SEVERAL ASPECTS OF SOME TECHNIQUES AVOIDING HOMOLOGOUS BLOOD TRANSFUSIONS

EEN AANTAL ASPECTEN VAN ENKELE TECHNIEKEN OM HOMOLOGE BLOEDTRANSFUSIES TE VERMIJDEN

PROEFSCHRIFT

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Chapter 1

INTRODUCTION

The use of homologous blood products during anesthesia and surgery is not without risks. Complications due to homologous blood transfusions include transfusion reactions, isosensitization, transmission of infections (including HIV, hepatitis, CMV) and immunosuppression (resulting in increased postoperative infections and possibly increased cancer recurrence) [1-3]. Thus, there are important reasons to try to avoid the transfusion of homologous blood products as much as possible. Several strategies exist which can be employed to decrease the amount of homologous blood products used in a patient perioperatively, including preoperative autologous blood donation, intraoperative cell saving, several hemodilution techniques and acceptance of a lower hematocrit perioperatively.

Preoperative autologous blood donation is only appropriate for elective procedures which can be planned several weeks in advance, without a chance of postponement, and in which an adequate amount of blood loss is anticipated to make the PABD effective. Therefore, this technique can only be used in a limited number of cases. Moreover PABD induces a decrease in natural killer cell activity [4].

The different hemodilution techniques can be subdivided according to certain characteristics, such as preoperative (acute) or peroperative (more gradual), and normovolemic or hypervolemic. During hemodilution the hemoglobin level is reduced, resulting in fewer erythrocytes being lost per amount of blood loss, but also in a decrease in oxygen carrying capacity. This reduction in oxygen carrying capacity can be compensated for by a number of mechanisms. These include an increase in cardiac output, a redistribution of the cardiac output, an increase in oxygen extraction ratio and a shift in the oxygen dissociation curve to the right [5-8]. With respect to hemodilution techniques and the amount of blood that can be saved by these techniques, the issue of the lower safe limit of the hematocrit perioperatively remains a matter of debate.

The aim of the work presented in this thesis was to evaluate several aspects of different hemodilution techniques, including effects on hemodynamics and oxygen transport and monitoring during hemodilution, in an experimental model as well as in humans. As experimental model we selected the pig, which under several conditions of stress has shown reactions most similar to those of humans than any other experimental animal models [9-11]. In the pig we evaluated the effect of normovolemic hemodilution on blood gas values, oxygen

transport, hemodynamics and distribution of cardiac output. Hemodilution could be advanced to a much lower hematocrit in this animal model than one would dare to try in human subjects. Also the redistribution of cardiac output to many organs and tissues could be measured in this anesthetized pig model, with special attention to the heart as one of the most vulnerable organs during hemodilution. The heart already has a high oxygen extraction ratio under normal circumstances. Furthermore the heart is the organ producing one of the main compensation mechanisms, that is an augmentation of the cardiac output which increases the work load of the heart and thus increases its oxygen demand. Since circulating catecholamines have been hypothesized as being one of the regulatory factors in the compensation mechanisms during hemodilution [12] their levels were also measured during one of the experimental studies. In the search for a parameter which could predict the lowest safe margin of hemodilution we also evaluated the balance between oxygen delivery and oxygen consumption at extreme hemodilution in pigs. The critical mixed venous oxygen pressure (Pvo_2), the critical mixed venous oxygen saturation (Svo_2), and the critical oxygen extraction ratio (ER) were measured in this experimental animal model. At present, no other parameters are available for monitoring of the oxygen delivery during hemodilution in human studies.

The studies in humans included several investigations on the technique of hypervolemic hemodilution, a technique which is much less time consuming than acute normovolemic hemodilution but, at least theoretically, carries the risk of acute volume overloading. Moderate hypervolemic hemodilution has been used in the treatment of acute stroke [13]. The use of hypervolemic hemodilution with a large volume load has not been used as a method for decreasing the amount of homologous blood used peroperatively. We studied the safety and efficacy of this technique, and its consequences on hemodynamic and oxygenation parameters in anesthetized humans. At first the method of hypervolemic hemodilution was only used in Jehovah's Witness patients, but after proving its safety it has also been used in many other patients. Due to unfortunate circumastances, we were also able to study the effects on hemodynamics and oxygenation of extreme hemodilution in one patient (a Jehovah's Witness, who refused the use of any homologous blood product) who subsequently died. In this patient we could calculate several parameters at the critical point of hemodilution, as we had previously done in pigs.

Normovolemic hemodilution (acute preoperative and a more gradual

peroperative technique) and its effects on hemodynamics and oxygenation, use of homologous blood products, blood loss and perioperative erythropoiesis were also studied, and compared to preoperative autologous blood donation and a control group to evaluate its efficacy in humans.

During hemodilution the systemic oxygen flux is decreased. This implies that monitoring of the balance between oxygen flux and oxygen consumption is needed. We evaluated the usefulness of some monitoring methods during hemodilution. First we studied the accuracy of pulmonary artery catheters able to continuously measure mixed venous oxygen saturation (an important parameter during acute hemodilution, reflecting the balance between oxygen consumption and oxygen delivery) during hypervolemic hemodilution in humans.

The slope of the oxygen dissociation curve might change during hemodilution and thus influence the amount of available oxygen. In an attempt to find a parameter which could more accurately predict the critical point of hemodilution and thus could be used as the monitoring parameter during hemodilution we evaluated the calculated extraction ratio of the available oxygen content (ERav) in an animal model and in anesthetized humans. This ERav uses the S_{35} (the oxygen saturation at a oxygen pressure in the blood of 35 mmHg) as a dynamic parameter also including the position of the oxygen dissociation curve, and therefore including changes of the position of the oxygen dissociation curve. Normally the P_{50} is used to describe the position of the oxygen dissociation curve. The P_{50} however can not be used to calculate the amount of oxygen available to the tissues. Use of the S_{35} makes it possible to calculate the amount of oxygen available in the arterial blood and thus to calculate the ERav. The ERav was evaluated in pigs during extreme hemodilution and in humans during hemodilution combined with a decrease in body temperature, which shifts the oxygen dissociation curve to the left.

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Chapter 2

HEMODILUTION AND OXYGEN TRANSPORT

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Introduction

Several risks are associated with transfusion of homologous blood and blood products. The risk of alloimmunisation is well known. Transmission of viral infections from homologous blood transfusion (e.g. hepatitis, and especially AIDS) draw increasing the attention [1-3]. In addition it is suggested that transfusion of homologous blood promotes markedly increased tumor growth and growth of established metastases, and induces more postoperative infections, because blood transfusions exert a long-term (months) immunosuppressive action, increasing during the first week after transfusion [4,5].

Transfusion with donor blood may be diminished by predeposited autologous blood [6], intraoperative autotransfusion with a cell-saver [7] and hemodilution techniques. With hemodilution, fewer red cells are lost because of the non-linear decrease in packed cell volume during replacement of blood with plasma substitutes [8]. Hemodilution can be achieved in several ways. First, by pre-operative withdrawal of blood or by peroperative blood loss and simultaneous infusion of plasma substitutes (normovolemic hemodilution), [9]. Second, by rapid infusion of fluid without blood withdrawal (hypervolemic hemodilution) [10,11].

In general, oxygen flux into the tissue and finally into the cell depends on many factors as for example arterial oxygen content (Hb and Hb oxygen saturation), systemic hemodynamics (cardiac output), blood flow properties in the microcirculation, capillary density in the tissue, hematocrit values in the capillaries, Hb affinity for oxygen, release of oxygen from red cells, tissue affinity for oxygen, tissue diffusion coefficient and oxygen transport over the cell membrane. Regulatory mechanisms by hormones (e.g. catecholamines) or by local metabolites in relation to receptors in the macro- and microcirculation play an important role. Hemodilution might interfere with or change many of these factors and regulatory mechanisms.

Hemodilution and systemic hemodynamics

It has been postulated that acute isovolemic hemodilution induces a

decrease in systemic vascular resistance (SVR) almost parallel to the decrease in blood viscosity, whereas cardiac output (CO) increases significantly without increase in myocardial contractility. Over a wide range of hematocrit (Hct) levels, the rise in CO compensates for the decreased oxygen transport capacity, thereby maintaining oxygen transport to tissue [12]. The extent of the rise in CO, however, differs from one study to the other, even when studying the same proportional change in Hct. In anesthetized dogs rises varying between 40% and 125% are reported [13-18], except in one study where the rise in CO did not exceed 10% [19]. In this study, however, filling pressures (left atrial and end diastolic pressure) did not change during so-called normovolemic hemodilution. Because of an increased venous return to the heart after a reduction of viscous resistance of blood by hemodilution, a significant increase in filling pressures of the heart during normovolemic hemodilution can be expected. Therefore, constant filling pressures in this study suggest the existence of hypovolemic instead of normovolemic hemodilution. In conscious dogs, comparing CO values of the different studies in relation to the proportional change in hematocrit, reveals that the CO response on hemodilution is less. Related to the degree of normovolemic hemodilution increases of CO of 75-120% were found [20-22].

Surprisingly, comparing the studies in conscious dogs with the studies in anesthetized dogs, the increase in CO in all anesthetized animal studies is closely related to the increase in stroke volume (SV), while heart rate (HR) remains constant while, in contrast, in all conscious dog experiments an increase in CO is mainly attributable to an increase in HR. In conscious dogs, plotting the change in CO against the change in HR by regression analysis a positive correlation with $r = 0.85$ was found [18]. The increase in SV, as observed during hemodilution in anesthetized species, has been attributed to several mechanisms; 1) increased venous return due to reduced whole blood viscosity with consequent increased filling pressures [23]; 2) facilitation of left ventricular emptying by reduced after load because of reduced viscosity and possible vasodilatation [15]; 3) increased myocardial contractility due to activation of cardiac sympathetic nerves [20].

Because dogs differ from humans in anatomy, distribution of coronary arteries and in sympathetic responses [24], we studied cardiovascular responses, hemodynamics, oxygen transport to tissue during normoxic acute isovolemic hemodilution in sedated and anesthetized pigs [25-27]. Ample evidence exists to demonstrate that the pig is closely related to the human both

anatomically and physiologically with respect to cardiovascular system, regional distribution of cardiac output, metabolism and maximum oxygen consumption [24,28,29]. In the sedated pigs we found an increase in CO of 40%, and also like conscious dogs, mostly related to an increase in HR, while in the fully anesthetized pigs an increase in CO with 100% was observed, as in anesthetized dogs, mainly due to an increase in SV. In contrast, others found in anesthetized pigs an increase in 30% correlated with an increase in HR while SV remained unchanged [30]. However, in this study the hemodilution was rather hypovolemic, because blood exchange was done keeping filling pressures of the heart unchanged, ignoring the normally increased filling pressures during normovolemic hemodilution.

Only a few studies report the effects of normovolemic hemodilution in anesthetized humans, while no report exists about acute hemodilution in conscious humans. In anesthetized humans, during normovolemic hemodilution (range Hct: 40-20%), CO increases with 25-35%, as in anesthetized animals, mainly due to increased SV, while HR remains unchanged [23,31-35]. Acute hypervolemic hemodilution in anesthetized humans induces an increase in CO, comparable with the increase in CO in normovolemic hemodilution and also without any change in HR [10].

In conclusion: 1) the increase in cardiac output during hemodilution in anesthetized species is mainly due to increased SV, possibly due to reduced viscosity; 2) in conscious or sedated animals, reduced viscosity is a less important determinant during hemodilution and the increase in cardiac output is directly related to an increase in HR; 3) hemodilution can only be called iso- or normovolemic when filling pressures of the heart are increased, compared to baseline values obtained before hemodilution is induced.

Hemodilution and systemic oxygenation

Oxygen flux is the product of CO and arterial oxygen content. During hemodilution oxygen flux might remain unchanged or even increased, depending on the degree of increase in CO. Further decrease in Hct might be followed by a decreased oxygen flux, because the increase in CO as a compensatory factor is exhausted. Any further decrease in arterial oxygen content leads to an increased

extraction ratio (ER = oxygen uptake divided by oxygen flux) until a certain maximum. Further reduction of Hct produces oxygen supply dependency of oxygen uptake (VO_2). In sedated pigs a significant drop in oxygen flux could be observed at a Hct of 15%, while oxygen supply dependency of the VO_2 started at a Hct of 10% [26]. The ER value at this point was 0.57, and the oxygen flux 350 $ml.m^{-2}.min^{-1}$ (= 15.0 $ml.kg^{-1}.min^{-1}$). In anesthetized pigs a significant increase in ER could be observed at a Hct of 13%, while at the final step of hemodilution (Hct = 9.3%) VO_2 was well maintained (ER = 0.61), and the oxygen flux was decreased to 7.8 $ml.kg^{-1}.min^{-1}$ [27]. Cain found in anesthetized dogs during anemic hypoxia, when oxygen supply dependency of VO_2 started at a Hct of 10%, a critical whole body ER of 0.79, and a critical O_2 flux of 10 $ml.kg^{-1}.min^{-1}$ [13,36]. In another study in anesthetized dogs a critical systemic oxygen flux of 7.9 $ml.kg^{-1}.min^{-1}$ and a critical ER = 0.69 were established [37].

In a fatal Jehovah Witness case we observed a decrease in oxygen flux when Hct dropped below 20%. Oxygen supply dependency of VO_2 started at a hemoglobin value of 4.0 g% (Hct = 13%). The oxygen flux at this point was 184 $ml.m^{-2}.min^{-1}$ (= 4.9 $ml.kg^{-1}.min^{-1}$) and the ER 0.46. The patient died at a Hct value of 8%. During the same stages of hemodilution, the cardiovascular responses of this patient were similar in comparison to other anesthetized humans and this case might therefore be representative for anesthetized humans.

During hemodilution the ER might change not only due to changes in O_2 flux but also because of changes in VO_2. In some reports increase in VO_2 at the initial stages of stepwise induced normovolemic hemodilution are reported [13,27,38]. It has been suggested that the extra oxygen use by the heart alone with hemodilution could account for this increase. An increase of total circulating catecholamine level during anemic hypoxia has been discussed [39] whereby the metabolic effect exerted by catecholamines is to increase whole-body resting VO_2 [40]. The critical point of hemodilution whereby any further decrease of Hct might induce oxygen supply dependency of VO_2 is of course also influenced by differences in VO_2. During full anesthesia VO_2 is lowered and therefore a lower Hct is better tolerated than during sedation alone or during consciousness. In sedated pigs we found a critical oxygen flux of 15.0 $ml.kg^{-1}.min^{-1}$, while in fully anesthetized pigs an oxygen flux of 7.5 $ml.kg^{-1}.min^{-1}$ was still sufficient to maintain a constant VO_2. In patients the induction of anesthesia decreases VO_2 with 10%, while VO_2 the first hours after anesthesia is increased

by 20% compared with preanesthetic values [10]. Therefore, in clinical practice, during surgery and anesthesia a more pronounced hemodilution is acceptable, than during the initial postoperative phase. Several factors might influence the increased oxygen demand postoperatively as for example shivering during recovery from anesthesia and increased catecholamine levels [41].

In conclusion: the critical point of hemodilution with respect to systemic oxygenation differs in anesthetized and in conscious or sedated species because of differences in VO_2 through: 1) differences in basal metabolism and 2) possible differences in catecholamine levels.

Hemodilution and regional hemodynamics and oxygenation

In general, in the face of a reduction in O_2 flux, to meet the different metabolic demands of different organs, regional redistribution of blood away from lower extracting beds towards more critical tissues might occur. The effect of hemodilution on regional flows has been studied in several models. Most studies used electromagnetic or Doppler flow probes and, in general, showed increases in flow to brain and heart (185-700% increase), out of proportion compared to the increase in CO, and with little or no change in flow to other organs [19,21,38,42]. Little or no change in flow to other organs was especially obvious in conscious animal models. Another study, using electromagnetic flow probes, but studying only the splanchnic area, showed that total hepatic blood flows and mesenteric arterial blood flow increased, but not compensating totally decreased oxygen content, inducing increased oxygen extractions of liver and small intestine [30]. However, in this study only a small increase in CO is observed, because hemodilution was induced, thereby keeping filling pressures unchanged.

The microsphere technique for determining regional flows and oxygen fluxes has been used in four studies. In sedated rats and anesthetized dogs increased flows to heart (100-130%) and brain (26-140%) are reported, not related to increased CO (12-43%), while flow to the spleen decreased and flow to other organs measured did not change, or changed only slightly [15,16,43]. In fully anesthetized pigs with hemodilution (Dextran 40, 50 $g.l^{-1}$, Isodex®) flows increased out of proportion compared to the increased CO (103%) to heart

(420%) and brain (170%) while, in contrast to the other microsphere studies, flows to all other organs increased proportional to the increased CO, except for skin flow (70% increase) and skeletal muscle flow (70% increase) [27]. In this study myocardial oxygen consumption increased (106%) as hematocrit was decreased. However, even at an Hct of 9%, left ventricular oxygen ER did not increase since the increase in myocardial blood flow produced an increase in myocardial oxygen flux sufficient to compensate the decreased arterial oxygen content and the increased myocardial oxygen demand. In conscious dogs myocardial VO_2 increased with 108% but was covered by more than seven-fold increase in coronary flow [38].

Redistribution of CO might be explained by changes in circulating catecholamines and by enhanced sympathetic activity [20]. Carbon monoxide hypoxia, used as a model for anemic hypoxia, increases total catecholamine levels in anesthetized dogs [39], while infusing drugs with ß-vasodilator activity during hypoxic hypoxia can cause a decreased ability to extract O_2 [44,45]. The use of α-adrenergic blockers was reported to lower oxygen extraction rate in the hypoxic dog [36]. It has been suggested that the main factor of a vasoconstrictor response during hypoxia is to ensure oxygen delivery to the brain, and therefore generalized vasoconstriction should be caused everywhere except in the brain [13]. In our pig study, no increase of catecholamines during hemodilution has been found, maybe because of, in these experiments, high-dose fentanyl anesthesia, known for blocking stress responses and catecholamine release. This might explain why in this study, in contrast to the other microsphere studies, flow to most organs increased proportional to the increased CO [27].

In-vivo studies of the microcirculation show that in general the Hct in the capillaries (Hmic) is substantially lower than the systemic Hct. This is explained by several mechanisms. At first, in the microvessels red blood cells (RBC) travel faster than plasma, because RBC are located more in the center of the vessel tube. The result is that blood adjoining to the vessel wall presents a "plasma layer". In general, when a solution floats through a tube, that part of the solution adjacent to the wall of the tube passes the tube more slowly due to the higher resistance. Therefore, plasma meets a higher resistance in floating through the capillaries. Because plasma needs more time to travel through the capillaries than RBC, at any moment of time more plasma than RBC will be present in the capillary resulting in a lower Hct. This phenomenon has been termed "plasma

skimming" [46]. However plasma skinning alone is not sufficient to account for the observed reduction in Hmic, which is in the order of 30-50% from systemic Hct. Therefore mass balance considerations require that the low Hmic seen is also compensated by flow of blood through high Hct shunts. Such capillary vessels that can fulfill this function has been described and are termed "thoroughfare channels" [47]. During hemodilution until a systemic Hct of 20 is reached, different mechanisms, not yet totally clarified, tend to maintain constant RBC influx and therefore Hmic [48]. Another important factor to be considered during hemodilution is that normally RBC's lose oxygen during their travel through the arterioles [48]. The loss of oxygen by the RBC is a function of the transit time. Since hemodilution causes blood flow to increase in the microvasculature it will decrease the transit time of RBC and, therefore, blood will arrive at the capillaries with a greater amount of oxygen [49]. Finally, during extreme hemodilution, RBC influx into the capillary will decrease and the spacing between two cells in the capillary will increase. Until a Hmic of 20%, blood in the capillaries is a continuous and homogenous source of oxygen to the tissue [50]. During extreme hemodilution, however, where spacing between red cells become dominant, RBC act more as point sources of oxygen to the tissue and the tissue becomes increasingly sensitive to the passage of each source [51].

In conclusion: 1) regional distribution of CO and regional oxygen flux might be regulated: a) by enhanced sympathetic activity and might therefore be more pronounced in conscious and sedated animals than in fully anesthetized species and b) by vasoactive metabolites, especially during extreme hemodilution and in organs with high metabolic rate; 2) until systemic Hct of 20% is reached, RBC influx into capillaries remain constant, keeping Hct in capillaries (normally 30-50% lower than systemic Hct) more independent from changes in systemic Hct; 3) during hemodilution RBC reaching capillaries carry more oxygen.

Hemodilution and oxyhemoglobin dissociation curve

A shift to the left of the oxyhemoglobin dissociation curve (ODC) limits oxygen delivery when blood flow is limited [52]. Acute shift to the right of coronary sinus, venous and arterial blood have been reported during signs of hypoxia of the hearts in humans [53-55]. In two studies, chronically reduced Hb

concentration is compensated for by improved oxygen unloading, afforded by the increased P_{50} [56,57]. In one study in dogs an acute change in ODC during acute hemodilution occurred but not before Hct dropped below 10% [12], while in anesthetized pigs at every step of hemodilution the ODC shifts to the right [11,58]. A close relationship was found between the shift in ODC and the changed, for pH corrected, mixed venous PO_2 [48]. This relationship is in agreement with the mentioned acute changes in P_{50} during signs of hypoxia of the heart. In a fatal Jehovah Witness case we found no change in P_{50} before Hct dropped below 10%. In the pig experiments a further direct significant linear relationship was observed between the shift to the right of ODC and the increase in O_2 ER also during oxygen supply dependency of VO_2, suggesting that the maximum of O_2 ER is also influenced by the position of the ODC. This might explain differences in the literature about the O_2 ER critical value because of possible differences during different experiments in the position of the ODC.

A new concept in monitoring systemic oxygenation that includes the effect of changes in ODC has been introduced [58]. Using the S_{35} (saturation of hemoglobin at PO_2 = 35 mmHg), changing with alterations in ODC, real arterial available oxygen content ($CavIO_2$) can be calculated being the maximum amount of oxygen that can be extracted from Hb in several organs before oxygen diffusion into tissue becomes compromised and VO_2 may decrease. The relation between VO_2 and $CavIO_2$ expressed by the extraction ratio of the arterial available oxygen content (ERav) should give realistic indices of oxygen supply and VO_2, including the effect of changes in ODC. Comparing our pig experiments with the fatal Jehovah Witness case revealed differences in critical ER (0.57 vs 0.46) but not in critical ERav.

In conclusion: changes in ODC might play a role in oxygen delivery during hemodilution and especially, as stated before [59], when oxygen reserves are minimal. The position of the ODC is an important determinant for the critical O_2 ER value during hemodilution, also when VO_2 becomes dependent on oxygen flux.

