Autoanalyzer were also measured. A right angle Ingold pH probe and Corning pH meter were employed to monitor muscle surface pH.[1] Cardiac output (CO) was measured by the thermodilution technique.[7] At each measurement, five readings were obtained and the mean was computed. A baseline sample was drawn

* Plasmanate (Cutter) contains 5% protein, mainly albumen, in 0.15M conc saline.

TABLE 2. *Cardiovascular Effects of Hemodilution*

		Baseline	Hemodil. I	Hemodil. II	Mid Op	Post Op
Cardiac Output ml/min						
	ML	2714	3744	4302		3387
	SM	5008	5822	7200	5980	7150
	RH	3207	4121	3334	4577	4843
	SP	5209	5800	7184	5891	5031
	Mean	4034	4871	5505	5482	5102
	±SEM	629	547	993	453	775
Arterial Blood Pressure						
	Mean	122/78	117/80	115/76	115/80	119/76
Central Venous Pressure						
	Mean	14.5	16.3	17.3	13.0	12.8
Pulmonary Artery Pressure						
	Mean	21/14	22/16	24/16	18/9	19/10
Heart Rate						
	Mean	83	80	83	80	73

to measure ^{51}Cr tagged RV. BV was then calculated as follows:

$$BV = \frac{RV}{LVH \times TBH}$$

where RV equals red cell mass and TBH equals total body hematocrit. TBH was calculated from the RV and PV measured the day pre-operatively. After Hemodilution I and II the quantity of shed blood was measured and samples drawn to measure the ^{51}Cr tagged RV. BV after Hemodilution I and II was then calculated using the TBH-to-LVH ratio measured preoperatively. In three patients the ^{51}Cr tagged RV and Evans' blue dye PV were measured on the first postoperative day.

Results

Cardiovascular Effects

Results of step-wise hemodilution with replacement of BV are shown in Table 2. Mean hematocrit after Hemodilution I was 29.3% and after Hemodilution II 21.5%. At midoperation hematocrit was 19.7%, at end of operation 25.7% (Table 3). Mean volume of blood withdrawn was 1975 ml. RV was reduced by 21.6% after Hemodilution I and 21.5% after Hemodilution II. The most striking cardiovascular effect was a rise in CO to a mean of 123.5% after Hemodilution I and 136.3% after Hemodilution II. At mid-operation CO was 124% and at end of operation 129%. With a slight fall in pulse rate, calculated stroke volume increased. Radial artery, central venous, pulmonary artery, and pulmonary artery wedge pressures remained unchanged. Calculated total peripheral resistance was reduced, to 80% after Hemodilution I and to 73% after Hemodilution II. By the end of hemodilution there was a mean reduction of temperature of 1.5 C.

Oxygen Transport

Paired arterial and central venous gases are shown in Table 1. With reduction in hemoglobin there was a decrease in oxygen carrying capacity and no increase in the arterio-venous oxygen content difference (AVO_2D) following hemodilution. Instead the AVO_2D decreased slightly as depicted in Fig. 2 and Table 1. However, at end of operation the AVO_2D had increased. This may have been the result of returning consciousness and increased muscular activity. Also intravascular volume may have been reduced at this time. The calculated systemic oxygen transport (SO_2T) (CO in ml/min × arterial oxygen content in ml/min) was slightly reduced after Hemodilution I to 88% and after II to 83%, a small reduction as compared to the reduction in oxygen carrying capacity, to 70% and 54.5% as shown in Fig. 3.

2–3 D.P.G. level, after so short a time, remained unchanged. One patient who received one unit of bank blood which contains reduced amounts of 2–3 D.P.G. had

TABLE 3. *Acute Hemodilution: Changes in Hematocrit*

	Day Pre-Op	Baseline	After Hemodil. I	After Hemodil. II	Mid Op	End of Op
LVH%						
ML	45.9	38.9	28.5	23.2	20.0	33.5
SM	47.3	44.4	33.9	19.8		21.8
RH	49.2	48.3	28.6	22.5	20.5	24.9
SP	38.2	36.5	26.0	20.8	18.6	22.6
Mean	45.2	42.0	29.3	21.5	19.7	25.7
±SEM	2.4	2.66	1.7	0.7	0.57	2.7

a reduced level at the end of operation. Measurement of the P50 showed no change in the position of the oxyhemoglobin dissociation curve.