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Chapter 3

CATECHOLAMINES AND REGIONAL HEMODYNAMICS DURING ISOVOLEMIC HEMODILUTION IN ANESTHETIZED PIGS

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Summary

The effects of stepwise isovolemic hemodilution on systemic and regional hemodynamics, oxygen flux, and circulating catecholamines were studied in six pigs anesthetized with midazolam and fentanyl. Reduction of the hematocrit from 28 to 9% resulted in doubling of the cardiac output, mainly due to an increase in stroke volume. Regional blood flows, measured using the radioactive microsphere technique, showed an increase in blood flow to all organs except liver (hepatic artery fraction) and adrenals, with a redistribution of cardiac output in favor of heart and brain (increase in blood flow 420 and 170%, respectively). Oxygen fluxes to most organs did not decrease until the hematocrit decreased to 9%, while total body oxygen consumption was well maintained. Left ventricular oxygen consumption increased, but because left ventricular blood flow also increased, left ventricular extraction ratio did not increase. Circulating catecholamines did not play any role in these regulatory mechanisms.

Introduction

Hemodilution reduces the oxygen-carrying capacity of the blood. Consequently the organs and tissues of the body have to extract more oxygen or augment perfusion to meet their oxygen demand. In anesthetized humans, cardiac output increases, but arteriovenous difference in oxygen saturation does not change during mild-to-moderate levels of acute hemodilution, indicating that enhancement of perfusion is a primary mechanism for compensation rather than an increased oxygen extraction [1,2]. There are few studies on the distribution of cardiac output during normoxic isovolemic hemodilution, and most of them employed electromagnetic flow probes, which limits the number of organs that can be studied and does not allow assessment of the distribution of flow within an organ. Only three studies used the radioactive microsphere technique to determine regional perfusion. Despite experimental shortcomings of these studies, such as only one step of hemodilution [3,4] and the use of nonsplenectomized dogs [3,5], all three studies indicate that a redistribution of cardiac output and oxygen transport occurs in favor of the vital organs (heart and brain).

It has been postulated that increased levels of catecholamines play a role in hemodynamic responses and the redistribution of cardiac output during isovolemic hemodilution [6], but, so far, levels of catecholamines have not been measured during hemodilution. This study was designed to evaluate in anesthetized pigs the effects of four steps of normoxic isovolemic hemodilution on the distribution of cardiac output, oxygen regional fluxes, and circulating catecholamines. The pig was selected for this animal model because under several conditions of stress the response of pigs, in contrast to dogs, are similar to those of humans [7-9].

Material and methods

GENERAL

Experimental preparation. After an overnight fast, 12 crossbred Landrace x Yorkshire pigs (28 ± 1 kg; HVC, Hedel, The Netherlands) were sedated with midazolam (Dormicum, 0.3 mg/kg im) and ketamine (10 mg/kg im), anesthetized with thiopental (5 mg/kg iv), intubated, and subsequently connected to a respirator (Servo 900b, Siemens, Sweden). Intermittent positive-pressure ventilation with a mixture of oxygen and nitrogen (1:2) and a positive end-expiratory pressure of ~4 Torr was applied to keep arterial blood gasses (ABL3 , Radiometer, Copenhagen, Denmark) within the normal range (PO_2 120-180 Torr, PcO_2 35-45 Torr, pH 7.35-7.45). Anesthesia was maintained throughout the experiment with midazolam (0.45 mg/kg followed by 0.45 $mg.kg^{-1}.h^{-1}$ iv) and fentanyl (12.5 μg/kg followed by 12.5 $\mu g.kg^{-1}.h^{-1}$ iv), while muscle relaxation was obtained with pancuronium bromide (0.1 mg/kg followed by 0.3 $mg.kg^{-1}.h^{-1}$ iv). Body temperature was maintained around 38°C with a heating pad. The bladder was cannulated to prevent vagal stimulation associated with distension of the bladder.

Catheters (8F) were positioned in the superior vena cava for the administration of anesthetics and dextran solution (to replace blood) and in the aortic arch and pulmonary artery for measurement of blood pressures and withdrawal of blood samples for determination of blood gases. Finally, catheters (8F) were placed in the descending aorta and the left ventricle (Millar microtipped catheter) for withdrawal of blood samples and for calibration of

regional blood flows assessed with the radioactive microsphere technique and measurement of left ventricular blood pressure and its first derivate (LvdP/d*t*), respectively. A midsternal thoracotomy was performed to expose the heart, and an electromagnetic flow probe (Skalar, Delft, The Netherlands) was placed around the ascending aorta. The left and right atria were cannulated for injection of radioactive microspheres (left atrium) and measurement of blood pressures. The great cardiac vein was cannulated for withdrawal of blood samples for determination of blood gases.

MEASUREMENTS

Systemic hemodynamics. Systemic hemodynamic measurements consisted of heart rate, ascending aortic blood flow, and blood pressures in the central aorta, pulmonary artery, left and right atrium, and left ventricle. The maximal rate of increase in left ventricular pressure ($LVdP/dt_{max}$) was obtained by electronic differentation of the left ventricular pressure. Stroke volume, pulmonary vascular resistance (PVR = MPAP -LAP/CO, where MPAP is mean pulmonary artery pressure, LAP is left atrial pressure, and CO is cardiac output), and systemic vascular resistance (SVR = MAP/CO, where MAP is mean arterial pressure) were calculated.

Blood gases, hematocrit, and viscosity. Blood samples were taken from the central aorta, great cardiac vein, and pulmonary artery for measurement of arterial, coronary venous, and mixed venous PO_2, PCO_2, pH, and hemoglobin and its oxygen saturation, respectively (OSM2 Radiometer). A viscosity meter (Low Shear 30, Contraves, Zürich, Switzerland) was used to measure arterial blood viscosity at shear rates ranging from 0.04 to 34.6/s.

Regional blood flows. Regional blood flows were measured using the radioactive microsphere technique [10]. About 10^6 microspheres [15 ± 1 (SD) μm diam, New England Nuclear, Dreiech, FRG], labeled with ^{46}Sc, ^{103}Ru, ^{141}Ce, ^{95}Nb, or ^{113}Sn, were injected in random order over a period of 30-45 s into the left atrium. For calculation of regional blood flow values, an arterial reference blood sample was withdrawn (flow rate 10 ml/min) from the descending aorta, starting just before and continuing until 1 min after the injection of microspheres. At the end of each experiment, the animal was killed with an overdose of pentobarbital sodium and several organs and tissues (heart, brain, liver, spleen, lungs, kidneys, adrenals, stomach, small intestine, skin, and skeletal muscle samples from different regions) were excised, weighed, and

placed in vials. Details of the counting of radioactivity and the processing of data have been published previously [11]. Blood flow to the various tissue samples (Q_{ti}) was calculated as

$$Q_{ti}\ (ml.min^{-1}.\ 100g^{-1}) = (I_{ti}/I_a) \times Q_a$$

where I_{ti} and I_a are the radioactivity (cpm) per 100 g tissue and that of the arterial blood sample, respectively, and Q_a is the withdrawal rate. CO was derived by adding myocardial blood flow (microsphere data) to the ascending aorta blood flow (electromagnetic flowmeter).

Oxygen fluxes and consumption. Systemic (O_2flux_{syst}) and tissue (O_2flux_{ti}) oxygen fluxes were calculated as

$$O_2flux_{syst}\ (ml\ O_2/min) = CO \times CaO_2$$

and

$$O_2flux_{ti}\ (ml\ O_2.min^{-1}.100g^{-1}) = Q_{ti} \times CaO_2$$

where CaO_2 is the arterial oxygen content (ml O_2/ml blood).

Systemic (total body) oxygen consumption ($VO_{2\ syst}$) was calculated as

$$VO_{2\ syst} = CO \times C(a\text{-}v)O_2$$

where $C(a\text{-}v)O_2$ is the difference in oxygen content between the arterial and mixed venous blood. Left ventricular myocardial oxygen consumption ($VO_{2\ LV}$) was calculated as

$$VO_{2\ LV} = Q_{LV} \times C(a\text{-}cv)O_2$$

where Q_{LV} is left ventricular blood flow ($ml.min^{-1}.100g^{-1}$) and $C(a\text{-}cv)O_2$ is the difference in oxygen content between arterial and coronary venous blood. Extraction ratios of the systemic and coronary circulation were calculated as

$$ER_{syst} = VO_{2\ syst}/O_2flux_{syst}$$

and

$$ER_{LV} = VO_{2\,LV}/O_2flux_{LV}$$

respectively.

Plasma levels of catecholamines. For determination of plasma levels of catecholamines (epinephrine, norepinephrine, and dopamine) 10 ml blood were collected from the central aorta into heparinized tubes containing 12 mg of glutathione. The plasma was separated immediately by centrifugation (4°C, 15 min, 3000 g) and stored at -80°C until assayed. Determination was done by high-performance liquid chromatography with fluorescence detection after extraction and derivation [12].

EXPERIMENTAL PROTOCOL

After all preparations had been completed, a stabilization period of ≥ 30 min was allowed. Before the protocol (2-15 min before administration of Dextran 40), all 12 animals received a 10-ml bolus injection of Dextran 1 (150 g/l in 0.9% salt solution, Promiten) to prevent possible anaphylactic reactions to Dextran 40. Subsequently, baseline systemic hemodynamic data were collected, blood samples were withdrawn for determination of blood gas values and catecholamines, and a batch of radioactive microspheres was injected into the left atrium. Six animals underwent four steps of isovolemic hemodilution. Hemodilution was induced by exchanging blood with isooncotic Dextran 40 (50 g/l in 0.9% saline, Isodex), which was warmed to 38°C and instilled slowly into the superior vena cava. Stepwise isovolemic hemodilution was induced by two steps of 10 ml/kg body wt and two steps of 15 ml/kg body wt, producing a total volume exchange of 50 ml/kg body wt. Ten minutes after each step of isovolemic hemodilution, all measurements were repeated. Six other animals served as controls, in which measurements were made at corresponding time points.

DATA PRESENTATION AND STATISTICAL ANALYSIS

Unless otherwise stated, all data are presented as arithmetic means ± SE. In the control animals, statistical analysis was performed with the Duncan new multiple range test once a parametric analysis of variance (randomized block design) had revealed that the samples represented different populations. The

hemodilution-induced changes were compared with the solvent group by use of an unpaired *t* test. Statistical significance was accepted at $P < 0.05$ (two-tailed).

DRUGS

The drugs used in this study were midazolam-HCl (Dormicum, Hoffmann-La Roche, Mijdrecht, The Netherlands), ketamine-HCl (Nimatik, AUV, Cuyk, The Netherlands), fentanyl citrate (Fentanyl-Janssen Pharmaceutical, Tilburg, The Netherlands), pancuronium bromide (Pavulon, Organon Teknika, Boxtel, The Netherlands), isooncotic Dextran 40 (50 g/l in 0.9% saline, Isodex, NPBI, Emmer-Compascuum, The Netherlands), and Dextran 1 (150 g/l in 0.9% saline, Promiten, NPBI, Emmer-Compascuum, The Netherlands).

Results

SYSTEMIC AND PULMONARY HEMODYNAMICS

Although all animals underwent the same anesthetic and surgical procedures and were randomly assigned to the two groups, there was a significant difference in baseline heart rate and $LVdP/dt_{max}$ between control animals and animals that underwent hemodilution (Table 1). All systemic hemodynamic parameters remained stable in control animals throughout the study period. In the hemodilution group, a decrease in the hematocrit was accompanied by a doubling of cardiac output, which was primarily due to an increase in stroke volume (by up to 55%) as changes in heart rate were considerably less (26%). The increase in stroke volume appears to result from an enhanced left ventricular filling (left ventricular end-diastolic pressure was elevated from 4.5 ± 0.7 to 6.8 ± 0.7 mmHg; $P < 0.05$), since $LVdP/dt_{max}$ did not change. Furthermore, despite the increase in cardiac output, mean arterial blood pressure was well maintained until the last hemodilution step, when a decrease from 108 ± 8 to 90 ± 5 mmHg was observed. These data also imply that a decrease in systemic vascular resistance by up to 60% prevented arterial blood pressure from increasing parallel to cardiac output. In comparison, pulmonary vascular resistance decreased slightly less (by up to 40%), resulting in a mild increase in pulmonary artery pressure (up to 27%).

Table 1. *Systemic and pulmonary effects of hemodilution in anesthetized pigs.*

Exchange blood volume, ml/kg		0 / 0	0 / 10	0 / 20	0 / 35	0 / 50
Hct, %	C	27.6 ± 0.9	27.2 ± 1.2	26.2 ± 0.9	25.3 ± 0.9	26.2 ± 0.7
	H	27.5 ± 0.7	20.3 ± 0.4*	16.7 ± 0.2*	12.2 ± 0.5*	9.3 ± 0.3*
CO, l/min	C	2.83 ± 0.14	2.85 ± 0.11	2.87 ± 0.14	2.98 ± 0.13	2.92 ± 0.12
	H	2.67 ± 0.23	3.75 ± 0.26*	4.26 ± 0.21*	5.02 ± 0.17*	5.42 ± 0.18*
HR, beats/min	C	142 ± 7	146 ± 7	152 ± 10	152 ± 10	153 ± 14
	H	113 ± 7+	118 ± 7	130 ± 3	134 ± 5	140 ± 4
SV, ml	C	19.9 ± 0.4	19.4 ± 0.7	19.2 ± 1.4	18.8 ± 2.1	19.8 ± 2.0
	H	22.8 ± 2.9	29.9 ± 2.9*	30.5 ± 2.5*	34.3 ± 2.7*	34.9 ± 2.2*
LVEDP, mmHg	C	4.5 ± 0.5	4.4 ± 0.6	4.3 ± 0.5	4.8 ± 0.5	4.8 ± 0.6
	H	4.5 ± 0.7	5.8 ± 0.8*	5.7 ± 0.8*	7.3 ± 0.8*	6.8 ± 0.7*
$LvdP/dt_{max}$, mmHg/s	C	4290 ± 270	4200 ± 200	4420 ± 270	4460 ± 390	4410 ± 570
	H	3370 ± 220+	3680 ± 290*	3980 ± 220	4000 ± 310	4050 ± 480
MAP, mmHg	C	108 ± 3	180 ± 3	111 ± 3	114 ± 4	113 ± 7
	H	109 ± 8	110 ± 6	112 ± 7	103 ± 6	90 ± 5*
SVR, $mmHg.l^{-1}.min$	C	37.9 ± 1.8	36.7 ± 1.3	38.5 ± 1.8	37.1 ± 2.5	38.4 ± 2.5
	H	39.0 ± 4.9	32.5 ± 3.3*	27.7 ± 2.4*	21.7 ± 1.3*	17.6 ± 1.1*
PAP, mmHg	C	18.0 ± 1.6	18.1 ± 1.8	18.7 ± 1.6	19.8 ± 1.3	20.9 ± 1.7
	H	19.5 ± 1.3	21.8 ± 1.9	22.9 ± 1.5	24.2 ± 2.0	24.5 ± 2.0
PVR, $mmHg.l^{-1}.min$	C	5.0 ± 0.8	4.8 ± 0.9	5.0 ± 0.7	5.1 ± 0.6	5.6 ± 0.8
	H	6.8 ± 1.1	5.1 ± 0.7	4.7 ± 0.5	3.9 ± 0.5	3.6 ± 0.4

Values are means ± SE for 6 control (C) and 6 hemodilution (H) animals. Hct, hematocrit; CO, cardiac output; HR, heart rate; SV, stroke volume; LVEDP, left ventricular end-diastolic pressure; $LVdP/dt_{max}$, maximum rise of left ventricular pressure; MAP, mean arterial blood pressure; SVR, systemic vascular resistance; PAP, pulmonary arterial blood pressure; PVR, pulmonary vascular resistance. * Change from baseline significantly different ($P < 0.05$) from change in the control animals. + Significant difference in baseline values, ($P < 0.05$).

Table 2. *Systemic oxygen tensions and saturations during hemodilution in anesthetized pigs.*

Hct, %	C	26.7 ± 0.9	27.2 ± 1.2	26.2 ± 0.9	25.3 ± 0.9	26.2 ± 0.7
	H	27.5 ± 0.7	20.3 ± 0.4*	16.7 ± 0.2*	12.2 ± 0.5*	9.3 ± 0.3*
PaO_2, Torr	C	139 ± 16	138 ± 17	141 ± 15	139 ± 17	135 ± 22
	H	166 ± 6	174 ± 11	164 ± 3	164 ± 9	158 ± 8
SaO_2, %	C	97 ± 0.3	97 ± 1.1	97 ± 0.7	96 ± 1.2	96 ± 1.6
	H	97 ± 0.3	97 ± 0.3	96 ± 0.3	95 ± 0.6	94 ± 0.5
PvO_2, Torr	C	36 ± 4	35 ± 3	34 ± 4	35 ± 5	35 ± 6
	H	38 ± 3	39 ± 4	38 ± 3	35 ± 3	31 ± 3*
SvO_2, %	C	56 ± 7	55 ± 8	53 ± 8	52 ± 1	52 ± 13
	H	57 ± 6	57 ± 7	52 ± 5	47 ± 6*	37 ± 7*
$VO_{2\ syst}$, ml/min	C	141 ± 10	150 ± 11	155 ± 11	163 ± 13	163 ± 16
	H	128 ± 8+	135 ± 9	144 ± 8	147 ± 8	141 ± 5
ER_{syst}	C	0.40 ± 0.03	0.42 ± 0.03	0.45 ± 0.03	0.46 ± 0.04	0.46 ± 0.05
	H	0.41 ± 0.03	0.42 ± 0.03	0.47 ± 0.03	0.54 ± 0.03*	0.61 ± 0.02

Values are means ± SE for 6 control (C) and 6 hemodilution (H) animals. PaO_2, arterial oxygen tension; SaO_2, arterial oxygen saturation; PvO_2, mixed venous oxygen tension; SvO_2, mixed venous oxygen saturation; $VO_{2\ syst}$, systemic oxygen consumption; ER_{syst}, systemic extraction ratio. * Change from baseline significantly different ($P < 0.05$) from change in the control animals. + Significant difference in baseline values, ($P < 0.05$).

Table 3. *Left ventricular oxygenation during hemodilution in anesthetized pigs.*

$PcvO_2$, Torr	C	21 ± 1	20 ± 1	21 ± 1	20 ± 1	20 ± 1
	H	24 ± 1	24 ± 1	25 ± 1	28 ± 1	30 ± 2
$ScvO_2$, %	C	23 ± 2	20 ± 1	23 ± 1	18 ± 2	21 ± 1
	H	21 ± 2	22 ± 1	23 ± 1	26 ± 3	28 ± 2
$VO_{2\ LV}$, $ml.min^{-1}.100\ g^{-1}$	C	14.9 ± 0.8	12.9 ± 2.5	15.1 ± 0.8	11.2 ± 3.4	15.9 ± 1.7
	H	11.7 ± 0.7	14.4 ± 0.7*	17.8 ± 0.7*	20.3 ± 0.6*	24.1 ± 0.5*
ER_{LV}	C	0.75 ± 0.02	0.78 ± 0.01	0.76 ± 0.01	0.82 ± 0.02	0.77 ± 0.01
	H	0.77 ± 0.02	0.77 ± 0.01	0.75 ± 0.02	0.72 ± 0.02*	0.70 ± 0.02*

Values are means ± SE for 6 control (C) and 6 hemodilution (H) animals. $PcvO_2$, coronary venous oxygen tension; $ScvO_2$, coronary venous oxygen saturation; $VO_{2\ LV}$, left ventricular oxygen consumption; ER_{LV}, left ventricular extraction ratio. * Change from baseline significantly different ($P < 0.05$) from change in the control animals.

SYSTEMIC OXYGENATION

In both the control and hemodilution groups, arterial oxygen parameters remained unchanged during the course of the study (Table 2). Hemodilution caused mild decreases in mixed venous oxygen tension and saturation. Consequently the systemic oxygen extraction ratio increased from 41 ± 3% at baseline to 61 ± 2% after the last volume exchange step, thereby compensating for the reduction in systemic oxygen flux. Total body oxygen consumption was well maintained, even at the lowest hematocrit.

REGIONAL BLOOD FLOWS AND OXYGEN FLUXES

In control animals, not only cardiac output but also all regional blood flows remained stable during the course of the study. Hemodilution caused increases in blood flow to all organs and tissues except the adrenals and liver (hepatic artery fraction only; baseline value 37 ± 5 $ml.min^{-1}.100\ g^{-1}$, not shown) in which flows did not change. In the spleen the increase (46 ± 18%) was significant only during the second step. The increase in flow to the heart (420%) was considerably larger than that to the brain (170%), kidneys (100%) and stomach (100%) (Figure 1). After the first volume exchange, skin flow (70%) and skeletal muscle flow (70%) had increased, but there were no additional changes when hematocrit decreased further. The increase in cerebral blood flow was homogeneously distributed over the cerebral hemispheres (160 ± 9%), diencephalon (170 ± 16%), cerebellum (110 ± 13%), and brain stem (150 ± 13%, not shown). Lung flow (bronchial flow and arteriovenous shunt flow) did not change in either the hemodilution or the control group (baseline values 23.9 ± 4.3 and 26.9 ± 3.5 $ml.min^{-1}.100\ g^{-1}$, respectively, not shown).

During the first three volume exchanges (up to 35 ml/kg), the increase in blood flow compensated for the reduction in oxygen-carrying capacity of the blood, thereby maintaining the oxygen flux to all organs except the skin (Figure 2). After the last volume exchange (hematocrit 9.3 ± 0.3%), however, oxygen flux to kidneys, brain, stomach, small intestine, and skin decreased significantly and was maintained only in the heart.

CORONARY CIRCULATION

The increase in flow to the heart was not homogeneously distributed over the four different chambers (Figure 3). Blood flow to right and left atria increased by up to 120 ± 20 and 390 ± 70%, respectively, and to the right ventricle by

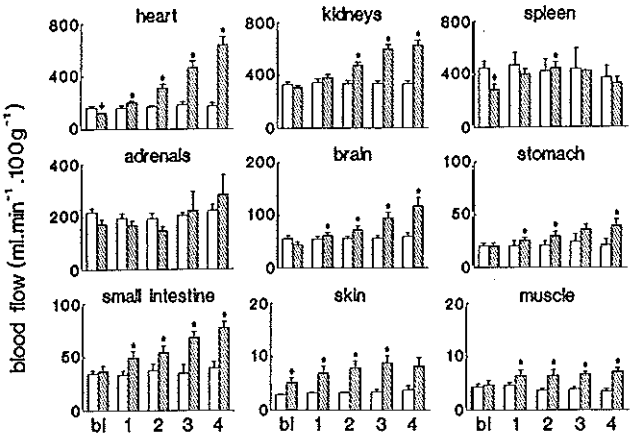

Figure 1. *Regional blood flows at 5 steps of hemodilution [baseline (bl) = 0, 1 = 10, 2 = 20, 3 = 35, 4 = 50 ml/kg body wt blood volume exchange] in 6 anesthetized pigs (hatched columns) and at corresponding time points in controls (open columns). Values are mean ± SE. * P < 0.05, mean change vs. control; + P < 0.05, control vs. hemodilution.*

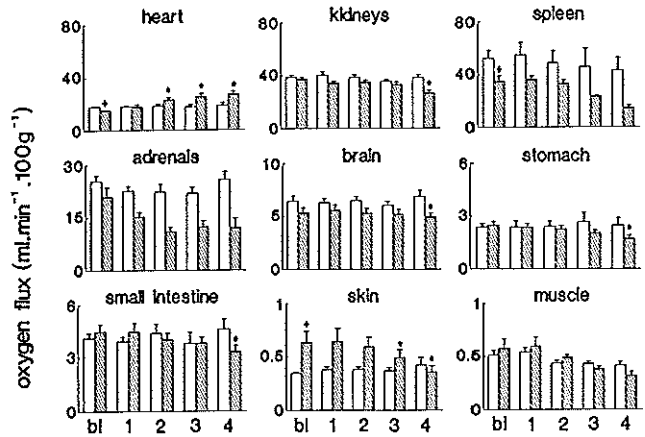

Figure 2. *Oxygen flux at 5 steps of hemodilution (see figure 1 legend) in 6 anesthetized pigs (hatched columns) and at corresponding time points in controls (open columns). Values are mean ± SE. * P < 0.05, mean change vs. control; + P < 0.05, control vs. hemodilution.*

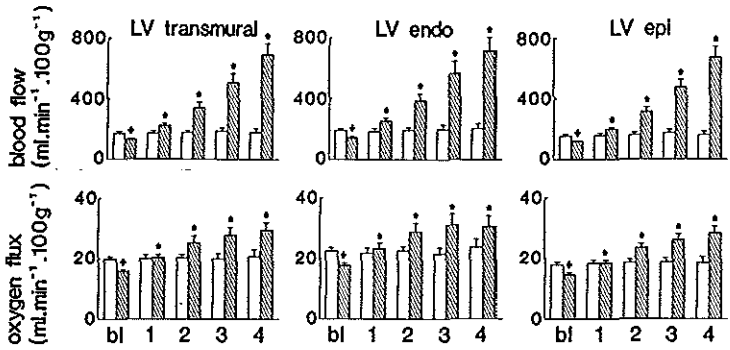

Figure 3. *Myocardial regional blood flows and oxygen fluxes at 5 steps of hemodilution (see figure 1 legend) in 6 anesthetized pigs (hatched columns) and at corresponding time points in controls (open columns). LV, left ventricular; endo, endocardium; epi, epicardium. Values are mean ± SE. * $P < 0.05$, mean change vs. control; + $P < 0.05$, control vs. hemodilution.*

up to 510 ± 55% after a volume exchange of 50 ml/kg (not shown). As a result, oxygen fluxes were maintained in both atria but actually increased in the right ventricle (110 ± 10%, not shown). The increase in left ventricular transmural blood flow (440 ± 60%) was more pronounced in the subepicardial layers (460 ± 60%) than in the subendocardial layers (400 ± 70%) so that subepicardial-to-subendocardial blood flow ratio decreased from 1.22 ± 0.003 to 1.06 ± 0.07 ($P < 0.05$).

As in the right ventricle, the oxygen flux was also enhanced in the left ventricle. Despite the increase in left ventricular oxygen consumption, coronary venous oxygen saturation was slightly higher after the last step of hemodilution, indicating a decreased left ventricular oxygen extraction (Table 3).

PLASMA LEVELS OF CATECHOLAMINES

In neither the control nor the hemodilution animals were plasma levels of norepinephrine and epinephrine significantly affected (Figure 4), although some variations occurred between individual animals. Dopamine levels remained

unchanged in the control animals but increased in three animals during the first two volume exchanges and resumed prehemodilution values after the third volume exchange.

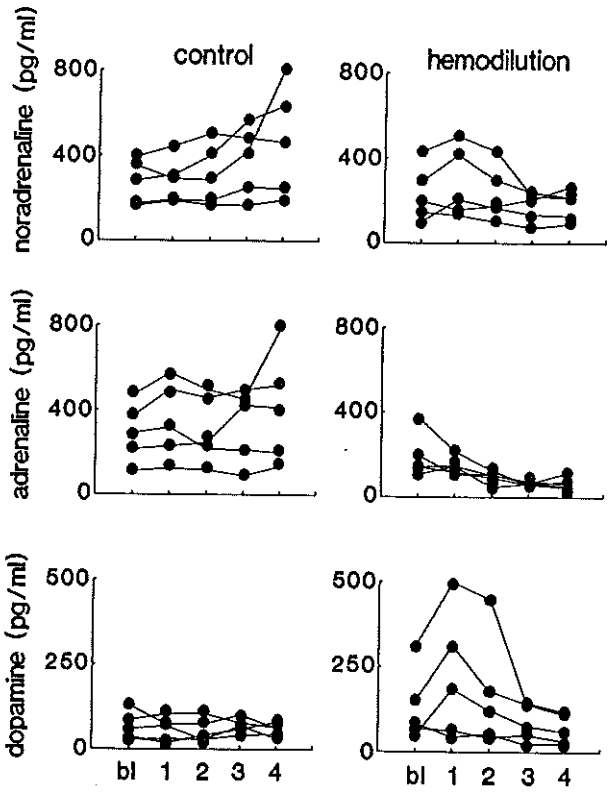

Figure 4. *Levels of catecholamines at 5 steps of hemodilution (see figure 1 legend) in 6 anesthetized pigs and at corresponding time points in controls.*

ARTERIAL BLOOD VISCOSITY

Arterial blood viscosity was markedly reduced after a total blood volume exchange of 50 ml/kg, which resulted in Newtonian behavior of the blood in the range of measured shear rates (Figure 5).

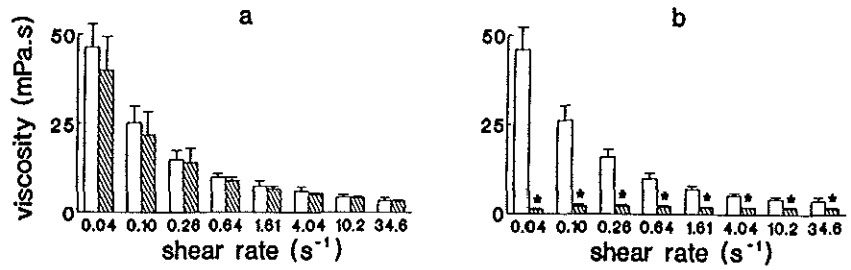

Figure 5. *Whole blood viscosity at different shear rates at baseline (A) and at 50 ml/kg body wt blood volume exchange (B) in anesthetized pigs (hatched columns) and at corresponding time points in controls (open columns).*

Discussion

The decrease in hemoglobin concentration during acute normovolemic hemodilution results in a reduction in the oxygen-carrying capacity of arterial blood. To maintain an adequate oxygen supply to tissues, this reduction can be compensated by increasing flow rates through augmentation or redistribution of cardiac output or by increasing the oxygen extraction ratio.

The baseline values of the hematocrit are in good agreement with those reported for conscious animals of the same age [13] but rather low compared with those reported for humans. Nevertheless, we were able to reduce hematocrit from 27.5 ± 0.7 to 9.3 ± 0.3%, a range we considered to be the most interesting for our study.

In Figure 6 the proportional change in cardiac output and heart rate is presented as proportional change in hematocrit (data from literature and this study). In anesthetized dogs the increase in cardiac output during hemodilution is mainly due to an increase in stroke volume [3,14,15]. Consistent with these studies, we observed in anesthetized pigs only a moderate increase in heart rate

with a more pronounced increase in cardiac output. In contrast to findings in anesthetized animals, hemodilution in conscious dogs produces an increase in cardiac output that is mainly attributable to an increase in heart rate [16,17]. In sedated pigs the increase in cardiac output was also mainly due to an increase in heart rate [18,19].

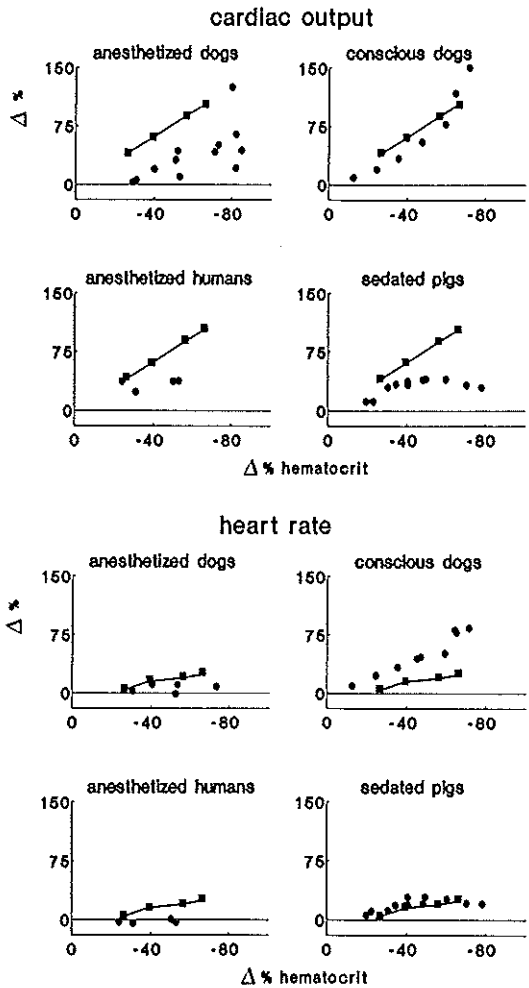

Figure 6. *Proportional change in cardiac output and heart rate as proportional change in hematocrit in anesthetized dogs [refs. 1, 2, 5, 6, 7, and 14], conscious dogs [refs. 9, 19, and 31], anesthetized humans [refs. 8, 13, and 25], and sedated pigs [refs. 28 and 29] compared with this study.*

Most studies in anesthetized dogs used pentobarbital-anesthetized dogs [3,5,14,15,20]. Pentobarbital, however, increases the accumulation of radioactive microspheres in the lungs, probably by opening systemic arteriovenous shunts, thereby reducing the nutritional cardiac output [21]. Thus an increase in cardiac output in pentobarbital-anesthetized dogs does not necessarily correlate with an increase in nutritional flow. In this study no increase in arteriovenous shunts was observed and, therefore, using an anesthetic regimen as in this study, each increase in cardiac output produces an increase in nutritional cardiac output.

As discussed before, in conscious dogs an increase in heart rate contributes more to the increase in cardiac output than elevation of stroke volume [6]. Several mechanisms have been proposed as being responsible for this increase in cardiac output, including a response to increased levels of circulating catecholamines. This hypothesis is based on the observation that carbon monoxide hypoxia, used as a model for anemic hypoxia, increases total catecholamine levels in anesthetized dogs [22]. Carbon monoxide hypoxia, however, not only decreases arterial oxygen content, as in anemic hypoxia, but also influences the shape of the oxygen dissociation curve and shifts it to the left, whereas in anemic hypoxia the oxygen dissociation curve maintains it form and, if altered, shifts to the right [23]. Moreover, blood viscosity is not influenced by carbon monoxide hypoxia but is decreased in anemic hypoxia. In this study plasma catecholamines did not increase during acute hemodilution but decreased, probably because of dilution of the blood. Baseline values of catecholamine levels in the present study are in good agreement with those reported for anesthetized pigs [24] and chronically instrumented conscious pigs [25]. Mersmann [24] reported epinephrine levels that were three times and norepinephrine and dopamine levels that were two times the highest values reported in the present study. Carlson et al. [20] showed that in conscious pigs hemorrhagic shock induced the greatest increase in catecholamine plasma levels in those animals with the highest baseline levels. These studies indicate that catecholamine release was not maximally stimulated during baseline conditions in the present study. It is therefore unlikely that normovolemic hemodilution caused increased catecholamine production. This finding is consistent with the observation that cardiac output increases in chronically adrenalectomized pentobarbital-anesthetized dogs, as well as in intact dogs, after severe acute exchange anemia [20]. Therefore, plasma catecholamines can probably be

excluded as one of the contributing factors, at least in anesthetized animals. From this study, however, it cannot be concluded that an increase in plasma catecholamines does not play a role in conscious or sedated animals.

The increase in stroke volume, as observed during hemodilution in anesthetized animals, has been attributed to several mechanisms: 1) increased venous return due to reduced whole blood viscosity with consequent increased left ventricular end-diastolic pressure [1], 2) facilitation of left ventricular emptying by reduced afterload (reduced blood viscosity and possibly vasodilatation) [3], and 3) increased myocardial contractility due to activation of cardiac sympathetic nerves [6].

The reduction in hematocrit, as observed in this study, produces a reduction in whole blood viscosity. The decrease in whole blood viscosity produces a decrease in the systemic vascular resistance and an increase in venous return, thereby increasing cardiac output [2]. The reduction in whole blood viscosity is most pronounced at low shear rates, indicating that the most vigorous effect of hemodilution has to be expected in the postcapillary area. Besides producing an increase in flow rate in the microcirculation, hemodilution also produces an improvement in flow in the microcirculation [26]. To what degree changes in blood viscosity measured in vitro affect vascular resistances cannot exactly be assessed, because in vivo viscosity is determined not only by hematocrit but also by vascular dimensions and flow velocity (shear rate) [3]. Flow velocity increases with progressive hemodilution, whereas vascular dimensions may be changed by either vasodilatation or vasoconstriction.

Besides the increase in cardiac output, to maintain oxygen supply to tissues during hemodilution, an increase in oxygen extraction ratio could compensate the decreased arterial oxygen content. In this study, however, because of increased flow rates, oxygen flux to most organs did not significantly decrease until the last step of hemodilution, and the systemic extraction ratio did not increase either. This is also reflected in mixed venous PO_2 and oxygen saturation, both of which remained constant.

Finally, besides the increase in total cardiac output and change in oxygen extraction ratio, a redistribution of regional flows may occur to meet the metabolic demands of different organs. This has already been studied in several models. Most studies used electromagnetic or Doppler flow probes and, in general, showed increases in flow to heart and brain with, in contrast to this study, little or no change in flow to other organs [15,17,27,28]. The

microsphere technique for determining regional flows during hemodilution has, to our knowledge, been used in three studies. In a study on hemodilution in conscious rats, increases in flow to heart and brain by 115 and 83%, respectively, and little or no change in flow to other organs (kidney, stomach, intestine, spleen, liver) were observed while cardiac output was not significantly increased [4]. In the other two studies using the microsphere technique, regional hemodynamics were investigated in pentobarbital-anesthetized dogs, but without the use of control animals to exclude the influence of the experimental model on hemodynamics and oxygen consumption [3,5]. Both groups reported a significant increase in flow to heart and brain while, in contrast to this study, flow to the spleen decreased and flow to other organs measured did not change or changed only slightly.

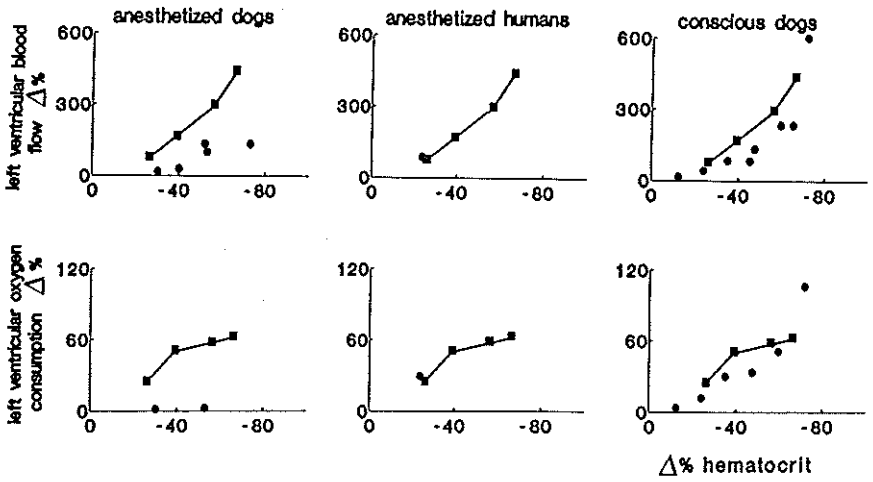

Figure 7. *Proportional change in left ventricular blood flow and oxygen consumption as proportional change in hematocrit in anesthetized dogs [refs. 5, 6, and 7], conscious dogs [ref 20], anesthetized humans [ref. 8], compared with this study.*

In this study, blood flow to the heart increased progressively with hemodilution. When comparing changes in all organs measured, the change in both absolute and relative flow was largest in the heart. Because the heart normally has a high oxygen extraction ratio, this can only be increased slightly when oxygen supply to the heart is decreased. As arterial oxygen content decreases with hemodilution, the main possibility for the heart to meet myocardial oxygen demand is by an increase in coronary flow, but myocardial oxygen consumption may also be influenced by hemodynamic changes during hemodilution and, therefore, an even greater increase in coronary flow might be needed.

The proportional change in left ventricular blood flow and left ventricular oxygen consumption, as found in the literature, is presented as proportional change in hematocrit in Figure 7. Moderate hemodilution in anesthetized humans and anesthetized dogs did not produce significant changes in left ventricular oxygen consumption [15,29]. In the dog study, however, cardiac output did not change significantly either. In conscious dogs hemodilution produced an increase in myocardial oxygen consumption which was met by both an increase in myocardial flow and an increase in oxygen extraction ratio [16]. However, because in conscious animals the increase in cardiac output is mainly due to an increase in heart rate, the effect of hemodilution on myocardial oxygen consumption in conscious animals is not comparable to the effect in anesthetized animals. In this study, myocardial oxygen consumption increased as hematocrit was decreased. However, left ventricular oxygen extraction ratio did not increase, because the increase in myocardial blood flow produced an increase in myocardial oxygen flux sufficient to compensate the increased myocardial oxygen demand.

Inasmuch as the subendocardial region of the myocardium is subjected to the greatest intramyocardial compressive forces, this region is perfused mainly during the diastole. To receive the same amount of blood as the subepicardial region, it has to have a lower vascular resistance, which causes the vasodilatory reserve capacity to become more limited and maximal coronary vasodilatation to occur first in the subendocardial region. In the present study, severe hemodilution in anesthetized pigs produced a redistribution of coronary flow away from the subendocardial muscle with the last step of hemodilution. However, as discussed before, oxygen flux to the left ventricle (endo- en epicardium) increased, whereas the left ventricular oxygen extraction ratio did

not, despite the increase in left ventricular oxygen consumption.

Another organ sensitive to a decrease in tissue oxygenation is the brain. Redistribution of the cardiac output resulted in an increase in absolute flow in the brain with every step of hemodilution, whereas relative flow did not increase until the last two steps. This caused no significant change in oxygen flux to the brain. With the increase in coronary and cerebral flow, one would expect relative flow to organs less in need of a constant oxygen supply (skin, muscle, liver, spleen, stomach, intestine, adrenals, and kidneys) to decrease. However, relative flow to liver (via hepatic artery), stomach, intestine, adrenals and kidneys and total liver flow (estimated by summation of flow via hepatic artery and flow in intestine, spleen and stomach) remained constant, while relative flow to the spleen decreased only at the lower levels of the hematocrit range.

The observed and discussed redistribution of cardiac output could be regulated by the autonomic nervous system, humoral substances, and a variety of local factors [4]. In the present study, circulating catecholamines have been excluded as a regulating factor during hemodilution in anesthetized pigs. The redistribution of renal flow from outer to inner cortex, as shown by the increase in inner-to-outer ratio, may suggest an increased renin-angiotensin activity, but may also resemble an intrarenal flow redistribution produced by enhanced sympathetic activity [5]. It has been suggested that the main function of this vasoconstrictor response is to ensure oxygen delivery to the brain during reduced total oxygen transport, and therefore generalized vasoconstriction should be caused everywhere except in the brain [30]. This vasoconstriction can be overcome by local factors through the production of a vasoactive metabolite or through a direct effect of the oxygen tension on vascular tissue, especially in an active organ with a high metabolic rate, such as the heart [14]. These factors could help explain the redistribution of cardiac output in favor of the heart and brain during hemodilution.

In conclusion, 1) during acute isovolemic hemodilution in anesthetized pigs, cardiac output increased significantly, mainly due to an increase in stroke volume; 2) in contrast to other reports, flow increased in all organs with, as reported by others, the largest increase in heart and brain; 3) unlike findings in dogs, oxygen flux to all organs remained constant, except in spleen and liver (via artery fraction); 4) left ventricular oxygen consumption increased, but with no increase in myocardial oxygen extraction ratio; systemic oxygen consumption remained constant; and 5) circulating catecholamines were excluded as a

regulatory mechanism of hemodynamics and regional flow patterns, at least in this experimental model.

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REGIONAL CARDIAC HEMODYNAMICS AND OXYGENATION DURING ISOVOLEMIC HEMODILUTION IN PIGS

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Introduction

Hemodilution causes a drop in hematocrit, thereby lowering the oxygen carrying capacity of blood, necessitating an increase in flow or an augmented oxygen extraction by the tissues to meet their metabolic demands. Under normal conditions the myocardial oxygen extraction is already high and the capacity to increase is limited. In the heart the decrease in arterial oxygen content during hemodilution is therefore is mainly compensated by an increase in coronary flow. This increase in flow can be achieved by both reduction of blood viscosity and coronary vasodilatation. The hemodynamic changes during hemodilution may increase myocardial oxygen consumption and, therefore, an even greater increase in coronary flow might be needed.

In order to establish whether the subendocardium, the most vulnerable of the myocardial layers, is still adequately perfused during isovolemic hemodilution we evaluated the effect of stepwise normovolemic hemodilution on regional myocardial blood flows and oxygen fluxes, and on myocardial oxygen consumption in anesthetized pigs. The pig was selected because the responses of pigs under several conditions of stress are similar to those in humans.

Material and methods

Twelve pigs (28 ± 1 kg) were sedated with midazolam (0.3 mg/kg i.m.) and ketamine (10 mg/kg i.m.) and subsequently anesthetized with thiopental (5 mg/kg i.v.). Anesthesia was maintained with fentanyl (12.5 μg/kg bolus followed by 12.5 μg/kg/h) and midazolam (0.45 mg/kg bolus followed by 0.45 mg/kg/h), while muscle relaxation was achieved with pancuronium bromide (0.1 mg/kg bolus followed by 0.3 mg/kg/h).

Catheters were positioned in the aortic arch, pulmonary artery, descending aorta and left ventricle. A midsternal thoracotomy was performed and an electromagnetic flow probe placed around the ascending aorta. The left and right atria and the great cardiac vein were cannulated.

Systemic hemodynamics, blood gasses (OSM2 Radiometer, Copenhagen) and hematocrit were measured at baseline and after each step of hemodilution. In control animals measurements were made at corresponding time points.

Regional blood flows of the heart were measured using the radioactive microsphere technique [1].

Systemic and myocardial oxygen fluxes and consumptions were calculated.

In six pigs hemodilution was induced by exchanging blood with iso-oncotic dextran 40, 50 g/l in 0.9% saline (Isodex®). Stepwise hemodilution was induced by two steps of 10 ml/kg followed by two steps of 15 ml/kg. Six other animals served as controls.

All data are presented as arithmetic means ± SE of mean.

Results

Hemodilution produced a doubling of the cardiac output, primarily due to an increase in stroke volume with only a moderate increase in heart rate. The mean arterial pressure was maintained until the last step of hemodilution because of systemic vasodilatation (Table 1) [2]. Mixed venous oxygen tension and saturation decreased slightly, resulting in an increase in systemic oxygen extraction ratio. Total body oxygen consumption was well maintained (Table 2).