Tissue Perfusion

Pyruvate and lactate levels remained unchanged during and after hemodilution. However at the end of operation, both values were elevated, the pyruvate-lactate level remaining unchanged.

Muscle surface pH showed a consistent rise after each hemodilution, approaching the pH of arterial blood. This was thought to be due to increased blood flow (Fig. 4). The large rise in muscle surface pH seen at mid-operation is thought to be due to positional change of the probe caused by moving the patient.

Blood Volume

Results of BV studies are shown in Table 4. As can be seen, at the time of baseline measurements, there was an increase in BV of 12% as compared to the day preoperatively. This was associated with a rise in plasma volume, and an appropriate fall in hematocrit, from a mean of 45.2% preoperatively, to 42.0% at the first measurement. Similar increases in BV have been described with halothane anesthesia. There was also an increase in BV after Hemodilution I and II. These were calculated however from the measured RCM and LVH, using the TBH-to-LVH ratio measured preoperatively. It is possible that this ratio changes under the conditions of hemodilution. In three patients BV measurements done one day postoperatively by the ^{51}Cr and Evans' blue dye method showed a mean value of 89.8% as compared to the preoperative volume.

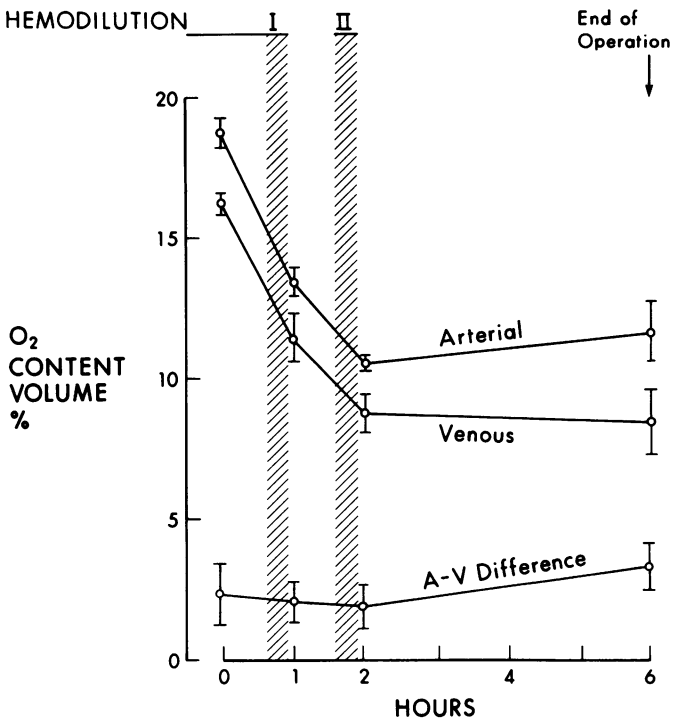

FIG. 2. The arterial and venous oxygen content difference with hemodilution and at the end of operation. Note the slight reduction in AV O_2 difference after each step in hemodilution shown in the bottom line. The vertical lines indicate the SEM.