Total myocardial blood flow increased 420%. This increase was not homogeneously distributed. Blood flow to right and left atria increased by up to 120 ± 20% and 390 ± 70%, respectively, while oxygen fluxes in both atria were maintained. Blood flow to right and left ventricle increased by up to 510 ± 55% and 440 ± 60%, respectively, resulting in an increase in oxygen fluxes to both ventricles.

Despite the increase in left ventricular myocardial oxygen consumption, coronary venous saturation after the last step of hemodilution was slightly increased, indicating a decreased left ventricular oxygen extraction ratio.

The increase in left ventricular blood flow was more pronounced in subepicardial layers than in subendocardial layers. Therefore, the subendocardial-subepicardial blood flow ratio decreased from 1.22 ± 0.03 to 1.06 ± 0.07 ($P < 0.05$) (Table 3).

Discussion

Hemodilution produces a reduction in the oxygen carrying capacity of the

Table 1. *Systemic and pulmonary effects of hemodilution in anesthetized pigs.*

Exchange	C	0	0	0	0	0
blood volume	H	0	10	20	35	50
Hct	C	27.6 ± 0.9	27.2 ± 1.2	26.2 ± 0.9	25.3 ± 0.9	26.2 ± 0.7
	H	27.5 ± 0.7	20.3 ± 0.4*	16.7 ± 0.2*	12.2 ± 0.5*	9.3 ± 0.3*
CO	C	2.83 ± 0.14	2.85 ± 0.11	2.87 ± 0.14	2.98 ± 0.13	2.92 ± 0.12
	H	2.67 ± 0.23	3.75 ± 0.26*	4.26 ± 0.21*	5.02 ± 0.17*	5.42 ± 0.18*
HR	C	142 ± 7	146 ± 7	152 ± 10	152 ± 10	153 ± 14
	H	113 ± 7+	118 ± 7	130 ± 3	134 ± 5	140 ± 4
SV	C	19.9 ± 0.4	19.4 ± 0.7	19.2 ± 1.4	18.8 ± 2.1	19.8 ± 2.0
	H	22.8 ± 2.9	29.9 ± 2.9*	30.5 ± 2.5*	34.3 ± 2.7*	34.9 ± 2.2*
LVEDP	C	4.5 ± 0.5	4.4 ± 0.6	4.3 ± 0.5	4.8 ± 0.5	4.8 ± 0.6
	H	4.5 ± 0.7	5.8 ± 0.8*	5.7 ± 0.8*	7.3 ± 0.8*	6.8 ± 0.7*
$LvdP/dt_{max}$	C	4290 ± 270	4200 ± 200	4420 ± 270	4460 ± 390	4410 ± 570
	H	3370 ± 220+	3680 ± 290*	3980 ± 220	4000 ± 310	4050 ± 480
MAP	C	108 ± 3	180 ± 3	111 ± 3	114 ± 4	113 ± 7
	H	109 ± 8	110 ± 6	112 ± 7	103 ± 6	90 ± 5*
SVR	C	37.9 ± 1.8	36.7 ± 1.3	38.5 ± 1.8	37.1 ± 2.5	38.4 ± 2.5
	H	39.0 ± 4.9	32.5 ± 3.3*	27.7 ± 2.4*	21.7 ± 1.3*	17.6 ± 1.1*
PAP	C	18.0 ± 1.6	18.1 ± 1.8	18.7 ± 1.6	19.8 ± 1.3	20.9 ± 1.7
	H	19.5 ± 1.3	21.8 ± 1.9	22.9 ± 1.5	24.2 ± 2.0	24.5 ± 2.0
PVR	C	5.0 ± 0.8	4.8 ± 0.9	5.0 ± 0.7	5.1 ± 0.6	5.6 ± 0.8
	H	6.8 ± 1.1	5.1 ± 0.7	4.7 ± 0.5	3.9 ± 0.5	3.6 ± 0.4

Blood volume exchange in ml/kg; C = control (n=6); H = isovolemic hemodilution (n=6); Hct = hematocrit (%); CO = cardiac output (l/min); HR = heart rate (beats/min); SV = stroke volume (ml); LVEDP = left ventricular end-diastolic pressure (mmHg); $LVdP/dt_{max}$ = maximum rise of left ventricular pressure (mmHg/sec); MAP = mean arterial blood pressure (mmHg); SVR = systemic vascular resistance (mmHg/l/min); PAP = pulmonary arterial blood pressure (mmHg); PVR = pulmonary vascular resistance (mmHg/l/min). Data are mean ± SEM; * change from baseline significantly different ($P < 0.05$) from change in the control animals. + significant difference in baseline values ($P < 0.05$). From: van Woerkens et al. [12].

Table 2. *Systemic and left ventricular oxygenation during hemodilution in anesthetized pigs.*

Hct	C	26.7 ± 0.9	27.2 ± 1.2	26.2 ± 0.9	25.3 ± 0.9	26.2 ± 0.7
	H	27.5 ± 0.7	20.3 ± 0.4*	16.7 ± 0.2*	12.2 ± 0.5*	9.3 ± 0.3*
PaO_2	C	139 ± 16	138 ± 17	141 ± 15	139 ± 17	135 ± 22
	H	166 ± 6	174 ± 11	164 ± 3	164 ± 9	158 ± 8
SaO_2	C	97 ± 0.3	97 ± 1.1	97 ± 0.7	96 ± 1.2	96 ± 1.6
	H	97 ± 0.3	97 ± 0.3	96 ± 0.3	95 ± 0.6	94 ± 0.5
PvO_2	C	36 ± 4	35 ± 3	34 ± 4	35 ± 5	35 ± 6
	H	38 ± 3	39 ± 4	38 ± 3	35 ± 3	31 ± 3*
SvO_2	C	56 ± 7	55 ± 8	53 ± 8	52 ± 1	52 ± 13
	H	57 ± 6	57 ± 7	52 ± 5	47 ± 6*	37 ± 7*
$VO_{2\ syst}$	C	141 ± 10	150 ± 11	155 ± 11	163 ± 13	163 ± 16
	H	128 ± 8	135 ± 9	144 ± 8	147 ± 8	141 ± 5
ER_{syst}	C	0.40 ± 0.03	0.42 ± 0.03	0.45 ± 0.03	0.46 ± 0.04	0.46 ± 0.05
	H	0.41 ± 0.03	0.42 ± 0.03	0.47 ± 0.03	0.54 ± 0.03*	0.61 ± 0.02
$PcvO_2$	C	21 ± 1	20 ± 1	21 ± 1	20 ± 1	20 ± 1
	H	24 ± 1	24 ± 1	25 ± 1	28 ± 1	30 ± 2
$ScvO_2$	C	23 ± 2	20 ± 1	23 ± 1	18 ± 2	21 ± 1
	H	21 ± 2	22 ± 1	23 ± 1	26 ± 3	28 ± 2
$V_{LV}O_2$	C	14.8 ± 0.8	12.9 ± 2.5	15.1 ± 0.8	11.2 ± 3.4	15.9 ± 1.7
	H	11.7 ± 0.7+	14.4 ± 0.7*	17.8 ± 0.7*	20.3 ± 0.6*	24.1 ± 0.5*
ER_{LV}	C	0.75 ± 0.02	0.78 ± 0.01	0.76 ± 0.01	0.82 ± 0.02	0.77 ± 0.01
	H	0.77 ± 0.02	0.77 ± 0.01	0.75 ± 0.02	0.72 ± 0.02*	0.70 ± 0.02*

C = control (n = 6); H = isovolemic hemodilution (n = 6); Hct = hematocrit (%); PaO_2 = arterial oxygen tension (mmHg); SaO_2 = arterial oxygen saturation (%); PvO_2 = mixed venous oxygen tension (mmHg); SvO_2 = mixed venous oxygen saturation (%); $VO_{2\ syst}$ = systemic oxygen consumption (ml/min); ER_{syst} = systemic extraction ratio; $PcvO_2$ = coronary venous oxygen tension (mmHg); $ScvO_2$ = coronary venous oxygen saturation (%); $V_{LV}O_2$ = left ventricular oxygen consumption (ml/min); ER_{LV} = left ventricular extraction ratio. Data are mean ± SEM; * change from baseline significantly different ($P < 0.05$) from the change in the control animals. + significant difference in baseline values ($P < 0.05$). From: van Woerkens et al [12].

Table 3. *Regional myocardial blood flows (ml/min/100g) and oxygen fluxes (ml/min/100g).*

Regional myocardial blood flows						
RA	C	163 ± 25	148 ± 23	153 ± 21	142 ± 29	142 ± 27
	H	157 ± 29	197 ± 34*	234 ± 45*	289 ± 51*	330 ± 37*
LA	C	82 ± 6	81 ± 9	105 ± 12	100 ± 19	85 ± 12
	H	75 ± 18	106 ± 19*	154 ± 20*	216 ± 35*	322 ± 34*
RV	C	124 ± 8	119 ± 11	127 ± 11	130 ± 13	132 ± 18
	H	104 ± 6	169 ± 11*	271 ± 16*	438 ± 54*	631 ± 74*
LV	C	170 ± 12	171 ± 15	175 ± 14	185 ± 22	180 ± 25
	H	130 ± 5+	221 ± 11*	341 ± 33*	505 ± 57*	690 ± 72*
LV endo	C	192 ± 13	185 ± 19	194 ± 17	201 ± 26	207 ± 29
	H	145 ± 6+	254 ± 21*	390 ± 44*	567 ± 79*	717 ± 94*
LV epi	C	154 ± 1	158 ± 14	160 ± 13	174 ± 20	161 ± 23
	H	119 ± 4+	201 ± 8*	314 ± 30*	472 ± 49*	670 ± 67*
Regional myocardial oxygen fluxes						
RA	C	18.8 ± 2.3	17.2 ± 2.0	17.6 ± 1.9	15.3 ± 2.8	16.3 ± 2.6
	H	19.3 ± 3.5	18.1 ± 3.0	17.3 ± 3.0	15.7 ± 2.1	14.0 ± 1.2
LA	C	9.5 ± 0.6	9.5 ± 0.8	12.1 ± 1.2	10.5 ± 1.6	9.8 ± 1.1
	H	9.3 ± 2.2	9.8 ± 1.8	11.4 ± 1.3	11.9 ± 1.6	13.0 ± 1.1
RV	C	14.5 ± 0.7	13.9 ± 0.8	14.8 ± 1.1	13.9 ± 1.1	15.1 ± 1.6
	H	12.7 ± 0.8	15.5 ± 1.1*	20.1 ± 1.0*	24.0 ± 2.0*	26.6 ± 1.9*
LV	C	19.8 ± 0.8	20.0 ± 1.3	20.2 ± 1.1	19.8 ± 1.8	20.7 ± 2.3
	H	15.9 ± 0.6+	20.2 ± 1.1*	25.3 ± 2.2*	27.8 ± 2.5*	29.4 ± 2.6*
LV endo	C	22.4 ± 1.1	21.7 ± 1.8	22.5 ± 1.6	21.5 ± 2.2	23.8 ± 2.6
	H	17.7 ± 0.7+	23.2 ± 1.8*	28.9 ± 2.9*	31.2 ± 3.6*	30.6 ± 3.6*
LVepi	C	17.9 ± 0.8	18.4 ± 1.1	18.5 ± 1.1	18.6 ± 1.6	18.5 ± 2.0
	H	14.6 ± 0.5+	18.4 ± 0.8*	23.3 ± 1.9*	26.0 ± 2.0*	28.4 ± 2.3*
endo/epi	C	1.25 ± 0.05	1.17 ± 0.06	1.21 ± 0.05	1.15 ± 0.03	1.28 ± 0.02
	H	1.22 ± 0.03	1.25 ± 0.06	1.23 ± 0.03	1.18 ± 0.05	1.06 ± 0.07

C = control (n=6); H = isovolemic hemodilution (n=6); RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle; LV endo = left ventricular endocardial region; LV epi = left ventricular epicardial region; endo/epi = endocardial epicardial flow ratio; Data are mean ± SEM; * change from baseline significantly different ($P < 0.05$) from change in the control animals; + significant difference in baseline values ($P < 0.05$). From: van Woerkens et al [12].

blood. In this study this is compensated for mainly by an increase in cardiac output but, at the last step of hemodilution, also by an increased systemic oxygen extraction ratio.

In order to meet the metabolic demands of different organs a redistribution of the cardiac output can occur. Hemodilution and its effects on myocardial blood flow and oxygen delivery has been studied in anesthetized dogs [3-7]. The decrease in arterial oxygen content is counteracted by an increase in cardiac output mainly due to an increase in stroke volume. In the study by Geha [6] no increase in cardiac output was observed during moderate hemodilution. However filling pressures did not change either, probably indicating hypovolemia [8].

Left ventricular oxygen consumption was maintained primarily by an increase in left ventricular blood flow, but an additional increase in left ventricular oxygen extraction ratio was observed. Due to the increase in coronary flow the vasodilatory reserve capacity was significantly reduced. In most studies the increased myocardial blood flow was sufficient to maintain regional myocardial oxygen supply [4,5,7].

Brazier et al. [3] estimated the myocardial oxygen consumption by the tension time index, which did not change significantly during moderate and severe hemodilution. The myocardial oxygen demand to supply ratio, however, fell with moderate hemodilution and decreased further during severe hemodilution. The endocardial/epicardial flow ratio decreased as the hemoglobin level fell below 5 g% and the augmented cardiac output could not be sustained.

Reduction of hematocrit to half the baseline value did not change coronary sinus oxygen tension in one study [5], while in another study coronary venous oxygen saturation even increased during hemodilution, despite the slight increase in myocardial oxygen consumption [7].

Stepwise hemodilution in anesthetized baboons produced an increase in left ventricular flow which was able to maintain both left ventricular oxygen delivery and left ventricular oxygen consumption until hematocrit levels of 6%. No increase in left ventricular oxygen consumption was observed. At a hematocrit of 10% maximal coronary vasodilatation had occurred and a further decrement in oxygen supply led to myocardial anaerobic metabolism as shown by left ventricular lactate production [9].

Moderate decreases in hematocrit levels in anesthetized humans (hematocrit reduced from 38% to 28%) also produces an increase in myocardial blood flow with a slight but not significant increase in myocardial oxygen

consumption. Coronary sinus oxygen tension did not change. The increase in cardiac output was associated with an increase in external cardiac work solely due to an increase in stroke volume. This can be obtained without a substantial rise in need of energy [10]. In conscious dogs the elevated cardiac output during hemodilution is mainly due to an increase in heart rate [11,12]. Myocardial oxygen consumption increases, necessitating an additional increase in myocardial blood flow in these studies in conscious dogs. During exercise myocardial oxygen consumption increases even further. The increased myocardial oxygen consumption was met both by an elevated coronary blood flow and an increased oxygen extraction ratio, accompanied by a decrease in coronary sinus oxygen saturation. The peak reactive hyperemic flow decreased under hemodilution, while at rest dilatory capacity was left even at a hematocrit of 10-15%. At moderate levels of exercise the dilatory capacity was exhausted at a hematocrit of 20-25% [12]. Reduction of hematocrit to 13% produced an increase in left ventricular blood flow in conscious dogs which is mainly distributed to the epicardium, indicating that the coronary reserve in subendocardium is almost completely exhausted [12].

In the present study an increase in myocardial blood flow of 420% with a doubling of the cardiac output mainly due to an increase in stroke volume was observed. In contrast to the studies discussed, in this study hemodilution resulted in a doubling of left ventricular oxygen consumption. However the increase in myocardial blood flow produced a rise in left ventricular oxygen flux sufficient to meet the elevated left ventricular oxygen consumption.

The increase in left ventricular blood flow exceeded the increase in cardiac output. Since the subendocardial region is subjected to the greatest intramyocardial forces of the myocardium, this region is perfused mainly during diastole. Therefore, it has to have a lower vascular resistance in order to receive the same amount of blood flow as the subepicardial region. The vasodilatatory reserve capacity in the subendocardial layers is therefore lower and maximal coronary vasodilatation occurs. During severe hemodilution a redistribution of the coronary flow away from the subendocardial layers was observed in the present study. When maximal vasodilatation and maximal oxygen extraction have occurred, a further increase in oxygen demand will lead to myocardial ischemia and the heart will not be able to sustain the increased cardiac output. This is more likely to happen when myocardial oxygen consumption is increased

(e.g. hypertension, valvular heart disease) or when myocardial oxygen delivery is further reduced. Myocardial oxygen delivery can be reduced by a reduction of the arterial oxygen content (hypoxia), a shortening of the diastolic filling period (tachycardia) or a lowered coronary driving pressure. Maximal coronary vasodilatation is compromised when coronary artery disease is present.

In conclusion hemodilution in anesthetized animals produces an increase in myocardial blood flow sufficient to meet the myocardial oxygen consumption. However, at low levels of hematocrit the endocardial/epicardial flow ratio is decreased and the vasodilatory reserve capacity of the coronary arteries is exhausted in the subendocardium. This limits the degree of hemodilution which can be reached. Additional caution is necessary if factors elevating the myocardial oxygen consumption or further reducing the (maximal) myocardial oxygen delivery are present.

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Chapter 4

BLOOD GAS ANALYSIS OF MIXED VENOUS BLOOD DURING NORMOXIC ACUTE ISOVOLEMIC HEMODILUTION IN PIGS

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Summary

Mixed venous oxygen saturation of hemoglobin (SvO_2) and mixed venous oxygen tension (PvO_2) may reflect the overall balance between oxygen consumption and delivery. Because of the potential value of monitoring SvO_2 and PvO_2 as indications of the state of tissue oxygenation, the aim of this study was to determine, during normoxic acute isovolemic hemodilution in pigs, the critical PvO_2, critical SvO_2, and critical oxygen extraction ratio (ER) at which oxygen uptake starts to decline during further induced hemodilution.

During stepwise induced isovolemic hemodilution, a gradual decline in SvO_2 and PvO_2 was observed in all animals. The mean ± SD of the critical PvO_2 of six animals was 32.3 ± 3.1 mmHg. The mean ± SD of the critical SvO_2 was 44.2 ± 7.9 %. The ER increased gradually. At an ER of 0.57 ± 0.08, oxygen uptake started to decline. A significant correlation was found between changes in SvO_2 and changes in ER. The degree of hemodilution were accompanied by an increase in cardiac index, pulmonary wedge pressure, heart rate, and left ventricular stroke work index. Only a slight decrease in systemic vascular resistance was observed. We conclude that measurements of PvO_2 and SvO_2 can be used as indicators of the critical point of hemodilution and that the SvO_2 during hemodilution reflects the overall balance between oxygen uptake and oxygen delivery, confirmed by the strong correlation found between SvO_2 and oxygen extraction ration.

Introduction

The mixed venous oxygen saturation of hemoglobin (SvO_2) and the mixed venous oxygen tension (PvO_2) reflect, under certain circumstances, the state of tissue oxygenation. Changes in cardiac output (CO), arterial oxygen content, and oxygen uptake (VO_2) influence these parameters [1]. To our knowledge, there are only two reports of PvO_2 studies during hemodilution. In one, during hypovolemia produced in dogs by removal of blood, the critical PvO_2 at which VO_2 began to decrease was found to be 29.9 mmHg [2]. In the other study, the critical PvO_2 in dogs during isovolemic induced anemic hypoxia was 44.8 torr [3]. In both studies, the SvO_2 at the point at which PvO_2 had so decreased that

VO_2 started to decrease during hemodilution is not mentioned. In several clinical situations hemodilution is beneficial, as it reduces the risks associated with the transfusion of homologous blood [4-7]. Because of the possible value of monitoring SvO_2 and PvO_2 in the evaluation of tissue oxygenation during hemodilution, the aim of this study was to determine, during normoxic acute isovolemic hemodilution in sedated paralyzed pigs, the critical PvO_2 , the critical SvO_2 , and the critical oxygen extraction ratio (ER) at which VO_2 starts to decline with further hemodilution.

Methods

This protocol was approved by the Animal Care and Use Committee of the Erasmus University, Rotterdam, The Netherlands.

Six male Yorkshire pigs (10.2 - 12.0 kg) were used. After giving 0.3 mg/kg midazolam intramuscular, a catheter was introduced into one of the ear veins and the trachea was intubated. Throughout the experiment procedure sedation was maintained with a continuous infusion of 0.2 $mg.kg^{-1}.h^{-1}$ midazolam. After intubation of the trachea 0.1 mg/kg pancuronium was given intravenously with an additional continuous infusion of 0.3 $mg.kg^{-1}.h^{-1}$. The pigs' lungs were then ventilated with air, using tidal volumes adequate to maintain end-tidal CO_2 between 4.5 and 5.0 kPa (33 and 38 mmHg). Catheters were placed in the left femoral artery , the right femoral vein, and the right femoral artery (the latter for arterial blood pressure monitoring). Via the left femoral vein a thermodilution catheter (Swan Ganz 93A-095-7F) was introduced into a pulmonary artery. In all animals the injectate port was located in the right atrium as proven on postmortem examination. The urinary bladder was catheterized. Body temperature (blood temperature) was measured with the thermistor electrode of the thermodilution catheter and was kept stable throughout the procedure by means of a heating pad. After all preparations were completed, the sedated paralyzed animals were ventilated until blood gas tensions, pH, and hemodynamic parameters were stabilized (average time 30 min). Pulse rate, arterial blood pressures, pulmonary arterial pressures, and the right atrial pressure were monitored continuously (Horizon 2000, Mennen Medical, Israel). After the stabilization period baseline measurements were made, including heart

rate, mean arterial blood pressure, systolic pulmonary arterial pressure, diastolic pulmonary arterial pressure, pulmonary wedge pressure, right atrial pressure, and CO. In addition, arterial and mixed venous blood samples were taken for measurements of PO_2 , pH and PCO_2 (ABL 330, Radiometer, Copenhagen) and for the measurement of hemoglobin and oxyhemoglobin content (Spectrophotometer OSM3, Radiometer, Copenhagen). Oxygen flux (O_2flux) was calculated as the product of arterial oxygen content and CO. Oxygen uptake by the tissue (VO_2) was defined as the product of CO and the arteriovenous oxygen content difference. The ER was calculated as VO_2 divided by O_2 flux.

The first step of isovolemic hemodilution with isooncotic dextran 40, 50 g/L in 0.9 % salt solution (Isodex, NPBI, The Netherlands) began after baseline measurements were completed. The dextran solution (warmed to 38°C) was instilled slowly into the right femoral vein at the same time and at the same rate that blood was removed from the left femoral artery. Stepwise isovolemic hemodilution was induced by steps of 10 mL/kg until a total exchange of 40 mL/kg had been reached and afterwards by steps of 5 mL/kg. New sets of data were obtained after each step of isovolemic hemodilution when blood gas tension, pH, and hemodynamic parameters were stabilized again (average time 5 min). The time between each step of blood exchange was 15 min.