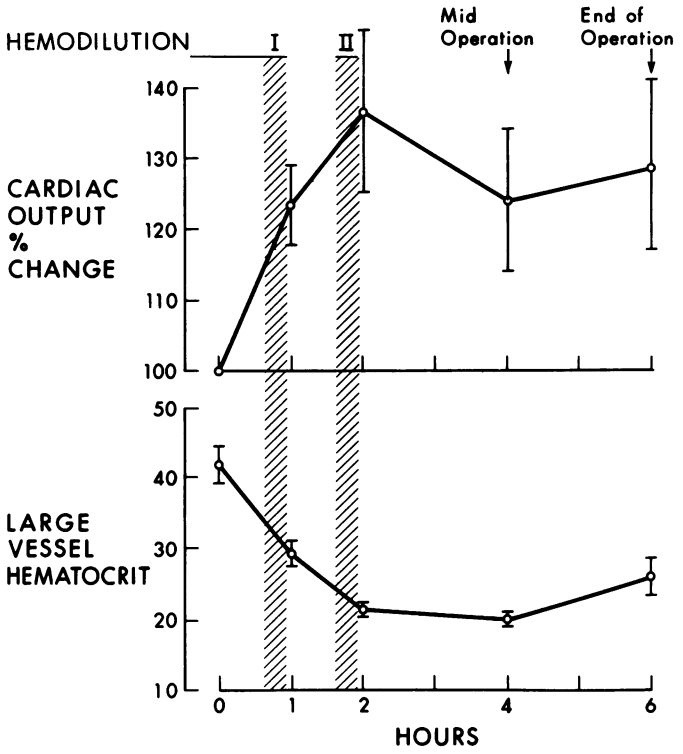

FIG. 1. Change in CO with reduction in hematocrit after hemodilution I and II. Vertical lines represent standard error of the mean (SEM). After hemodilution I: CO was 125%, Hct 29%. After hemodilution II: CO was 136% and Hct 21.5%.

Discussion

Acute hemodilution with BV replacement resulted in an increase in CO (Fig. 1). As the pulse rate remained stable, the increase in CO was largely the result of an increase in stroke volume (SV). There are several possible explanations for the increase in CO. These include the possible effects of fluoroxene anesthesia, hypovolemia, a decrease in tissue oxygenation, and the action of catecholamines or the autonomic nervous system. The most acceptable explanation however is the effect of hemodilution on viscosity and peripheral resistance.

Cullen *et al.*[2] showed that fluoroxene administered to volunteer subjects for 90 minutes at concentrations of 5 and 9% had no effect on CO, although causing a slight rise in CVP. The addition of nitrous oxide to 5% fluoroxene anesthesia produces an alpha-adrenergic sympathomimetic response and does not increase CO.[31] In the present study, with a mean concentration of fluoroxene of 5%,

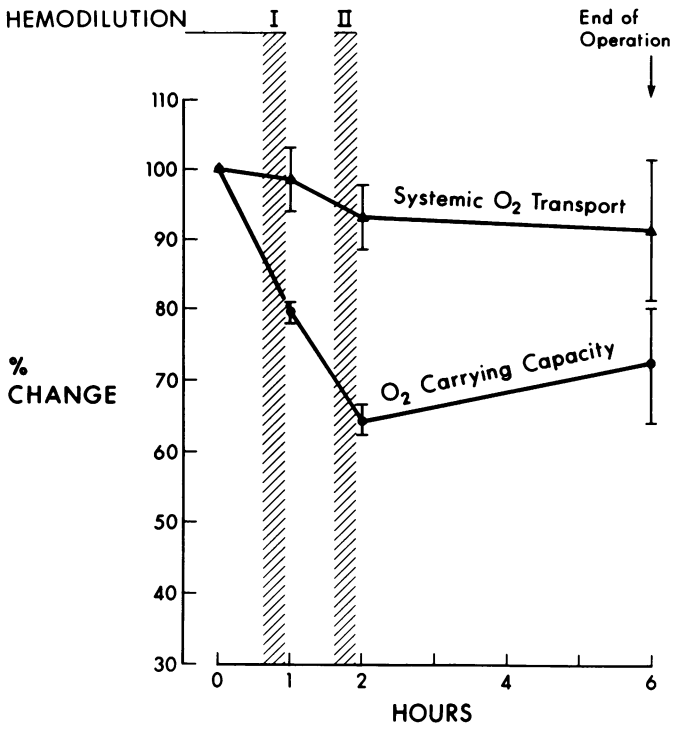

FIG. 3. The effects of hemodilution on muscle surface, arterial and venous pH. Note the slight rise in muscle surface pH after each step of hemodilution. The rise in muscle surface pH seen at mid-operation is thought to be due to positional changes of the probe caused by moving the patient.

cardiovascular effects cannot be ascribed to the anesthetic agent.

Glick *et al.*[9] studied the effects of hemodilution on hemodynamics in nonanesthetized dogs, with and without cardiac autonomic denervation. In the denervated dog, CO rose but to a lesser degree as compared to the intact animal. Also, the rise in CO in the denervated animals resulted from an increase in SV rather than in increase in HR as occurred in the intact animals. It is of interest that in our group of patients under the influence of anesthesia, the major effect was also a rise in SV rather than an increase in HR.

As shown in Table 4, BV increased after Hemodilution I and II as calculated from RV, LVH, and the LVH-to-TBH ratio. Changes of BV of this magnitude (10–20%) however have been shown to have little effect on CO.[6,30,33] Schnabel *et al.*[30] found that increases of blood volume of 22.5% were associated with a rise in CO. This was accompanied however by a rise in right atrial pressure of 242%. Right atrial and pulmonary capillary wedge pressures remained stable in the present study making hypervolemia an unlikely explanation for the rise in CO. Fowler *et al.*[5] also showed that there was no increase in CO associated with similar degrees of anemia in hypervolemic as compared to normovolemic experimental animals. Murray *et al.*,[24] on the other hand, showed that with hypervolemia CO was greater than that for equivalent degree of anemia at normovolemia. In their study however BV was expanded by about 50% and was associated with a rise in right atrial pressure.

It is unlikely that a decrease in PO_2 and tissue oxygenation was responsible for the increase in CO. Indicators of tissue perfusion, muscle surface pH, venous pH, PO_2, and PCO_2, pyruvate, and lactate levels remained unchanged or improved, making this explanation unlikely. It has also been found in the dog that 3 atmospheres of oxygen, which restores arterial oxygen content to pre-hemodilution level, does not abolish the rise in CO.[4] Likewise, Messmer *et al.*[20] showed that hemodilution did not cause a decrease in local oxygen tension in different organs using a tissue PO_2 electrode.

Rheologic studies done by others[19,21,28] have demonstrated a parallel decrease in total peripheral resistance and whole blood viscosity with progressive hemodilution. Guyton and Richardson[13] demonstrated that the decrease in peripheral resistance resulted in increased venous return and thus increased CO. Reduced viscosity resulting from hemodilution may play a major role in increasing the CO.

In the presence of hypovolemia, hemodilution causes a lesser increase in CO.[21] Watkins *et al.*,[34] studying gradual hemorrhage in normal volunteers found that the major compensatory response was an increase in oxygen extrac-