To establish the mean critical $PvO_2 \pm SD$, VO_2 was plotted against the PvO_2 in each animal. The critical point of PvO_2 after which VO_2 gradually decreased was analytically chosen from the intersection of the two best-fit regression lines, determined by a least sum of squares techniques as described by Schumacker et al. [2]. The mean $\pm$ SD of the PvO_2 at this critical point was defined as the critical $PvO_2 \pm SD$. The critical SvO_2 and critical ER were also determined by the least sum of squares technique.

All values are expressed as mean $\pm$ SD. In each figure the same animals are presented in the same order. The accepted probability for a statistical significance between means was $P < 0.05$. The statistical significance of difference was tested by a Wilcoxon signed-rank test. Regression lines were estimated by methods of least squares. For regression analysis, the Spearman rank correlation coefficient was used.

Table 1 *Hemodynamic responses after each step of blood exchange*

Blood exchange (mL/kg body wt)	MAP (mmHg)	MPAP (mmHg)	PWP (mmHg)	HR (beats/min)	CI ($L.min^{-1}.m^{-2}$)	LVSWI ($g.cm^{-1}.m^{-2}$)	SVR ($dyne.s^{-1}.cm^{-5}$)	PVR ($dyne.s^{-1}.cm^{-5}$)	Hct (%)
0 (baseline)	96 ±13	17.7±4.5	7.8±6.6	167±20	5.1±1.0	34.0±8.9	3538±1101	482±163	30.0±3.6
10	98 ±10	18.5±2.6	8.8±7.0	185±33	5.7±0.7 *	35.1±8.4	3196±987 *	429±63	23.7±2.2 *
20	109 ±14	22.0±5.2	10.3±8.8	196±27 *	6.8±1.1 *	44.9±12.2 *	2945±722 *	424±105	20.1±1.8 *
30	114 ±9 *	23.3±5.1	9.0±9.5	213±15 *	6.8±1.1 *	46.7±13.3 *	3141±1037	410±81	18.3±2.2 *
40	117 ±9 *	23.8±3.6	9.7±8.2 *	216±15 *	7.2±0.9 *	47.3±14.4 *	3037±937	466±223	15.6±1.5 *
50	117 ±8 *	24.2±3.1 *	10.5±6.9 *	210±15 *	7.3±0.8 *	48.9±16.6 *	3049±994 *	490±248	13.2±0.8 *
60	116 ±13 *	23.5±3.8 *	10.2±6.5 *	208±18 *	7.1±0.6 *	47.7±14.7 *	3147±1123	468±211	12.0±1.1 *
65	115 ±10 *	23.3±3.9	10.7±6.2 *	206±19	7.1±0.8 *	47.1±15.3 *	3087±964	428±162	10.8±0.8 *
70	116 ±11 *	23.3±4.4	11.0±6.6 *	201±23	7.1±0.9 *	49.6±17.3 *	3130±1069	427±191	9.8±0.6 *
75	114 ±11 *	23.3±4.6	11.0±6.5 *	204±16	7.0±1.0 *	46.1±15.1 *	3095±963	429±141	9.7±0.8 *
80	111 ±12	22.2±4.2	9.8±6.6 *	202±17	6.8±0.8 *	47.3±14.2 *	3132±1079	445±205	9.0±1.2 *
85	108 ±12	22.5±3.9	10.5±6.9 *	201±19	6.8±0.8 *	44.4±17.1	3008±1024 *	435±175	8.4±0.8 *
90	104 ±9	21.5±3.8	9.8±5.4 *	205±20	6.7±0.7 *	40.7±15.1	2960±1130 *	416±191	7.8±0.9 *
95	98 ±8	21.0±2.9	10.5±5.9 *	197±20	6.6±0.7 *	38.2±10.2	2724±857 *	389±111	6.9±0.7 *
100	91 ±10	20.7±3.9	11.0±5.2 *	200±18	6.6±0.9 *	34.4±13.1	2580±807 *	364±105 *	6.6±0.8 *

MAP, mean arterial blood pressure; MPAP, mean pulmonary artery pressure; PWP, pulmonary wedge pressure; HR heart rate; CI, cardiac index; LVSWI, left ventricular stroke work index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; Hct, hematocrit.

Values are mean ± SD (n = 6).

* $P < 0.05$ in comparison to baseline.

Results

Hemodynamic Responses

During hemodilution there was a significant increase in cardiac index (CI) of up to > 40% (Table 1). The CI did not return to baseline values. Even at a blood exchange of 100 mL/kg the CI increased 30% above baseline values; at the same time total peripheral vascular resistance (SVR) decreased only slightly (by 10-15%). Left ventricular stroke work index increased 45%, accompanied by an increase of 30% in heart rate. A gradual increase in pulmonary wedge pressure up to 40% above baseline values was observed, presumably due to an increase in venous return to the heart.

In each animal, there was a gradual decline in PvO_2 during stepwise induced hemodilution. When VO_2 was plotted against PvO_2 in each animal, the critical PvO_2 at which VO_2 starts to decline could be established from the intersection of the two best-fit regression lines (Figure 1). The mean of the critical PvO_2 of the six animals was 32.3 ± 3.1 mmHg. The mean critical SvO_2 was 44.2 ± 7.9 (Figure 2). Plotting the VO_2 against the ER in each animal gives a critical ER value of 0.57 ± 0.08 (Figure 3). During hemodilution a direct correlation was found between the SvO_2 and the critical ER value (Figure 4). Hemodilution up to a 100 mL/kg exchange of blood volume did not significantly alter the arterial pH, PO_2, or PCO_2. The baseline pH in the mixed venous blood was 7.41 ± 0.02; with 100 mL/kg blood exchange it was 7.35 ± 0.05. Levels of mixed venous pH, PvO_2, SvO_2, O_2flux, VO_2, and the ER after each step of induced hemodilution are summarized in Table 2.

Discussion

Yorkshire pigs were chosen for this study because the pig is so closely related to the human, anatomically and physiologically. The cardiovascular system and metabolism of pigs and humans show similarities with respect to the size and distribution of coronary vessels, blood pressure, heart rate, CI, regional distribution of CO, and maximum oxygen consumption [8-10].

Continuous monitoring of SvO_2 has been used as an indicator of the effects of various therapeutic maneuvers in critically ill patients, as a predictor in

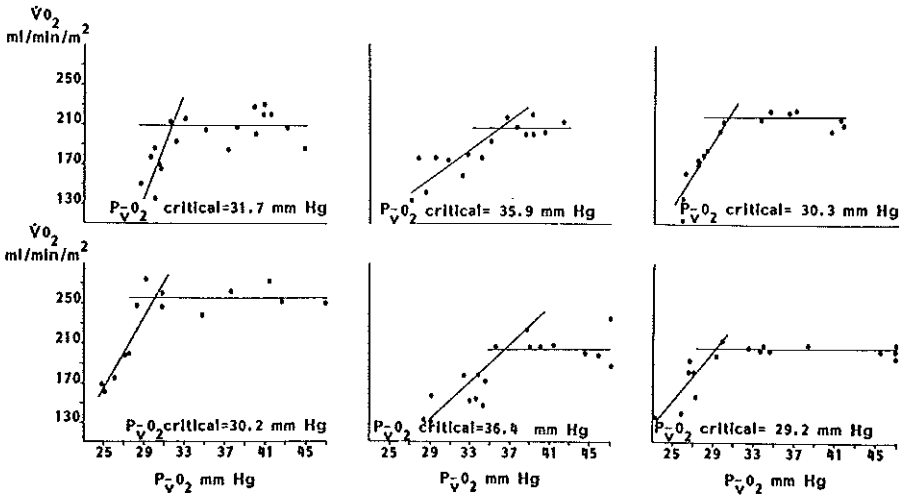

Fig 1. *VO_2 plotted against PvO_2 in each animal. The mean PvO_2 critical was 32.3 ± 3.1 mmHg.*

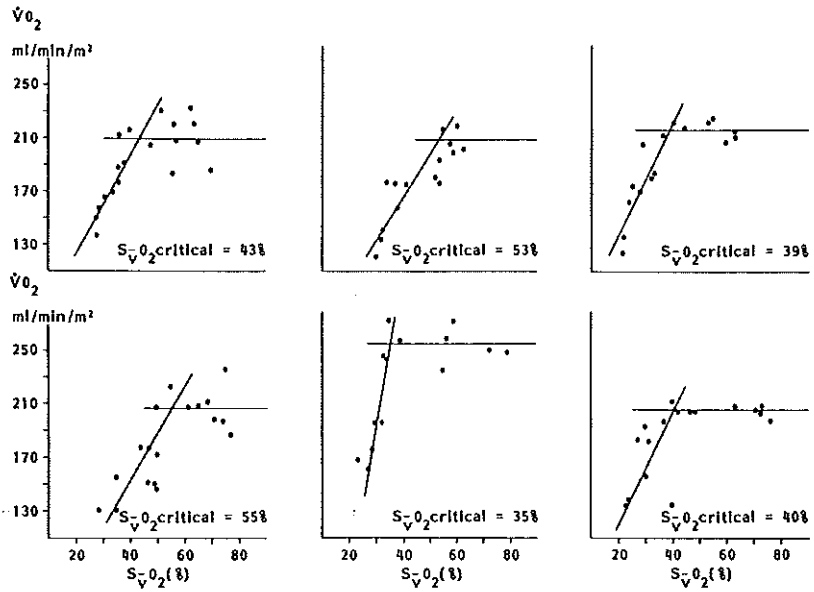

Fig 2. *VO_2 plotted against SvO_2 in each animal. The mean SvO_2 critical was 44.2 ± 7.9%.*

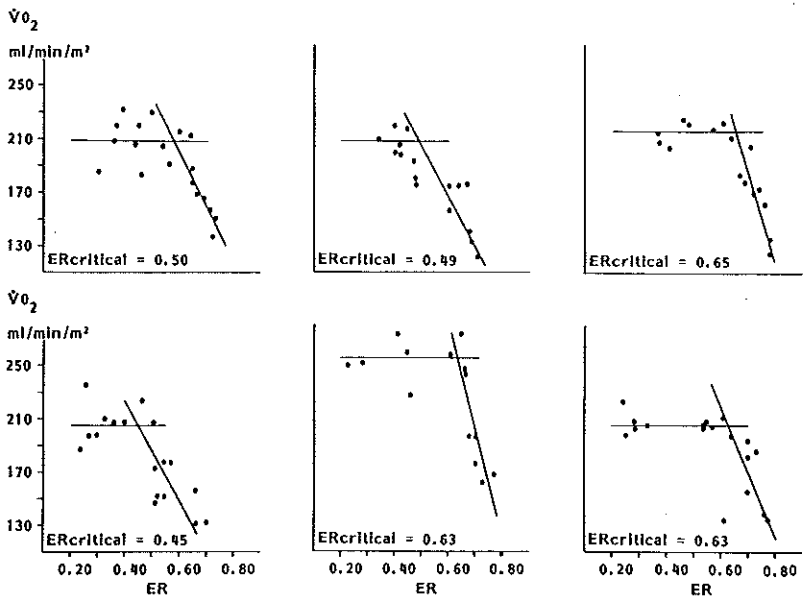

Fig 3. *VO_2 plotted against ER in each animal. The mean ER critical was 0.57 ± 0.08.*

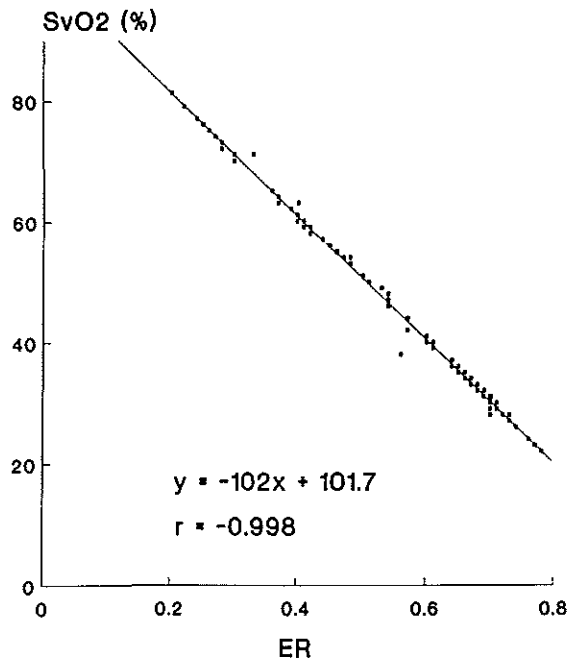

Fig 4. *Scatterplot of SvO_2 against the ER.*

Table 2 *Systemic oxygenation and mixed venous blood oxygenation after each step of blood exchange*

Blood exchange (ml/kg body wt)	Hb (g%)	PvO_2 (mmHg)	SvO_2 (%)	pHa	pHv	O_2flux ($ml.min^{-1}.m^{-2}$)	VO_2 ($mL.min^{-1}.m^{-2}$)	ER
0 (baseline)	10.0 ±1.2	45.2±4.8	70.3±8.1	7.45±0.03	7.41±0.02	738±202	208±19	0.30±0.08
10	7.9 ±0.8 *	44.4±4.1	68.8±7.4	7.45±0.03	7.41±0.02	649±123	200±11	0.32±0.07
20	6.7 ±0.7 *	43.9±3.6	67.5±7.3	7.44±0.02	7.41±0.02	669±157	201±50	0.33±0.07
30	6.1 ±0.8 *	40.9±3.5 *	62.5±7.7 *	7.45±0.02	7.42±0.02	593±101	221±27	0.38±0.07
40	5.2 ±0.5 *	40.5±4.1 *	60.1±6.8 *	7.44±0.01	7.41±0.02	539±65	220±21	0.42±0.04
50	4.4 ±0.3 *	37.3±2.9 *	54.9±7.0 *	7.45±0.02	7.41±0.02	464±47 *	213±19	0.46±0.06 *
60	4.0 ±0.4 *	34.2±3.5 *	47.9±8.4 *	7.45±0.03	7.40±0.03	405±53 *	213±27	0.53±0.08 *
65	3.6 ±0.3 *	32.9±2.9 *	43.6±7.8 *	7.44±0.03	7.40±0.03	375±45 *	213±32	0.56±0.07 *
70	3.3 ±0.2 *	32.0±2.4 *	42.1±7.8 *	7.44±0.02	7.40±0.02	345±43 *	201±26	0.59±0.08 *
75	3.3 ±0.3 *	31.1±2.6 *	40.1±7.4 *	7.44±0.03	7.40±0.03	328±43 *	192±32	0.59±0.07 *
80	3.0 ±0.4 *	29.8±2.2 *	37.4±6.8 *	7.44±0.02	7.40±0.02	304±40 *	191±19 *	0.63±0.06 *
85	2.8 ±0.3 *	29.6±2.6 *	35.8±8.4 *	7.43±0.03	7.39±0.03	280±25 *	180±19 *	065±0.08 *
90	2.6 ±0.3 *	28.3±2.9 *	33.4±8.1 *	7.44±0.01	7.38±0.03 *	260±25 *	173±14 *	0.67±0.07 *
95	2.3 ±0.3 *	28.3±2.9 *	32.6±4.0 *	7.42±0.03	7.36±0.04 *	234±41 *	156±18 *	0.68±0.08 *
100	2.2 ±0.3 *	27.4±2.1 *	28.3±5.2 *	7.41±0.04	7.35±0.05 *	216±34 *	155±23 *	0.72±0.05 *

Hb, hemoglobin; PvO_2, mixed venous oxygen tension; SvO_2, mixed venous oxygen saturation of hemoglobin; pHa, arterial pH; pHv, mixed venous pH; O_2flux = oxygen delivery; VO_2, oxygen uptake; ER, oxygen extraction ratio.

Values are mean ± SD (n = 6).

* $P < 0.05$ in comparison to baseline.

hemodynamically unstable patients, and for measurement of oxygen transport patterns [11-13]. In a prospective study, SvO_2 was found to correlate well with oxygen utilization coefficient; SvO_2 therefore reflects the overall balance between oxygen consumption and delivery in critically ill surgical patients [14].

To our knowledge, no reports are available concerning SvO_2 during isovolemic hemodilution, or concerning the critical SvO_2 at which VO_2 starts to decline during further stepwise isovolemic hemodilution. In this study, the effect of a decrease in oxygen supply on oxygen uptake during normoxic acute isovolemic hemodilution started when SvO_2 was 44.2 ± 7.9%. As in the prospective study in critically ill patients [14], we found a direct correlation between the SvO_2 and the ER during stepwise induced hemodilution.

Another parameter studied by us is the critical PvO_2. In our study, the critical PvO_2 at which VO_2 became dependent on oxygen flux was 32.3 ± 3.1 torr. To our knowledge, in only two other studies -one during isovolemic hemodilution, the other during hypovolemic hemorrhage- is the critical PvO_2 reported. During hypovolemic hemorrhage in dogs, a critical PvO_2 of 29.9 ± 2.3 was found [2]. These data, however, cannot be compared to our data because of the differences in experimental procedure (hypovolemia via removal of blood volume with a fixed arterial oxygen content versus isovolemic hemodilution and consequent decreased arterial oxygen content). In the other study using dogs, Cain reported a critical PvO_2 of 44.8 torr during isovolemic induced anemic hypoxia, at which point oxygen uptake began to decrease [3]. The large difference between the results of Cain's study and ours may be explained in two ways. First, the critical PvO_2 in Cain's study was identified in a different manner. The percentage change in VO_2 in comparison to control VO_2 was plotted against the PvO_2 to obtain the critical PvO_2. The single linear regression line obtained in this way was intersected with the point of 100% oxygen uptake, placing more weight on the value of the baseline VO_2 and less on the observed increase in VO_2 at the initial stage of hemodilution.

The other reason for the observed differences in critical PvO_2 during hemodilution may be the differences in cardiovascular and sympathetic responses between dogs and pigs and the differences in the anatomy and distribution of coronary arteries in both animals [8,10]. The differences in responses of CI and SVR on hemodilution between Cain's report and our study support this hypothesis. In our study, a 40% increase in CI was observed. The percentage increase in CO in dogs in comparison to the values obtained before

isovolemic anemia was induced was more pronounced in Cain's study (130%). Cain observed a decrease in SVR of 60% at the initial stage of isovolemic induced anemic hypoxia and of 74% at the final stage, whereas in our study in pigs the decrease in SVR was not more than 10-15% of the baseline value. Only in the final stage of anemic hypoxia during isovolemic hemodilution was the decrease in SVR enhanced to 25% - probably because at the moment the hypoxic induced vasodilation became more dominant than the reported reflex vasoconstriction activity during anemia [15].

The differences in cardiovascular and hemodynamic responses between pig and dog may also explain the difference in critical ER in the two species (and in the two studies). In dogs, a critical ER value of 0.79 has been reported [16], whereas in our study of pigs, the ER level was 0.57 when whole body oxygen uptake started to decline.

Because of the strong correlation found between SvO_2 and ER, we suggest that the monitoring of SvO_2 may be important as an indicator of the state of tissue oxygenation during normovolemic hemodilution. In sedated, paralyzed pigs a critical SvO_2 of 44.2 ± 7.9 and a critical PvO_2 of 32.3 ± 3.1 mmHg was found, at which point oxygen uptake started to decline during further hemodilution.

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EXTRACTION RATIO AND MIXED VENOUS OXYGEN SATURATION: A FALSE RELATIONSHIP

Percival CJ.

Anesth Analg 1991; 72: 713-718.

To the editor:

I read with interest the article of Trouwborst et al. [1] concerning the mixed venous blood gas analysis during normoxic acute isovolemic hemodilution in pigs. With ever-increasing numbers of patients asking that homologous blood transfusions be avoided, I think that this information is particular timely. Anesthesiologists need to know which indices are predictive of the limits of safe isovolemic hemodilution, and I think that the authors' results certainly have implications in humans. However, when they describe "the strong correlation found between mixed venous oxygen saturation (SvO_2) and extraction ratio (ER)" and depict this relationship in Figure 4, they have made an error of the type described by Archie [2] as "mathematical coupling". They define ER as follows, where VO_2 = oxygen consumption, CO = cardiac output, CaO_2 = arterial oxygen content, CvO_2 = mixed venous oxygen content, SvO_2 = mixed venous oxygen saturation, SaO_2 = arterial oxygen saturation, and O_2flux = oxygen delivery:

$$ER = \frac{VO_2}{O_2flux} = \frac{(CO)(CaO_2 - CvO_2)}{(CO)(CaO_2)}$$

$$= 1 - \frac{CvO_2}{CaO_2} = 1 - \frac{SvO_2}{SaO_2} = 1 - SvO_2$$

(because SaO_2 approaches 1). Therefore, the graph in Figure 4 is basically Y = 1 - X. The authors used percent and found essentially that Y = 100 - 100X where X or, in this case SvO_2, is greater than zero, but less than one. In calculating rather than measuring VO_2, the graph is predictable without gathering any data at all. I suspect there is a correlation between SvO_2 and ER, but any

attempt to describe it using these data is not meaningful.

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IN RESPONSE

Trouwborst A, van Woerkens ECSM.

Indeed, with oxygenation calculations using the indirect Fick method, a source of error can easily be introduced by mathematical coupling of data. Comparing SvO_2 values with ER, mathematical coupling might exist because in calculating the ER, SvO_2 itself is one of the variables. We therefore agree with Dr. Percival that the statement "a strong correlation exists between SvO_2 and ER" deserves further discussion. He suggests that we used in the calculation of the ER the equation

$$1 - \frac{CvO_2}{CaO_2} = 1 - \frac{SvO_2}{SaO_2}$$

which was not the case. In our calculations

$$1 - \frac{CvO_2}{CaO_2} =$$

$$1 - \frac{\text{Hb (mixed venous)} \times 1.34 \times SvO_2 + PvO_2 \times 0.003}{\text{Hb (arterial)} \times 1.34 \times SaO_2 + PaO_2 \times 0.003}$$

which includes two factors ignored by Dr. Percival: physically dissolved oxygen fraction and the difference between arterial and mixed venous hemoglobin (Hb) content. Furthermore, Dr. Percival makes the assumption that SaO_2 is almost 100%.

Under normal physiologic conditions (e.g., normal Hb content and normal SaO_2) the amount of dissolved oxygen as part of the total arterial oxygen content is minimal (2.0-2.5%) and might therefore be excluded in algorithms. However, decreasing Hb content, as in our experiments, at each step of hemodilution, the amount of dissolved oxygen as a percentage of total arterial oxygen content increases and becomes more and more important as one of the variables in calculating the ER.

The difference between arterial Hb content and mixed venous Hb content forces one to consider in the algorithm the Hb values. The equation ER = 1 - SvO_2 is therefore an oversimplification and a common source of error in several

situations (e.g., hemodilution, hypoxemia, hyperoxemia). We do not agree with Dr. Percival that in our presented experiments the relationship between SvO_2 and ER was predictable without gathering any data at all. Furthermore, it has been stated that by keeping the range of the independent variable, SvO_2, as large as possible (as in our study), the effects of coupled error are minimized [1].

Nevertheless, we agree that in part the correlation as presented might be influenced by mathematic coupling because of calculating VO_2 rather than measuring VO_2. Meanwhile, some pilot hemodilution experiments have been performed using a totally closed circuit anaesthesia machine developed in our department (Physioflex, Weesp, The Netherlands) [2] that measures rather than calculates VO_2. In these experiments (three animals), a strong correlation has been found between ER and SvO_2, supporting the statement about the correlation between ER and SvO_2.