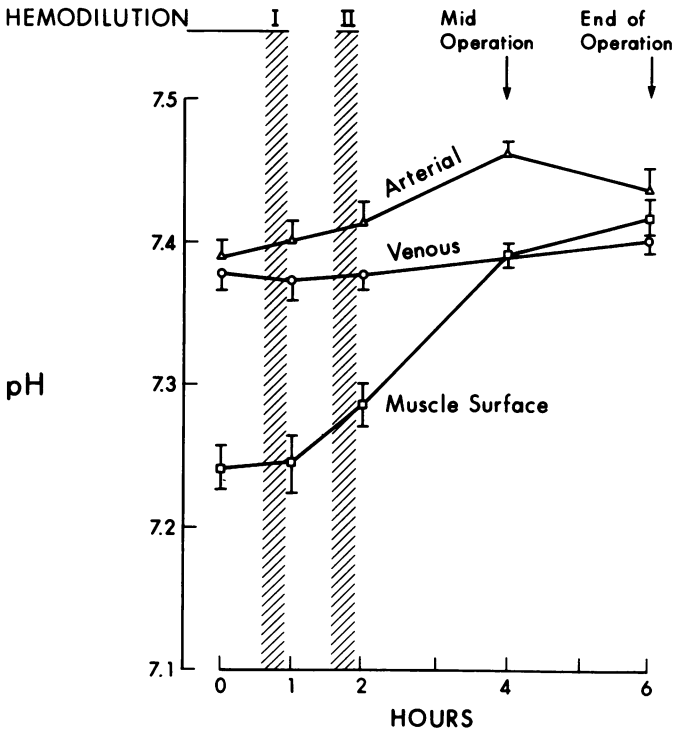

FIG. 4. The changes in systemic oxygen transport (SO_2T) and oxygen carrying capacity (O_2CC) with hemodilution. As O_2CC falls to 70% and 54.5% after hemodilution I and II the SO_2T falls to 88% and 83%.

TABLE 4. *Changes in Blood Volume with Hemodilution*

		Day Pre-Op	Baseline	After Hemodil. I	After Hemodil. II	Day Post-Op
BV						
	ML	3664	4469	4710	5166	3594
	SM	4989	5543	6024	8131	3959
	RH	4143	4351	5238	5533	3812
	SP	3671	4112	4437	4816	
	Mean	4117	4618	5102	5911	3788
	±SEM	312	316	349	754	106
RV						
	ML	1619	1669	1293	1141	1214
	SM	2104	2191	1812	1433	794
	RH	1743	1804	1288	1070	977
	SP	1171	1261	969	842	
	Mean	1659	1731	1341	1122	995
	±SEM	192	192	174	122	122
PV						
	ML	2045				2380
	SM	2885				3165
	RH	2400				2835
	SP	2500				
	Mean	2458				2793
	±SEM	173				228

tion ratio and that CO did not increase. This may be explained by a reduction in BV caused by the repeated phlebotomy without adequate replacement. In studies of normovolemic hemodilution in experimental animals[8,19,21,23] there was no significant increase in AV oxygen difference. In the present study the AVO_2D fell as shown in Fig. 2. This underscores the importance of maintaining BV in the presence of acute reductions in hematocrit.

Systemic oxygen transport is the amount of oxygen carried in the systemic circulation per minute and is calculated from COX arterial O_2 content. In hemodilution because of the reduction in oxygen carrying capacity, systemic oxygen transport will remain constant only if there is a compensatory rise in CO. In this study there was a slight decline in SO_2T after each step of hemodilution (Fig. 3). Because of the compensatory increase in CO however, this was far less than the reduction in O_2 carrying capacity.

There has been controversy over the concept of the ideal hematocrit, i.e. the hematocrit at which CO and O_2 carrying capacity are so balanced as to result in a maximum SO_2T. This is dependent on BV to some extent and may explain the difference in results obtained in several related studies. Guyton[13] and Gump,[12] using lactated Ringer's solution as the hemodiluting agent, found a stepwise fall in oxygen transport capacity and concluded that 40% was the "ideal hematocrit." Messmer *et al.*,[19,21] using Dextran, found that the increase in CO "over compensated" until a hematocrit of 30% was reached, concluding that 30% was the ideal hematocrit in the dog. This was not substantiated by Murray *et al.*, who also gave Dextran in dogs.[23] In our study, reduction of hematocrit to a mean of 29.3% then 21.5% was associated with a stepwise slight fall in systemic O_2 transport (Fig. 3).

Despite the small reduction in SO_2T, tissue perfusion and oxygenation remained excellent. Muscle surface pH increased with stepwise hemodilution and tended to approximate the arterial levels (Fig. 4). This may be explained by the increase in blood flow to the skeletal muscle which has been shown to occur with experimental hemodilution.[19,26] Likewise central venous pH rose and the central venous pyruvate, lactate and pCO_2 remained unchanged.

The patients studied tolerated the procedure well. Because of the infusion of lactated Ringer's solution, the patients had a diuresis both intra- and postoperatively. Mean blood loss was 2,500 ml. During the first half of the procedure, blood loss was replaced with lactated Ringer's solution and plasmanate. In the second half of the procedure, just after measurements had been made, the patients' own blood was reinfused. This sufficed for intraoperative requirements in all patients except one in whom an additional unit of bank blood was required intraoperatively. There were no postoperative complications in this group of patients.

This study has shown that the major compensatory factor in acute normovolemic hemodilution is an increase in CO and that hemodilution to hematocrit levels of 21% was well tolerated in these patients anesthetized with fluoroxene for total hip replacements. Effective compensation is dependent on cardiac, pulmonary and renal function, and patients with diseases of these systems were excluded from hemodilution. It is not known whether

these findings can be extrapolated to other situations such as acute trauma or burns.

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References

1. Couch, N. P., Dmochowski, J., Van de Water, J. M., *et al.*: Muscle Surface pH as an Index of Peripheral Perfusion in Man. Ann. Surg., 173:173, 1971.
2. Cullen, B. F., Eger, E. I., Smith, N. T., *et al.*: Cardiovascular Effects of Fluoroxene in Man. Anesthesiology, 32:218, 1970.
3. Dagher, E. J., Lyons, J. H., Ginlayson, D.C., *et al.*: Blood Volume Measurement: A Critical Study, Prediction of Normal Values: Controlled Measurement of Sequential Changes: Choice of a Bedside Method. Adv. Surg., I:69, 1965.
4. Dedichen, H., Race, D. and Schenk, W. G.: Hemodilution and Concommitant Hyperbaric Oxygenation. Effects of Cardiovascular Function. J. Thorac. Cardiovasc. Surg., 53:341, 1967.
5. Fowler, N. O., Frarch, R. H. and Bloom, W. L.: Hemodynamic Effects of Anemia with and Without Plasma Volume Expansion, Circ. Res., IV:319, 1956.
6. Frye, R. L., Braunwald, E. and Cohen, E. R.: Studies on Starlin's Law of the Heart. I. The Circulatory Response to Acute Hypervolemia and its Modification by Ganglionic Blockade. J. Clin. Invest., 39:1043, 1960.
7. Ganz, W. A.: A New Technique for Measurement of Cardiac Output by Thermodilution in Man. Am. J. Cardiol., 27:392, 1971.
8. Gaston, C., Rodriguez, J. A., Dzindzio, B., *et al.*: Effect of Acute Isovolemic Anemia on Cardiac Output and Estimated Hepatic Blood Flow in the Conscious Dog. Circ. Res., 32:530, 1973.
9. Glick, C., Plauth, W. H., Jr. and Braunwald, E.: Role of Autonomic Nervous System in the Circulatory Response to Acutely Induced Anemia in Unanesthetized Dogs. J. Clin. Invest., 43:2112, 1964.
10. Gloster, J. A. and Harris, P.: Observations on an Enzyme Method for the Estimation of Pyruvate in Blood. Blin. Chim. Acta., 7:206, 1962.
11. Grable, E., Finck, A. J., Abrams, A.L., *et al.*: The Effect of Cyclopropane and on the Blood Volume in Man. Anesthesiology, 23:828, 1962.
12. Gump, F. E., Butler, H. and Kinney, J. M.: Oxygen Transport and Consumption during Acute Hemodilution. Ann. Surg., 168:54, 1968.
13. Guyton, A. C. and Richardson, T. Q.: Effect of Hematocrit on Venous Return. Circ. Res., 9:157, 1961.
14. Hallowell, P., Bland, M. B., Buckley, M. J., *et al.*: The Reduction of Banked Blood Requirement by Fresh Autologous Blood Transfusion in Open Heart Surgery. Abstracts of scientic papers, American Society of Anesthesiologists Annual Meeting, Boston, 1972.
15. Hohonst Method of Lactate Measurement in Methods of Enzymatic Analysis. H. U. Bergmeyer, editor. New York, Academic Press, 266, 1965.