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Chapter 5

A COMPARATIVE STUDY OF DIFFERENT TECHNIQUES AVOIDING HOMOLOGOUS BLOOD TRANSFUSIONS DURING MAJOR SURGICAL BLOOD LOSS

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Submitted

Abstract

Background: The use of homologous blood products involves several important risks. Some methods which can be employed to reduce the amount of homologous blood used perioperatively, including several hemodilution techniques and preoperative autologous blood donation (PABD) are investigated.

Methods: Forty patients (ASA 1 or 2) undergoing radical prostatectomy under general anesthesia were randomly assigned to one of four groups (acute normovolemic hemodilution (ANH); PABD; normovolemic hemodilution peroperative (NHD); and a control group). Full sets of hemodynamic and oxygenation parameters were obtained peroperatively and during 18 hours postoperatively. Perioperatively the course of reticulocytes and hemoglobin level was evaluated and the amount of autologous and homologous blood products used was measured.

Results: Hemodynamic changes included an increase in cardiac output with almost no change in heart rate, and a decrease in systemic vascular resistance. During normovolemic hemodilution the pulmonary wedge pressure increased. Oxygen extraction ratio increased and mixed venous oxygen pressure decreased. The more critical value of a PvO_2 of 33 mmHg was reached in 18 of 30 hemodilution patients due to decreased oxygen delivery, and in 3 of 10 control patients due to a leftward shift in the oxygen dissociation curve (ODC). The amount of homologous blood used was lowest in the PABD group.

Conclusions: Less homologous blood products were used with PABD than with ANH. Pulmonary wedge pressure increases as hematocrit is reduced. At a mean hemoglobin of 4.8 $\pm$ 0.2 mmol/l the PvO_2 decreases below the more critical value of 33 mmHg in some hemodilution patients.

Introduction

The use of homologous blood transfusions involves several risks, including isosensitization, febrile reactions, disseminated intravascular coagulopathy, immunosuppression (causing an increased risk of postoperative infections and possibly of cancer recurrence) and transmission of several infectious agents (hepatitis, cytomegalic virus, syphilis, herpes, malaria, tryptonosomiasis, HIV) [1-

4]. Mismatching of blood can lead to disastrous events. Certain patients, such as Jehovah's Witnesses, refuse the use of homologous blood transfusions on religious grounds. Finally, the costs of homologous blood continue to increase steadily.

In an attempt to reduce the number of homologous blood transfusions during surgery several techniques can be employed, including preoperative autologous blood donation and acceptance of a lower hemoglobin level in the perioperative period.

Of particular interest are the hemodilution methods, since it has been demonstrated that during anesthesia the body can compensate for the decreased arterial oxygen content by increasing the cardiac output. The amount of blood which can be saved using acute normovolemic hemodilution remains a matter of debate [5,6]. Some claim significant savings [7,8], while others report a very limited usefulness of acute normovolemic hemodilution as a bloodsaving method [9,10]. To our knowledge, few human studies have been conducted giving a full set of physiological hemodynamic and oxygenation parameters (including PvO_2 as an indicator of tissue oxygenation) during hemodilution under general anesthesia (Table 1). Most of these studies used only limited hemodilution [11-14], a small number of patients [3,15,16], or were performed in children [3,16].

The aim of this randomized prospective controlled study in anesthetized adult humans is to compare three different techniques including acute normovolemic hemodilution, preoperative autologous blood donation and normovolemic hemodilution used during severe blood loss, to reduce homologous blood transfusions peroperatively (and 18 hours postoperatively) and to evaluate their normal physiological effect on hemodynamics, oxygen transport (including effects on the oxygen hemoglobin dissociation curve), blood loss, erythropoiesis and transfusion needs. In the literature such a randomized prospective controlled study in adults addressing a more pronounced level of hemodilution is lacking. In the present study, compared to other studies in adults from the literature, hemodilution will be more pronounced in order to establish the hemoglobin level at a more critical point of mixed venous PvO_2 [17] during stepwise induced normovolemic hemodilution.

Table 1. *Studies on hemodilution in anesthetized humans with sets of hemodynamic and oxygenation parameters.*

Reference number	Study design			n	hct/Hb	Remarks on studies
	R	P	C			
3	no	yes	no	8	hct: 9 ± 2.2	high FiO_2 children
11	yes	yes	yes	10	hct: 28.2	no PvO_2
12	yes	yes	yes	20	hct: 31 ± 1.4	epidural anesthesia cardiovascular medication continued
13	no	yes	no	20	Hb: 8.8 ± 0.3 g%	> 65 yr; no PvO_2 stable filling pressures
14	yes	yes	yes	60	Hb: 9.9 ± 0.2 g%	chronic ß blocker therapy pre CABG
15	no	yes	no	4	hct: 21.5 ± 0.7	high FiO_2
16	no	yes	no	6	hct: 16 ± 1	children

Study design: R = randomized; P = prospective; C = controlled; n = number of patients studied; hct/Hb = lowest hematocrit or hemoglobin level reached during hemodilution.

Patients and methods

PATIENTS

After obtaining informed consent patients scheduled for radical prostatectomy were included in the study and randomly assigned to one of four groups. Radical prostatectomy was carried out for locally confined (T2) or locally extensive (T3) prostate cancer. Patients with cardiovascular instability (untreated elevated blood pressure, cardiac ischemia, recent myocardial infarction, use of ß-blockers), severe pulmonary disease, impairment of renal function, increased bleeding tendency, recent cerebrovascular accident or anemia (hemoglobin level < 7.5 mmol/l) were excluded from the study. All patients were informed in detail on the protocol and gave written informed consent before start of the

procedure. The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam-Dijkzigt.

DEMOGRAPHICS

The demographic data are given in Table 2. Mean age of the patients was 61 ± 1 years, mean bodyweight 82 ± 2 kg. There were no relevant differences between the four groups with respect to age, bodyweight or heigth.

Table 2. *Demographic data of the study population.*

group	age (yrs)	weight (kg)	heigth (m)	BSA (m^2)
1	62 ± 1.4	77 ± 3	1.76 ± 0.02	1.93 ± 0.03
2	61 ± 1.8	86 ± 4	1.79 ± 0.02	2.07 ± 0.06
3	63 ± 1.7	86 ± 4	1.79 ± 0.02	2.05 ± 0.06
4	60 ± 1.9	81 ± 9	1.77 ± 0.02	1.98 ± 0.04

Group 1 = ANH; group 2 = PABD; group 3 = NHD; group 4 = control; BSA = body surface area; yrs = years; kg = kilograms; m = meters; m^2 = square meters.
Values presented as mean ± SEM.

The four groups were treated as follows:
Group 1: preoperative acute normovolemic hemodilution (ANH).
After induction of anesthesia and baseline measurements, autologous blood was collected from the patient and simultaneously replaced with dextran 40, 50 g/L in 0.9% salt solution (Isodex®, NPBI, The Netherlands) until the hematocrit

reached 0.25-0.30. Blood loss during surgery was replaced with dextran 40 (Isodex®) until the hematocrit reached 0.20-0.25. Thereafter blood loss was initially replaced with the autologous whole blood, starting with the 500 ml of blood collected last (the unit with the lowest hematocrit).

Group 2: preoperative autologous blood donation (PABD)

Autologous blood was harvested approximately once a week during a 3-4 week period preoperatively and stored at the bloodbank. All patients received oral iron supplementation during this period until the day of the operation. Hemoglobin level and hematocrit were measured at each blood donation. Blood loss during surgery was replaced with dextran 40 (Isodex®) until the hematocrit reached 0.20-0.25. Thereafter further blood loss was initially replaced with autologous packed cells and fresh frozen plasma (starting with the unit which was collected most recently).

Group 3: peroperative normovolemic hemodilution (NHD).

Blood loss during surgery was replaced with dextran 40 (Isodex®) until the hematocrit had decreased to the level of 0.20-0.25, when homologous blood transfusion was started.

Group 4: control group.

Blood loss during surgery was replaced with dextran 40 (Isodex®) until total blood loss reached 10 ml/kg body weight, followed by homologous blood transfusion (one unit of 250 ml packed cells combined with 250 ml of colloid for every 500 ml of blood loss).

METHODS

All patients received 2.5 mg midazolam intramuscularly or 7.5 mg midazolam orally preoperatively. After induction of anesthesia with thiopental (4 mg/kg) and fentanyl (0.25 mg), and achievement of muscle relaxation with pancuronium bromide (0.1 mg/kg), all patients were intubated and ventilated to maintain normocarbia. Anesthesia was maintained with a mixture of oxygen in nitrous oxide and a low dose of enflurane (end tidal 0.4-0.8%), supplemented with intravenous fentanyl. A 21 gauge catheter was placed into the right or left radial artery. A pulmonary artery thermodilution catheter (Swan-Ganz, American Edwards Laboratories) was introduced into the pulmonary artery via the internal jugular vein. All patients received an urine catheter.

The fasting period was compensated by administration of 10 ml/kg bodyweight of Ringers' lactate. During surgery the Ringers' lactate infusion was

continued at a rate of 8 ml/kg bodyweight per hour to compensate for insensible losses. Initially blood loss was replaced by colloids as described and blood transfusion was started as soon as the hematocrit level reached 0.20-0.25 (except for the control group in whom blood transfusion was started after blood loss of 10 ml/kg independent of hematocrit) or the oxygen extraction ratio exceeded the acceptable level of 0.40. At the end of surgery the target hemoglobin level was 6.0 mmol/l. Postoperatively a blood transfusion was given if the hemoglobin level was < 6.0 mmol/l. Infusion of fresh frozen plasma in groups 1 (ANH), 3 (NHD), and 4 (control) was started as soon as total blood loss exceeded 70 ml/kg bodyweight, or a coagulation problem was considered on clinical grounds. Infusion of autologous fresh frozen plasma in group 2 (PABD) was started simultaneously with the first autologous unit of packed cells. In all patients dextran 40 (Isodex®) was used as colloid until the total amount of dextran 40 reached 1.5 g/kg bodyweight. Thereafter gelatin solution (Geloplasma®, Roger Bellon, Neuilly-sur-Seine, France) was used as colloid.

MEASUREMENTS

One day preoperatively laboratory measurements of hemoglobin concentration (Hb), hematocrit (ht), number of erythrocytes, thrombocytes and reticulocytes were obtained. These measurements were repeated on the first, third and seventh day postoperatively, on the day the patient was discharged from hospital, and at approximately four weeks after surgery. In the PABD group hemoglobin levels and hematocrit were measured before each donation.

After induction of anesthesia but prior to surgery all hemodynamic and oxygenation parameters were measured. These measurements were repeated after acute normovolemic hemodilution in group 1, and after each 500 ml of blood loss, at the end of surgery, and at 2, 6, 12 and 18 hours postoperatively in all 4 groups. Blood loss was measured by measuring the volume of collected blood and adding the amount as estimated by weighing of the gauze pads before and after use.

Hemodynamic measurements consisted of mean arterial pressure (MAP), mean pulmonary pressure (MPAP), pulmonary capillary wedge pressure (PWP), cardiac output (CO) and heart rate (HR). Oxygenation measurements were made by simultaneously obtaining an arterial and mixed venous blood sample and determining oxygen pressure (PO_2), carbon dioxide pressure (PCO_2) and pH (ABL330, Radiometer, Copenhagen) and oxygen saturation (SO_2) (OSM3,

Radiometer, Copenhagen) in these samples. Hemoglobin level and hematocrit were also measured in these blood samples.

From these measurements cardiac index (CI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), total oxygen flux index (DO_2I), arteriovenous oxygen content difference (avO_2diff), total oxygen consumption index (VO_2I) and oxygen extraction ratio (ER) were calculated. To evaluate the position of the oxygen dissociation curve the P_{50} (PO_2 at which hemoglobin is 50% saturated with oxygen) was calculated as described previously [18].

STATISTICAL ANALYSIS

Data are presented as mean ± SEM. Continuous variables were compared between the four groups by one-way analysis of variance, for each measurement occasion separately. This was followed by all pairwise group comparisons, corrected for multiple comparisons by Fisher's Least Significant Difference method. Comparisons between measurement times within the same group were performed using the t-test for paired observations. The number of transfusions was compared between the four groups using the test of Kruskal and Wallis, for each measurement occasion separately. If the result of this test was significant, all pairwise comparisons between groups were done using Wilcoxon's two sample test.

The relationship between PWP and hematocrit was studied with a random coefficients linear regression model, using the SAS program PROC MIXED [19]. In this model a linear relationship between PWP (dependent variable) and hematocrit (independent variable) was assumed on patient level, where the intercept and slope was allowed to differ between patients. The relationship between PvO_2 and hemoglobin was analyzed analogously, but in this case a quadratic relationship had to be assumed, the coefficient of the quadratic term being significantly negative.

Results

MISSING DATA (see Tables)

We planned to make measurements at each 500 ml of blood loss. However, when blood loss was too rapid it was impossible to make measurements at every 500 ml, resulting in missing data in some patients at a few points peroperatively. In two cases (one patient in the ANH group and one patient in the NHD group) there was no bed available on the intensive care unit resulting in some missing data postoperatively. These patients were kept on the recovery ward for 6 hours postoperatively, after which period the arterial line and pulmonary artery catheter were removed. Some patients chose to undergo postoperative follow-up in a hospital elsewhere, so that some values on reticulocytes, hemoglobin and hematocrit postoperative are also missing.

BLOOD LOSS AND TRANSFUSION NEEDS

Data on peroperative and postoperative (first 18 hours) blood loss and use of autologous and homologous blood products are given in Table 3. There was no significant difference in blood loss between the four groups. Autologous blood was only available in groups 1 and 2, by means of acute normovolemic hemodilution and by preoperative autologous blood donation, respectively. As expected, the use of homologous blood products was highest in the control group. The number of homologous blood products used in the control group peroperatively was significantly higher than used in groups 1 (ANH) and 2 (PABD). There was no significant difference between the control group and the group in which peroperative normovolemic hemodilution (NHD) was employed. The lowest use of homologous blood products was in the group with preoperative autologous blood donation (PABD); however, this amount did not reach statistical significance compared with the amount used in group 1 (ANH). None of the patients in the control group or in the group using only peroperative normovolemic hemodilution (NHD) could be managed without homologous blood. In the ANH group 3 out of 10 patients did not receive any homologous blood peroperatively, while in the PABD group this number was even 7 out of 10 patients. However in the first 18 hours postoperatively 1 additional patient in the ANH group and 3 patients in the PABD group needed homologous blood, resulting in a total of 6 patients (2 in the ANH group and 4 in the PABD group)

Table 3. *Blood loss and transfusion needs of the four groups.*

group	blood loss (ml)		autologous blood donated (U)	autologous blood transfused (U)		homologous blood transfused (U)	
	perop	postop		perop	periop	perop	periop
1	3620 ± 560	620 ± 160	2.9± 0.1	2.8 ± 0.2	2.9 ± 0.2	2.0 ± 0.7[34]	3.5 ± 1.3[4]
	1800-7600	100-1800	2-3.8	2-3.7	2-3.8	0-7	0-14
2	3870 ± 400	350 ± 70	4.0± 0	3.6 ± 0.3	3.8 ± 0.3	0.5 ± 0.3[34]	1.3 ± 0.4[3]
	1700-6000	120-860	4	1-4	2-4	0-3	0-3
3	4480 ± 460	550 ± 100				4.3 ± 0.5[12]	4.8 ± 0.6[2]
	2100-8000	200-1200				2-7	2-8
4	3910 ± 430	470 ± 100				5.9 ± 0.8[12]	5.9 ± 0.8[1]
	2350-7000	80-1000				3-12	3-12

Group 1 = ANH; group 2 = PABD; group 3 = NHD; group 4 = control. Perop = perioperative; postop = postoperative (first 24 hours). Autologous blood: in group 1 500 ml of whole blood equals 1 unit; in group 2 1 packed cells and 1 fresh frozen plasma equals 1 unit.

Values are presented as mean ± SEM, and as the range.

[1234] = statistical significant difference between groups 1,2,3 or 4, respectively; $P < 0.05$ (only blood loss and number of homologous blood product analysed).

who did not receive homologous blood perioperatively.

PERIOPERATIVE ERYTHROPOIESIS (Table 4)

The number of reticulocytes was already increased in group 2 on the day preoperatively, due to the process of donating 3-4 units of blood in the previous weeks thus stimulating the erythropoiesis. The increase in postoperative hemoglobin level started on the third day postoperatively in this group and remained higher than the hemoglobin level of groups 1 and 3 from this day on; however this increase is probably not attributable to the number of blood transfusions given in this period. During days 2-7 postoperatively a total of three units packed cells was given to 2 patients in group 1 (ANH) and to 2 patients in group 3 (NHD), and 2 units to 1 patient in group 2 (PABD) and even 2 units to 1 patient in group 4 (control). Blood loss could not be measured accurately in this period, because drain production consisted of both blood loss, lymphatic fluid and in some instances of urine (due to leakage) in a varying amount, but it seems unlikely that a significant difference would have existed between the 4 groups. The difference in rise in hemoglobin level between the group with predeposited autologous blood and the two other hemodilution groups did not reach statistical significance, perhaps due to the small number of patients.

HEMODYNAMICS (Table 5)

At the lowest hemoglobin level for each patient the mean increase in cardiac index was 37 ± 7%, 61 ± 18%, and 49 ± 10% in the hemodilution groups 1, 2 and 3, respectively, and 18 ± 11% in the control group in whom only very limited hemodilution was used. Heart rate did not change significantly from baseline measurements in all groups, indicating that the increase in cardiac output was due to an increase in stroke volume.

During hemodilution, mean arterial blood pressure did not change significantly from baseline values to the measurements at the nadir of the hemoglobin level, while mean increase in arterial pulmonary blood pressure was 36 ± 13% in group 1 (ANH), 87 ± 23% in group 2 and 67 ± 10% in group 3. The control group also showed a slight increase in MPAP (33 ± 7%) as hematocrit in this group decreased from 39.2 ± 1.2 to 29.6 ± 0.7%. Combined with the observed increase in cardiac output this resulted in a decrease in SVRI, with no or only small changes in PVRI.

Table 3. *Blood loss and transfusion needs of the four groups.*

group	blood loss (ml)		autologous blood donated (U)	autologous blood transfused (U)		homologous blood transfused (U)	
	perop	postop		perop	periop	perop	periop
1	3620 ± 560	620 ± 160	2.9± 0.1	2.8 ± 0.2	2.9 ± 0.2	2.0 ± 0.7[34]	3.5 ± 1.3[4]
	1800-7600	100-1800	2-3.8	2-3.7	2-3.8	0-7	0-14
2	3870 ± 400	350 ± 70	4.0± 0	3.6 ± 0.3	3.8 ± 0.3	0.5 ± 0.3[34]	1.3 ± 0.4[34]
	1700-6000	120-860	4	1-4	2-4	0-3	0-3
3	4480 ± 460	550 ± 100				4.3 ± 0.5[12]	4.8 ± 0.6[2]
	2100-8000	200-1200				2-7	2-8
4	3910 ± 430	470 ± 100				5.9 ± 0.8[12]	5.9 ± 0.8[12]
	2350-7000	80-1000				3-12	3-12

Group 1 = ANH; group 2 = PABD; group 3 = NHD; group 4 = control. Perop = perioperative; postop = postoperative (first 24 hours). Autologous blood: in group 1 500 ml of whole blood equals 1 unit; in group 2 1 packed cells and 1 fresh frozen plasma equals 1 unit.

Values are presented as mean ± SEM, and as the range.

[1234] = statistical significant difference between groups 1,2,3 or 4, respectively; $P < 0.05$ (only blood loss and number of homologous blood product analysed).

Pulmonary wedge pressure increased in all hemodilution groups, but least (4.3 ± 0.7 mmHg) in group 1 (ANH). The change in mean PWP was 7.7 ± 1.0 mmHg and 7.6 ± 1.6 mmHg in groups 2 and 3, respectively at the measurement at which the hemoglobin level reached its nadir compared to baseline values. In the control group mean PWP increased 3.8 ± 1.2 mmHg from baseline to the measurement at 1000 ml blood loss with a concomitant decrease in hematocrit from 39.2 ± 1.2 to 30.6 ± 1.0%. PWP in the control group showed no essential change after this measurement. Statistical analysis showed a linear realtionship between the change in hematocrit and the change in PWP (Figure 1). PWP was lower in group 1 (ANH), but showed almost the same relationship in the remaining groups. In the hemodilution patients at the end of surgery and in the first 2 hours thereafter, the increase in hematocrit due to blood transfusions was followed by a decrease in PWP despite the additional volume loading caused by the administration of the packed red cells.

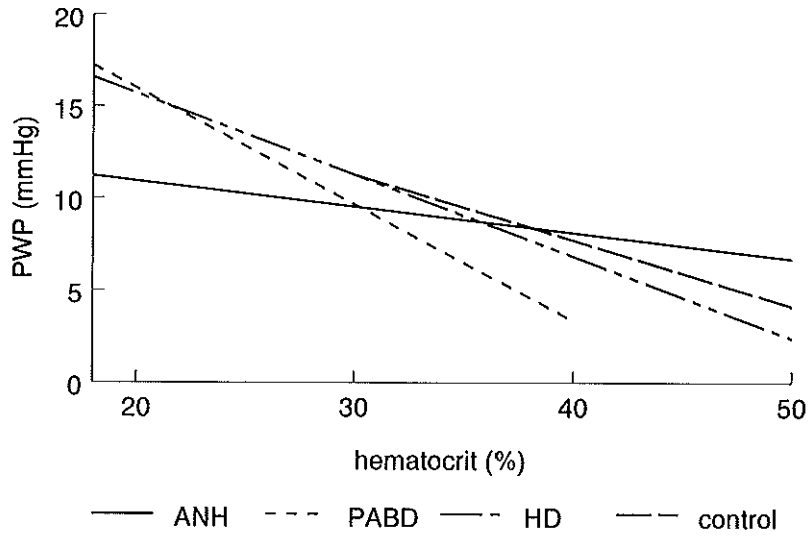

Figure 1.
Relationship between hematocrit and PWP for each study group. The relationship between PWP and hematocrit was studied with a random coefficients linear regression model, using the SAS program PROC MIXED [19].