16. Laver, M. B. and Buckley, M. J: Extreme Hemodilution in the Surgical Patient. Hemodilution: Theoretical Basis and Clinical Application. Int. Symp., Rottach-Egern, 1971. Basel, Karger, 215, 1972.
17. Lowry Modified Method. Using Sigma Chemical Company Kit. St. Louis
18. Lowry, O. H., Passonneau, J. V., Hasselberger, F. X., *et al.*: Effect of Ischemia on Known Substrates and Cofactors of the Glycolytic Pathway in Brain. J. Biol. Chem., 239:18, 1964.
19. Messmer, K., Lewis, D. H., Sunder-Plassman, L., *et al.*: Acute Normovolemic Hemodilution. Changes of Central Hemodynamics and Microcirculatory Flow in Skeletal Muscle. Europ. Surg. Res., 4:55, 1972.
20. Messmer, K., Gornandt, L., Sinagowitz, E., *et al.*: Local Oxygen Tension and Tissue of Different Organs During Limited Normovolemic Hemodilution. FM Conf Europ Soc Microcirculation, Aberdeen, 1972.
21. Messmer, K., Sunder-Plassman, L., Klovekorn, W. P., *et al.*: Circulatory Significance of Hemodilution: Rheologic Changes and Limitations. Adv. Microcirc., 4:1, 1972.
22. Moore, F. D., Oelsen, K. H., McMurray, J. D., *et al.*: The Body Cell Mass and Support Environment. Philadelphia, W. B. Saunders, 1963.
23. Murray, G. F., Gold, P. and Johnson, B. L.: Systematic Oxygen Transport in Induced Normovolemic Anemia and Polycythemia. Am. J. Physiol., 203:720, 1962.
24. Murray, J. F., Gold, P. and Johnson, L., Jr.: The Circulatory Effect of Hematocrit Variations in Normovolemic and Hypervolemic Dogs. J. Clin. Invest., 42:1150, 1963.
25. Ochsner, J. L., Mills, N., Leonard, G. L. and Lawson, N.: Fresh Autologous Blood Transfusions with Extracorporeal Circulation. Ann. Surg., 177:811, 1973.
26. Race, D., Dedichen, H. and Schenk, W. G.: Regional Blood Flow during Dextran-induced Normovolemic Hemodilution in Dogs. J. Thorac. Cardiovasc. Surg., 53:578, 1967.
27. Replogle, R. L. and Merrill, E. W.: Experimental Polycythemia and Hemodilution. Physiologic and Rheologic Effects. J. Thorac. Cardiovasc. Surg., 4:582, 1970.
28. Replogle, R. L. and Merrill, E. W.: Hemodilution: Rheologic, Hemodynamic, and Metabolic Consequences in Shock. Surg. Forum., 81:157, 1967.
29. Rush, B. F., Richardson, J. D., Bosomworth, P., *et al.*: Limitations of Blood Replacement with Electrolyte Solutions. Arch. Surg., 98:49, 1969.
30. Schnabel, T. G. J., Eliasch, H., Thomasson, B., *et al.*: The Effect of Experimentally Induced Hypervolemia on Cardiac Function in Normal Subjects and Patients with Mitral Stenosis. J. Clin. Invest., 38:117, 1959.
31. Smith, N. T., Eger, E. I., Cullen, B. F., *et al.*: The Cardiovascular Responses to the Addition of Nitrous Oxide to Fluoroxene in Man. Br. J. Anesth., 44:142, 1972.
32. Torrance, J. D. and Lenfant, C.: Methods for Determination of O_2 Dissociation Curves, Including Bohr Effect. Res. Physiol., 8:127, 1969–1970.
33. Warren, J. V., Brannon, E. S., Weens, H. S., *et al.*: Effect of the Blood Volume and Right Atrial Pressure on the Circulation of Normal Subjects by Intravenous Infusions. Am. J. Med., 4:193, 1948.
34. Watkins, G. M., Bevilacqua, R. G., Brennan, M. R., *et al.*: Controlled Anemia in Normal Man: Cardiac Output, Oxygen Transport and Extraction. Surg. Forum., 1:187, 1972.