Table 5. *Hemodynamic data on the groups during the study period.*

parameter	group	baseline	ANH	1000	1500	2000
n	1	10	10	10	9	9
	2	10		8	8	8
	3	10		10	9	10
	4	10		10	9	9
ht	1	40.7 ± 0.9[23]	26.9 ± 0.5[b]	22.6 ± 0.6[b234]	21.3 ± 0.5[b234]	20.0 ± 0.6[b34]
%	2	33.5 ± 1.1[134]	±	25.1 ± 1.0[b134]	23.9 ± 0.8[b134]	21.3 ± 0.8[b4]
	3	37.6 ± 0.9[12]	±	29.2 ± 0.7[b12]	26.4 ± 0.9[b12]	23.0 ± 0.8[b14]
	4	39.2 ± 1.2[2]	±	30.6 ± 1.0[b12]	30.7 ± 0.9[b12]	30.2 ± 0.8[b123]
HR	1	68 ± 4	66 ± 3	69 ± 5[4]	68 ± 2[4]	73 ± 5[4]
beats/min	2	65 ± 3		67 ± 3	65 ± 3	66 ± 2
	3	66 ± 2		65 ± 1	67 ± 1	67 ± 2
	4	66 ± 3		62 ± 2[b1]	61 ± 2[b1]	60 ± 2[b1]
MAP	1	73 ± 3[24]	77 ± 4	75 ± 4[2]	73 ± 5[2]	76 ± 5[4]
mmHg	2	84 ± 3[1]		90 ± 6[1]	89 ± 6[1]	84 ± 3
	3	80 ± 3		88 ± 7	79 ± 5	83 ± 2
	4	82 ± 3[1]		85 ± 3	85 ± 4	87 ± 4[1]
MPAP	1	14.9 ± 0.9	20.7 ± 1.4[b]	18.0 ± 1.1[b2]	19.9 ± 0.8[b]	19.9 ± 1.4[b2]
mmHg	2	15.2 ± 1.9		23.1 ± 2.1[1]	23.0 ± 1.9[b]	24.8 ± 1.6[b1]
	3	15.1 ± 1.3		19.9 ± 1.7[b]	21.6 ± 1.4[b]	23.4 ± 1.2[b]
	4	16.1 ± 1.2		20.1 ± 1.2[b]	20.3 ± 1.8	22.8 ± 1.3[b]
PWP	1	6.4 ± 0.9	11.0 ± 0.9[b]	9.8 ± 0.8[b]	10.7 ± 0.6[b]	11.2 ± 0.7[b2]
mmHg	2	7.4 ± 1.4		12.9 ± 0.9	13.3 ± 1.3[b]	14.8 ± 1.5[b1]
	3	8.6 ± 0.9		11.1 ± 1.2[b]	13.1 ± 1.1[b]	13.7 ± 0.9[b]
	4	7.5 ± 0.7		11.3 ± 1.3[b]	10.8 ± 1.7	12.4 ± 1.4[b]
CI	1	1.91 ± 0.15	2.46 ± 0.16[b]	2.38 ± 0.13[b]	2.47 ± 0.17[b]	2.70 ± 0.21[b]
$l.min^{-1}.m^{-2}$	2	1.92 ± 0.10		2.27 ± 0.16[b]	2.60 ± 0.21[b]	2.67 ± 0.12[b]
	3	1.83 ± 0.09		2.26 ± 0.09[b]	2.46 ± 0.11[b]	2.67 ± 0.13[b]
	4	1.99 ± 0.12		2.28 ± 0.12	2.28 ± 0.11	2.31 ± 0.12
SVRI	1	2850 ± 180	170 ± 130[b]	2220 ± 100[b234]	2090 ± 150[b4]	2000 ± 110[b4]
Ds/cm^5	2	3350 ± 210		2740 ± 170[b1]	2390 ± 190[b]	2170 ± 130[b4]
	3	3210 ± 160		2830 ± 220[1]	2220 ± 170[b]	2250 ± 130[b4]
	4	3090 ± 190		2700 ± 150[b1]	2670 ± 160[1]	2680 ± 140[b12]
PVRI	1	378 ± 46	3302 ± 50	286 ± 22[b]	298 ± 29	274 ± 38[b]
Ds/cm^5	2	358 ± 77		380 ± 52	298 ± 33	306 ± 33
	3	280 ± 20		312 ± 26	276 ± 37	300 ± 33
	4	357 ± 35		314 ± 35	345 ± 45	363 ± 36

n = number of patients at each measurement; group 1 = ANH; group 2 = PABD; group 3 = PNH; group 4 = control; ANH = after acute normovolemic hemodilution (only group 1); 1000, 2000 = measurement at blood loss of 1000 ml and 2000 ml, respectively; nadir Hb = lowest hemoglobin level; end = end of surgery; 2h, 6h, 12h, 18h = 2, 6 , 12, and 18 hours postoperatively, respectively;

Table 5. *Continued.*

nadir Hb	end	2h	6h	18h
10	10	10	10	10
10	10	10	10	10
10	10	9	10	9
10	10	9	10	10
19.7 ± 0.5[b4]	25.7 ± 0.6[b4]	31.4 ± 1.3[b4]	31.4 ± 1.3[b4]	30.1 ± 0.8[b4]
20.3 ± 0.8[b4]	25.1 ± 0.8[b4]	29.9 ± 0.5[b4]	30.3 ± 0.5[b34]	29.8 ± 0.9[b4]
21.4 ± 0.5[b4]	27.1 ± 0.7[b4]	31.8 ± 0.5[b4]	33.0 ± 0.5[b2]	31.1 ± 0.7[b4]
29.6 ± 0.7[b123]	31.8 ± 0.9[b123]	35.6 ± 0.8[b123]	34.9 ± 0.9[b12]	33.4 ± 0.7[b123]
71 ± 5	69 ± 4[4]	99 ± 7[b]	87 ± 6[b]	86 ± 4[b]
68 ± 3	65 ± 3	88 ± 5[b]	82 ± 4[b]	84 ± 5[b]
66 ± 2	69 ± 2[4]	85 ± 3[b]	82 ± 3[b]	81 ± 3[b]
60 ± 2[b]	60 ± 2[b13]	88 ± 4[b]	82 ± 6[b]	80 ± 5[b]
71 ± 4[24]	78 ± 4[3]	93 ± 8[b]	88 ± 4[b]	88 ± 3[b]
86 ± 2[1]	85 ± 3	97 ± 5[b]	98 ± 3[b]	97 ± 4
80 ± 3	88 ± 4[1]	93 ± 3[b]	91 ± 4	92 ± 4
85 ± 2[1]	85 ± 2	89 ± 1	96 ± 5[b]	92 ± 3
19.6 ± 1.4[b23]	23.2 ± 1.3[b]	16.8 ± 1.2	17.0 ± 1.2	18.8 ± 1.7
24.9 ± 1.4[b1]	25.5 ± 1.9[b]	21.3 ± 2.2	18.7 ± 1.5	19.2 ± 1.1[b]
24.6 ± 1.8[b1]	27.4 ± 1.8[b]	18.4 ± 1.4	18.0 ± 1.3	18.1 ± 1.7
21.0 ± 1.4[b]	24.2 ± 1.8[b]	17.5 ± 1.6	18.8 ± 2.0	16.9 ± 1.7
10.7 ± 0.6[b23]	12.3 ± 1.1[b]	6.0 ± 1.0[2]	6.8 ± 1.1	7.3 ± 1.1
15.1 ± 1.0[b14]	13.0 ± 1.0[b]	10.3 ± 1.9[14]	9.8 ± 1.2	9.0 ± 1.0
16.2 ± 1.5[b14]	16.1 ± 1.8[b]	9.7 ± 1.5[4]	7.1 ± 1.4	6.8 ± 1.4
11.6 ± 1.1[b23]	12.5 ± 1.4[b]	5.8 ± 0.9[23]	8.0 ± 1.4	6.4 ± 1.2
2.59 ± 0.20[b]	2.76 ± 0.18[b]	4.44 ± 0.37[b]	4.00 ± 0.37[b]	3.94 ± 0.18[b]
3.14 ± 0.47[b]	2.69 ± 0.23[b]	4.60 ± 0.37[b]	3.61 ± 0.27[b]	3.68 ± 0.27[b]
2.67 ± 0.13[b]	2.80 ± 0.13[b]	3.90 ± 0.18[b]	3.25 ± 0.13[b]	3.48 ± 0.10[b]
2.29 ± 0.17	2.43 ± 0.19	3.77 ± 0.33[b]	3.47 ± 0.35[b]	3.71 ± 0.10[b]
1900 ± 70[b4]	1970 ± 210[b]	1670 ± 190[b]	1810 ± 180[b]	1690 ± 140[b]
2070 ± 160[b4]	2210 ± 140[b]	1640 ± 200[b]	2130 ± 230[b]	1970 ± 130[b]
2050 ± 140[b4]	2190 ± 130[b]	1800 ± 110[b]	2140 ± 160[b]	1980 ± 80[b]
2900 ± 460[123]	2770 ± 490	1900 ± 200[b]	2110 ± 270[b]	1930 ± 110[b]
280 ± 35[b]	315 ± 35	201 ± 14[b]	221 ± 31[b]	237 ± 33[b]
274 ± 36	350 ± 47	201 ± 24	214 ± 35[b]	237 ± 29
268 ± 49	330 ± 25	180 ± 24[b4]	269 ± 30	264 ± 24
408 ± 82	438 ± 86	257 ± 24[b3]	262 ± 28	225 ± 15[b]

Hb = hemoglobin; HR = heart rate; MAP = mean arterial blood pressure; MPAP = mean pulmonary artery blood pressure; PWP = pulmonary wedge pressure; CI = cardiac index; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index. All values are presented as mean ± SEM.
[1234] = statistical significant difference between groups 1,2,3 or 4, respectively.; [b] = statistical significant difference from baseline within group; $P < 0.05$.

OXYGENATION AND OXYGEN CALCULATIONS (Tables 6 and 7)

There were no significant changes in arterial blood gas values peroperatively in any group, except for an increase in arterial oxygen pressure and saturation in the control group which may be due to the lower baseline values in this group (Table 6). Arterial pH showed the same slight decrease in all four groups.

During the procedure mixed venous blood gases showed a decrease in both mixed venous oxygen pressure and mixed venous oxygen saturation. As the hemoglobin level decreased, despite the simultaneous increase in cardiac output, oxygen delivery decreased. This resulted in an increase in oxygen extraction ratio, as already indicated by the decrease in mixed venous oxygen pressure and saturation. Systemic oxygen consumption was maintained throughout the entire operative period.

Peroperatively the slope of the oxygen dissociation curve became slightly shifted to the left as indicated by the decrease in P_{50} (PO_2 at which hemoglobin is 50% saturated with oxygen, corrected to body temperature of 37 °C and pH = 7.40). This change is seen in all four groups and started during the transfusion of homologous blood. The baseline value of the P_{50} was higher in group 2 (PABD), indicating a rightward shift in the oxygen dissociation curve originating from the donation of four units of autologous blood.

PvO_2 AND HEMOGLOBIN

In each patient individually we evaluated whether the mixed venous oxygen pressure at one point peroperatively decreased below the critical point of 33 mmHg. If a patient did reach this PvO_2 for the first time the corresponding hemoglobin level was noted. In the three hemodilution groups combined (groups 1, 2, and 3) in 18 patients this value of PvO_2 of 33 mmHg was reached for the first time at a mean hemoglobin level of 4.8 ± 0.2 mmol/l. Also in three patients in the control group (group 4) the PvO_2 decreased below 33 mmHg at some point peroperatively. In these patients the decrease in PvO_2 was directly related to a more pronounced decrease in P_{50} related to the transfusion of homologous blood.

Statistical analysis of the relationship between hemoglobin level and PvO_2 showed a curvilinear relationship between these two parameters, as shown in Figure 2. There were no significant differences in the form of this curvilinear relationship, but there were minor differences in the vertical position of each individual curve.

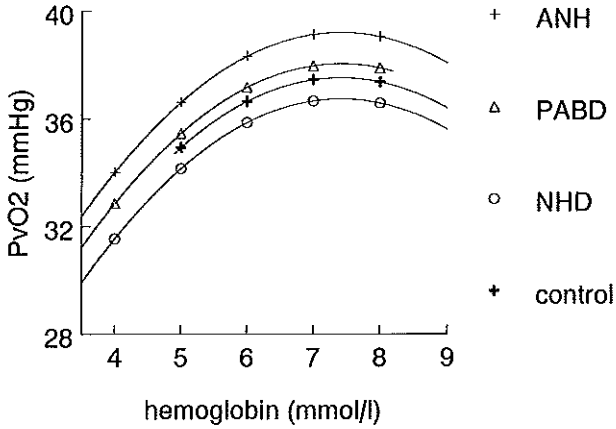

Figure 2.
Relationship between hemoglobin level and PvO_2 for each study group. The relationship between PvO_2 and hemoglobin level was studied with a random coefficients linear regression model, using the SAS program PROC MIXED [19].

ADVERSE EVENTS

Group 1 (ANH): postoperatively one patient complained of angina pectoris and dyspnoea due to a combination of lung embolisms and a pneumonia. He was treated with antibiotics and anticoagulants and recovered completely.

Group 2 (PABD): one patient underwent a relaparotomy on the eighth day postoperatively due to dehiscence of the cysto-urethral anastomosis. Another patient received anticoagulants because of a thrombophlebitis.

Group 3 (NHD): one patient developed thrombosis two weeks postoperatively and received anticoagulants.

Group 4 (control): one patient complained postoperatively of loss of shortterm memory; peroperatively this patient had a low PvO_2 value of 30.6 mmHg and at the same moment a P_{50} of 23.4 mmHg. One patient unexpectedly died from a myocardial infarction a few weeks after the operation and after discharge from the hospital. One patient underwent a relaparotomy because of wound dehiscence.

Table 6. *Blood gas analyses data during the study period.*

parameter	group	baseline	ANH	1000	1500	2000
n	1	10	10	10	9	9
	2	10		8	8	8
	3	10		10	9	10
	4	10		10	9	9
PaO_2	1	133 ± 11	142 ±7	143±8	142±6	145±7
mmHg	2	133 ± 7		134±3	139±5	138±5
	3	139 ± 11		149±7	146±7	152±7
	4	117 ± 9		147±6[b]	147±7[b]	148±6[b]
$PaCO_2$	1	37 ± 1	37±1	36±1	36±1	36±1
mmHg	2	36 ± 1		37±1	37±1	38±1
	3	37 ± 1		38±1	37±1	38±1
	4	36 ± 1		37±1	37±1	37±1
pHa	1	7.43 ± 0.02	7.40±0.01[b]	7.42±0.01	7.40±0.01	7.41±0.01[b]
	2	7.44 ± 0.01		7.40±0.01[b]	7.41±0.01[b]	7.39±0.01[b]
	3	7.43 ± 0.02		7.40±0.02[b]	7.40±0.02[b]	7.40±0.02[b]
	4	7.42 ± 0.01		7.40±0.01[b]	7.37±0.03	7.39±0.01[b]
SaO_2	1	99 ± 0.3	99±0.2	99±0.2	99±0.2	99±0.1
%	2	99 ± 0.3[4]		99±0.2	100±0.2[4]	99±0.3
	3	99 ± 0.2[4]		99±0.1	99±0.2	99±0.2
	4	98 ± 0.5[23]		99±0.2[b]	99±0.3[2]	99±0.2[b]
PvO_2	1	38 ± 1	38±1	34±1[b4]	34±1[b]	33±1[b4]
mmHg	2	38 ± 1		37±1	36±1	35±1[b]
	3	37 ± 1		37±1	36±1	35±1
	4	37 ± 1		38±1[1]	38±1	37±1[1]
SvO_2	1	72 ± 2	72±2	65±1[b4]	65±1[b]	65±2[b4]
%	2	70 ± 2		65±2[b4]	66±2[b]	63±2[b4]
	3	72 ± 1		69±2	69±1[b]	67±2[b4]
	4	72 ± 1		71±1[12]	71±1	72±1[123]

n = number of patients at each measurement; group 1 = ANH; group 2 = PABD; group 3 = PNH; group 4 = control; ANH = after acute normovolemic hemodilution (only group 1); 1000, 2000 = measurement at blood loss of 1000 ml and 2000 ml, respectively; nadir Hb = lowest hemoglobin level; end = end of surgery; 2h, 6h, 12h, 18h = 2, 6 , 12, and 18 hours postoperatively, respectively;

Table 6. *Continued.*

nadir Hb	end	2h	6h	18h
10	10	9	10	7
10	10	9	10	10
10	10	10	10	9
10	10	9	9	10
143±9	132±6	107±12	109±10	89±6
134±5	130±7	88±5[b]	103±5[b]	84±5[b]
151±7	147±9	92±6[b]	105±5[b]	81±4[b]
145±7[b]	143±7[b]	91±7	101±5	78±4[b]
36±1	38±1	41±1	41±2	40±1[3]
38±1[b]	37±1	41±1[b]	40±1[b]	37±1
38±1	39±1[b]	40±1[b]	39±1	36±1[14]
36±1	36±1	40±1[b]	39±1[b]	39±1[b3]
7.41±0.01	7.40±0.01[3]	7.38±0.02	7.38±0.02	7.41±0.01[2]
7.40±0.01[b]	7.41±0.01[b3]	7.38±0.01[b]	7.40±0.01[b]	7.44±0.01[14]
7.40±0.02[b]	7.37±0.01[b12]	7.37±0.01[b]	7.39±0.01[b]	7.42±0.01
7.39±0.01[b]	7.38±0.01[b]	7.36±0.01[b]	7.38±0.01[b]	7.40±0.01[2]
99±0.3	99±0.2[3]	97±0.7	97±0.7	97±0.5[b]
99±0.3	99±0.3	97±1.2	98±0.5	97±0.6[b4]
99±0.2	99±0.2[1]	97±0.5[b]	98±0.3[b]	97±0.5[b]
99±0.2[b]	99±0.2	96±0.8	98±0.4	96±0.6[b2]
32±1[b4]	35±1	36±2	36±2	34±1
33±1[b4]	33±1[b4]	37±1	36±1	35±2
33±1[b4]	34±2	34±1	34±1[b]	33±1[b]
37±1[123]	36±1[2]	37±1	36±1	33±1
62±1[b4]	70±2	72±2	71±3	71±1
63±2[b4]	65±2[b4]	73±1	71±2	70±2
65±2[b4]	68±2	70±1	71±1	69±1
71±1[123]	71±1[2]	73±1	74±1	68±3

PaO_2 = arterial oxygen pressure; $PaCO_2$ = arterial carbon dioxide tension; pHa = arterial pH; SaO_2 = arterial oxygen saturation of hemoglobin; PvO_2 = mixed venous oxygen tension; SvO_2 = mixed venous oxygen saturation of hemoglobin.

All values are presented as mean ± SEM.

[1234] = statistical significant difference between groups 1,2,3 or 4, respectively. [b] = statistical significant difference from baseline within group; $P < 0.05$.

Table 7. *Oxygen data during the study period.*

parameter	group	baseline	ANH	1000	1500	2000
n	1	10	10	9	9	9
	2	10		8	8	8
	3	10		9	9	10
	4	10		9	9	9
Hb	1	8.3 ± 0.2^{23}	5.6 ± 0.1^{b}	4.7 ± 0.1^{b234}	4.4 ± 0.1^{b34}	4.2 ± 0.1^{b34}
mmol/l	2	6.8 ± 0.2^{134}		5.2 ± 0.2^{b134}	5.0 ± 0.2^{b4}	4.4 ± 0.1^{b4}
	3	7.7 ± 0.2^{13}		6.1 ± 0.1^{b12}	5.3 ± 0.2^{b14}	4.8 ± 0.2^{b14}
	4	8.2 ± 0.2^{2}		6.5 ± 0.2^{b12}	6.5 ± 0.2^{b123}	6.3 ± 0.1^{b123}
DO_2I	1	343 ± 25	304 ± 18^{b}	241 ± 19^{b34}	242 ± 15^{b}	254 ± 19^{b4}
$ml.min^{-1}m^{-2}$	2	289 ± 19^{4}		264 ± 20^{4}	293 ± 31	262 ± 16^{b4}
	3	309 ± 15		302 ± 15^{14}	296 ± 15	283 ± 17
	4	346 ± 19^{2}		323 ± 10^{12}	324 ± 15	315 ± 16^{12}
VO_2I	1	92 ± 3	86 ± 4	87 ± 3	86 ± 2	91 ± 4
$ml.min^{-1}.m^{-2}$	2	87 ± 3		93 ± 3	99 ± 5^{b}	99 ± 5^{b}
	3	88 ± 5		92 ± 5	96 ± 6	96 ± 3
	4	93 ± 4		95 ± 4	95 ± 4	91 ± 4
ER	1	0.275 ± 0.016	0.290 ± 0.015	0.355 ± 0.013^{b4}	0.364 ± 0.014^{b}	0.368 ± 0.017^{b4}
	2	0.308 ± 0.015		0.362 ± 0.021^{b4}	0.351 ± 0.022^{b}	0.384 ± 0.019^{b4}
	3	0.281 ± 0.010		0.319 ± 0.015^{b}	0.325 ± 0.015^{b}	0.344 ± 0.016^{b4}
	4	0.273 ± 0.012		0.294 ± 0.013^{12}	0.295 ± 0.011	0.292 ± 0.009^{123}
P_{50}corr	1	26.5 ± 0.4^{2}	26.4 ± 0.5	26.1 ± 0.3^{b2}	26.2 ± 0.3^{2}	26.0 ± 0.4^{b4}
mmHg	2	27.7 ± 0.2^{134}		27.5 ± 0.2^{134}	27.3 ± 0.2^{134}	26.9 ± 0.3^{34}
	3	26.3 ± 0.2^{2}		26.4 ± 0.2^{2}	26.1 ± 0.3^{2}	25.8 ± 0.3^{b2}
	4	26.3 ± 0.4^{2}		26.0 ± 0.3^{2}	25.7 ± 0.5^{2}	24.9 ± 0.4^{b12}
AUT	1	0	0	0.08 ± 0.06	0.40 ± 0.15^{2}	1.00 ± 0.10^{2}
U	2	0		0	0^{1}	0.50 ± 0.17^{1}
AUT	1	0	0	2	5	9
number of patients	2	0		0	0	5
HOM	1	0	0	0^{4}	0^{4}	0^{4}
U	2	0		0^{4}	0^{4}	0^{4}
	3	0		0^{4}	0^{4}	0^{4}
	4	0		0.37 ± 0.08^{12}	1.23 ± 0.15^{12}	2.31 ± 0.07^{12}
HOM	1	0	0	0	0	0
number of	2	0		0	0	0
patients	3	0		0	0	0
	4	0		7	9	9

Group 1 = ANH; group 2 = PABD; group 3 = PNH; group 4 = control; ANH = after acute normovolemic hemodilution (only group 1);
1000, 2000 = measurement at blood loss of 1000 ml and 2000 ml, respectively; nadir Hb = lowest hemoglobin level; end = end of surgery; 2h, 6h, 12h, 18h = 2, 6 , 12, and 18 hours postoperatively, respectively; n = number of patients at each measurement; ht = hematocrit; DO_2I = oxygen delivery index; VO_2I = oxygen consumption index; ER = oxygen extraction ratio; P_{50}corr = P_{50} (Po_2 at which hemoglobin is 50% saturated) corrected to body temperature of 37°C and pH = 7.40;

Table 7. *Continued.*

nadir Hb	end	2h	6h	18h
10	10	9	10	7
10	10	9	10	10
10	10	10	10	9
10	10	9	9	10
4.1±0.1[b]	5.5±0.2[b4]	6.5±0.3[b4]	6.6±0.3[b4]	6.4±0.1[b4]
4.2±0.2[b]	5.3±0.1[b4]	6.2±0.1[34]	6.4±0.1[34]	6.2±0.2[b4]
4.4±0.1[b]	5.7±0.1[b4]	6.6±0.12[b4]	6.9±0.1[b24]	6.6±0.2[b4]
6.2±0.1[b]	6.7±0.2[b123]	7.5±0.1[b123]	7.5±0.1[b123]	7.1±0.1[b123]
226±16[b4]	337±26	610±43[b]	557±42[b]	532±26[b]
280±39	317±26	589±43[b]	502±42[b]	469±43[b]
265±15[b]	352±17[b]	550±26[b]	485±21[b]	482±19[b]
311±22[1]	356±30	600±57[b]	554±55[b]	549±18[b]
89±4[2]	100±4[b]	157±11[b]	153±7[b]	148±5[b2]
104±6[b1]	111±4[b]	146±10[b]	139±10[b]	130±6[b1]
96±4	114±6[b]	151±4[b]	137±6[b]	140±6[b]
90±6	103±8	147±13[b]	141±12[b]	142±6[b]
0.386±0.011[b4]	0.309±0.019[b2]	0.272±0.017	0.277±0.024	0.280±0.012
0.383±0.022[b4]	0.359±0.017[b14]	0.249±0.005[b]	0.283±0.018	0.288±0.015
0.368±0.017[b4]	0.329±0.018[b]	0.281±0.013	0.285±0.010	0.292±0.011
0.288±0.010[123]	0.292±0.009[2]	0.248±0.010	0.270±0.015	0.260±0.012
26.2±0.5[4]	25.1±0.4[b]	24.3±0.3[b]	24.0±0.3[b2]	24.4±0.3[b2]
26.3±0.4[b4]	25.4±0.4[b3]	24.6±0.2[b34]	25.3±0.3[b134]	26.1±0.6[b134]
25.3±0.3[b]	24.1±0.4[b2]	23.5±0.3[b2]	23.6±0.2[b2]	24.6±0.5[b2]
25.0±0.4[b12]	25.0±0.5[b]	23.7±0.3[b2]	23.9±0.4[b2]	24.3±0.5[b2]
1.21±0.32	2.80±0.17[2]	2.90±0.15[2]	2.90±0.15[2]	2.90±0.15[2]
1.20±0.29	3.60±0.31[1]	3.63±0.30[1]	3.80±0.20[1]	3.80±0.20[1]
7	10	10	10	10
8	10	10	10	10
0.10±0.10[4]	2.00±0.70[34]	2.10±0.69[34]	2.60±1.06[34]	3.40±1.35[34]
0[4]	0.56±0.34[34]	0.90±0.35[34]	1.10±0.41[34]	1.40±0.43[34]
0.55±0.28[4]	4.10±0.48[12]	4.50±0.62[12]	4.60±0.60[12]	4.50±0.60[12]
2.35±0.42[123]	5.85±0.84[12]	5.90±0.82[12]	5.90±0.82[12]	5.90±0.82[12]
1	7	7	7	8
0	3	5	5	6
3	10	10	10	10
9	10	10	10	10

AUT U = number of units of autologous blood transfused; AUT number of patients = number of patients who received an autologous blood transfusion up to that point; HOM U = number of units of homologous blood transfused; HOM number of patients = number of patients who received a homologous blood transfusion up to that point.

All values are presented as mean ± SEM.

[1234] = statistical significant difference between groups 1,2,3 or 4, respectively. [b] = statistical significant difference from baseline within group; $P < 0.05$.

Discussion

During this study seven staff members and five residents in training at the Department of Urology, all at different levels of experience, were involved. The study was carried out during a period that can be considered part of a "learning curve" for many. This is reflected in large volumes of blood loss which have drastically decreased in recent years.

In an attempt to reduce the amount of homologous blood products used peroperatively a number of methods can be employed including preoperative autologous blood donation, acute normovolemic hemodilution and peroperative normovolemic hemodilution. During oncologic procedures the use of the cell saver is still considered to be contraindicated, but this point remains controversial. We chose not to use the cell saver due to the risk of inducing metastasis. Induced hypotension is not without risks and its efficiency has been questioned[20]. It should not be employed at the same time as hemodilution techniques, because induced hypotension will interfere with the compensation mechanisms occurring during hemodilution. The use of erythropoietin preoperatively has been employed to increase the efficiency of predepositing autologous blood [21,22], as an adjunct to acute normovolemic hemodilution [23] or to accelerate the recovery from anemia postoperatively [24]. Erythropoietin treatment has been associated with an increased risk of thrombosis and hypertension [25] and the costs of erythropoietin therapy are high. A meticulous surgical technique also helps to diminish the amount of homologous blood required.

Preoperative autologous blood donation is known to be an effective method to decrease the amount of homologous blood used perioperatively during major surgical blood loss [26,27] and is confirmed by the results of the present study. The amount of homologous blood used in the PABD group was least in all four groups, and many patients (4 out of 10) could be managed without any homologous blood perioperatively. PABD could probably be made more effective by beginning erythropoietin treatment before the start of the donations [21,22]. Iron supplementation should always be given during PABD. There are, however, several disadvantages associated with PABD. These include the risk of adverse events (mainly cardiovascular accidents) due to the donation and wastage of autologous blood due to postponement of surgery or due to less blood loss

during the operation than expected. Average wastage of autologous predeposited blood has been reported to be 30-50% [28,29], which also increases the costs. The procedure is time consuming for both the patient and bloodbank personnel. There is also a risk of administrative error, introducing the possibility of transfusion reactions and transmission of infectious diseases. Furthermore, a decrease in natural killer cell activity has been reported with preoperative blood donation [30]. Finally, PABD can only be employed for procedures which can be planned several weeks ahead.

The technique of acute normovolemic hemodilution offers several advantages over preoperative autologous blood donation. This technique does not require planning of the surgical procedure several weeks beforehand. The blood that is withdrawn during ANH is usually kept in the operation room thus minimising the risk of giving a wrong unit to the wrong patient. Because the blood is whole blood containing fresh erythrocytes, functioning thrombocytes and labile clotting factors this should have a beneficial effect on clotting parameters which may diminish postoperative blood loss and reduce the amount of homologous blood used. The procedure is relatively inexpensive. Disadvantages include extra workload for the anesthesia personnel and the fact that ANH is less efficient in avoiding blood transfusions than PABD, as is also shown in the present study.

The technique of hemodilution as a method for limiting the amount of homologous blood needed perioperatively has been addressed extensively in both animal and human studies. The degree of efficacy has been one of the questions [5,6,10,31]. Mathematical models evaluating the efficiacy of normovolemic hemodilution have resulted in contradicting conclusions. It has been concluded that savings attributable to normovolemic hemodilution are less than previously expected [5,10,31]. However a mathematical analysis of ANH showed that this method can diminish or (in some circumstances) even eliminate the need for allogenic transfusion [6]. Clinical studies employing acute normovolemic hemodilution have also shown conflicting results with respect to the decrease in the use of homologous blood [7,9,28]. The amount of homologous blood saved by using ANH depends on several factors, including the initial and the target hematocrit, and circulating blood volume. In the present study a significant difference was found between the amount of homologous blood used in the control group and in the group with ANH but with no significant difference in blood loss. This might have been improved by lowering the target hematocrit below the 25% as employed in this study, thereby

increasing the amount of blood withdrawn above 1450 ± 80 ml and making the procedure of ANH even more effective. The minimal acceptable hematocrit, however, has not yet been proven.

We investigated whether any evaluation could be made regarding the critical value of the hemoglobin level during hemodilution and whether a conclusion could be drawn concerning a possible transfusion trigger. In order to do this we evaluated the hemoglobin level at which in each individual patient the PvO_2 started to decrease below the more critical level of 33 mmHg [17]. Indeed, in the present study 60% of the hemodilution patients did reach such level of PvO_2; the mean corresponding hemoglobin level in these patients at that point was 4.8 ± 0.2 mmol/l. Therefore, at a hemoglobin level lower than 4.8 mmol/l in some patients the chance of reaching the more critical level of tissue oxygenation during hemodilution starts to increase. However, in 3 patients in the control group the PvO_2 also decreased below 33 mmHg at some points during the study. Further analysis showed that in these 3 patients the P_{50} showed the greatest decrease of all patients at this measurement. Mean change in P_{50} (from baseline to the measurement at which PvO_2 for the first time decreased below 33 mmHg) in these 3 control patients was -2.75 ± 0.47 versus -0.03 ± 0.31 in the 18 hemodilution patients. Therefore, in these control patients a more pronounced leftward shift of the oxygen dissociation curve (ODC) was observed than in the patients in the hemodilution groups. Thus, the change in PvO_2 in the patients in the control group was caused by a mechanism (leftward shift of the oxygen dissociation curve) other than the change in the other groups (decrease in oxygen flux). The leftward shift of the oxygen dissociation curve can probably be explained by the administration of homologous blood with low 2,3-DPG level, since the different transfusion practice was the major difference between the control group and the hemodilution groups.

Such a leftward shift of the ODC with transfusion of donor blood might impair the tissue oxygenation as reflected by the decrease in PvO_2, while a shift to the right of the ODC as found in the patients who donated their own blood (PABD group) in this study might be beneficial. Our observation of a rightward shift of the ODC with donation of blood is in accordance with earlier observations [32]. In pigs we observed at every step of hemodilution an acute shift of the ODC to the right [17,18] while in one study in dogs an acute shift to the right during acute anemia occurred, but not before hematocrit dropped below 10% [33]. In our studies in pigs a close relationship was found between the shift

in ODC and the changes in the for pH corrected PvO_2 [18]. In the present study in anesthetized patients we did not observe such an acute change in the position of the ODC during hemodilution. However, it has been suggested that changes in ODC might play a role in oxygen delivery, especially when oxygen reserves are minimal [34].

The value of the pulmonary wedge pressure as an indicator of normovolemia during hemodilution is unclear. Several studies used central venous pressure or pulmonary wedge pressure as an indicator to keep their subjects normovolemic during the induction of hemodilution [13,35]. Others, however, found an increase in central venous pressure or pulmonary wedge pressure as the hematocrit decreased [3,15]. In the present study we found a linear relationship between the hemoglobin level and the measured pulmonary wedge pressure (Figure 1). The recorded values in group1 (ANH) were lower than all three other groups and can probably be explained by the procedure followed in this group. Acute normovolemic hemodilution was induced immediately after induction of anesthesia. This was followed by a period with only limited blood loss (lymphnode dissection), which lasted approximately 1-2 hours. During this period the gelatin solution used as colloid could have already been partly excreted; this would have induced a slightly hypovolemic situation. The relationships between the other three groups are very similar (although the control group has no measurements at low hematocrit values), and no increase over time was observed in the control group once the lowest hematocrit was reached in this group. This indicates that the observed increase in PWP can not be explained by any factor other than the hemodilution itself. Therefore we speculate that the normal PWP value during normovolemia is dependent on the hematocrit and that during hemodilution higher PWP values should be pursued. Increased PWP values in the hemodilution groups can also be explained by the fact that the change in plasma volume caused by the infused plasma substitutes might have exceeded the volume of blood loss; this, however, is unlikely. In another study in humans the infusion of one liter of dextran 40 (Isodex®) increased plasma volume in vivo by only 640 ml, while one liter of the gelatin solution (Geloplasma®) increased plasma volume by only 470 ml [36]. It is therefore more likely that, in the present study, the volume of blood loss was not totally replaced by the infused amount of plasma substitutes. Furthermore, in the control group infusion of 250 ml of packed red cells together with 250 ml of colloid for every 500 ml of blood loss and keeping the hematocrit constant, did

not cause an increase in PWP, while in the hemodilution patients at the end of surgery and in the first 2 hours postoperatively the increase in hematocrit associated with the transfusion of blood decreased the PWP despite the volume loading. In studies keeping central venous pressure or pulmonary wedge pressure at baseline values during hemodilution the increase in cardiac output is much less, while heart rate may increase [37,38]. During hemodilution blood viscosity is decreased resulting in an acceleration of blood flow, especially in low flow vessels such as the venous circulation. Increased flow at the venous site might have increased venous return and therefore the filling pressures of the heart.

Hemodilution causes a decrease in oxygen carrying capacity, which is compensated by an increase in cardiac output, mainly due to an increase in stroke volume combined with an increase in oxygen extraction ratio. Some hemodilution studies in humans showed a decrease in heart rate during moderate hemodilution [11,13,39]. In several studies applying moderate normovolemic or hypervolemic hemodilution in humans it was shown that oxygen delivery and tissue oxygenation are well maintained with no change in arteriovenous oxygen difference [15,40,41]. However, in contrast, several other studies applying normovolemic hemodilution in humans have shown an increase in cardiac output accompanied by an increase in oxygen extraction ratio [2,3,11,13,15,16,39,42]. It has also been shown in dogs that hemodilution can alter the slope of the oxygen dissocation curve, improving oxygen unloading [43]. In the present study we observed in all three hemodilution groups, as well as in the control group in which very limited hemodilution was induced, an increase in cardiac index with no significant change in heart rate but with an increase in oxygen extraction ratio. The hemodynamic changes observed were comparable to these observed in other studies on hemodilution during general anesthesia (Figure 3). One of the obvious differences in hemodynamic changes during hemodilution that was observed between the three hemodilution groups was the increase in pulmonary wedge pressure, which was less pronounced in the group with acute normovolemic hemodilution (as discussed above). This might have caused slight hypovolemia which is also suggested by the fact that the initial increase in cardiac index is somewhat less pronounced in this group thus resulting in the largest decrease in oxygen flux. The calculated decrease in oxygen flux in the ANH group was 33 ± 4% with a simultaneous decrease in hemoglobin level of 51 ± 1%, while this decrease in oxygen flux was 5 ± 8% and 13 ± 6% in

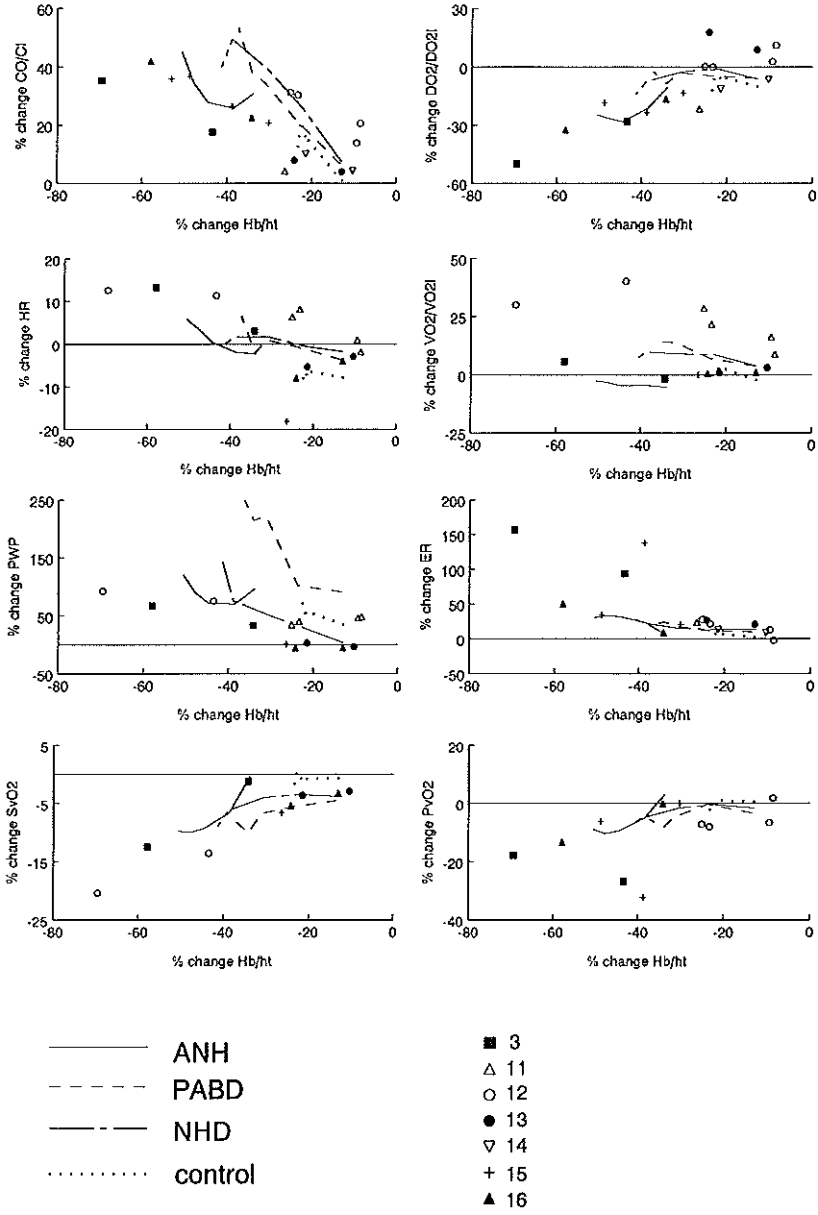

Figure 3.

Comparison of changes in several hemodynamic and oxygenation parameters in other studies in anesthetized humans [3,11,12,13,14,15,16] and the present study.

groups 2 (PABD) and 3 (NHD), respectively with a concomitant decrease in hemoglobin of 38 ± 3% and 44 ± 1%, respectively. This stresses the importance of maintaining normovolemia during hemodilution in order to maintain the compensation mechanisms at the optimal level. This probably means that keeping central venous pressure or pulmonary wedge pressure constant during induction of hemodilution results in a more or less hypovolemic state and thus restricts the compensation mechanisms during the decline in hemoglobin level.

The conclusions drawn from the present study are:

1. PABD is more effective in reducing the amount of homologous blood needed peroperatively than ANH (or NHD).
2. During normovolemic hemodilution the pulmonary wedge pressure increases as hematocrit decreases.
3. In 60% of the hemodilution patients PvO_2 started to decline below 33 mmHg at a mean hemoglobin level of 4.8 ± 0.2 mmol/l.
4. In some patients receiving homologous blood the PvO_2 reached critical values due to a leftward shift of the oxygen dissociation curve.

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Chapter 6

ACUTE HYPERVOLAEMIC HAEMODILUTION TO AVOID BLOOD TRANSFUSIONS DURING MAJOR SURGERY

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Summary

16 patients underwent acute hypervolaemic haemodilution with dextran 40 and Ringers lactate, to see whether this procedure could avoid perioperative blood transfusion. Packed cell volume (PCV) and oxygen extraction decreased, and cardiac index and pulmonary wedge pressure increased, although end-systolic area was unchanged. PCV was not significantly different between patients who lost less than or greater than 20% of their initial blood volume. This preoperative manoeuvre, which reduces loss of red blood cells, allowed major surgery to be completed safely without blood transfusion.

Introduction

The risk of alloimmunisation and transmission of viral infection from homologous blood transfusion is well known. In addition, it is suggested that transfusion may promote tumor growth [1]. Some patients may refuse blood transfusions on religious grounds [2]. Transfusion with donor blood may be diminished by predeposited autologous blood [3], intraoperative autotransfusion with a cell-saver [4], and haemodilution techniques. With haemodilution, fewer red cells are lost because of the non-linear decrease in packed cell volume after the procedure [5].Preoperative acute haemodilution can be achieved in two ways. First, by withdrawal of blood and simultaneous infusion of plasma substitutes (normovolaemic haemodilution) [6]. Second, by rapid infusion of fluid without blood withdrawal (hypervolaemic haemodilution). We have evaluated the effects of hypervolaemic haemodilution on haemodynamics, left ventricular size, systemic oxygenation, and packed cell volume to establish whether this technique avoids blood transfusions peroperatively.

Patients and methods

16 consecutive Jehovah's Witness patients (3 males, 13 females; mean age [SD], 51 [14] years) were admitted for major surgery and refused both homologous blood products and autologous transfusion. All patients gave

informed consent to the study protocol, which was approved by an ethical committee at the Erasmus University Hospital, Rotterdam.

On the day of surgery two intravenous cannulae were inserted. The radial artery was cannulated and a thermodilution catheter ('Swan Ganz', AEL, USA) introduced into a pulmonary artery via the internal jugular vein. 2.5 mg intravenous midazolam was given before catheter placement. Heart rate, arterial blood pressure, pulmonary artery pressures, and right atrial pressure were monitored continuously ('Horizon 2000', Mennen Medical, Israel). After 30 min stabilisation, baseline values of mean arterial pressure (MAP), mean pulmonary artery pressure (PAP), pulmonary wedge pressure (PWP) and cardiac output (CO) were obtained. In addition, arterial and mixed venous blood samples were taken for measurements of haemoglobin (Hb), Hb oxygen saturation ('Spectrophotometer OSM3', Radiometer, Copenhagen), packed cell volume (PCV), and PO_2, PCO_2, and pH ('ABL 330', Radiometer, Copenhagen). Systemic vascular resistance, pulmonary vascular resistance, oxygen flux, and oxygen uptake were calculated from these data. Oxygen flux is the product of arterial oxygen content and cardiac output. Oxygen uptake is the product of cardiac output and the arteriovenous oxygen content difference. The oxygen extraction ratio is calculated by dividing oxygen uptake by oxygen flux.

Anaesthesia was induced with fentanyl 5 μg/kg, thiopentone 5 mg/kg, and pancuronium 0.1 mg/kg. After tracheal intubation, the lung were ventilated with 70% nitrous oxide in oxygen, and tidal volume was adjusted to achieve normocapnia. Anaesthesia was maintained with fentanyl and enflurane (end-tidal 0.4 vol %) and muscle relaxation was achieved with pancuronium. The bladder was catheterised.

A transoesophageal ultrasound transducer (5 MHz 'Toshiba', connected to a Toshiba 'SSH 160' machine) was placed for continuous real-time visualisation of the heart. The transducer was positioned to obtain a two-dimensional short-axis view of the left ventricle at the level of the papillary muscle. After the optimum view had been obtained, the steering mechanisms of the transducer were locked to maintain the identical cross-sectional view throughout the period of volume loading. Simultaneously with the haemodynamic recordings, the images were recorded on 'VHS' videotape for subsequent analysis. The end-diastolic and end-systolic enclosed areas of the left ventricle were measured after tracing the endocardial borders. Three consecutive beats were averaged.

After 15 min stabilisation, haemodynamic and echocardiographic

measurements together with an analysis of blood gases were made. We undertook hypervolaemic haemodilution in three equal steps. 500 ml dextran 40 and 500 ml Ringers lactate were infused over 10 min. All measurement were repeated after each step. After surgery began, the same variables, except for the echocardiographic values, were recorded after the 500 ml blood loss. Peroperatively, Ringers lactate was infused in a volume equal to the urine output plus 8 ml/kg per h (to compensate for fluid loss from the wound). Blood loss was replaced by an equal volume of gelatin solution.

Immediately before surgery was completed, the forced infusion was stopped. Measurements were repeated at the end of surgery, and at 20 min, 2 h, and 4 h thereafter.

The reported baseline blood volumes are calculated values [7]. The accepted probability for a statistical difference between means was $p < 0.05$. Statistical analysis of results was by Students's *t*-test and the Wilcoxon signed-rank test.

Results

11 patients underwent a laparotomy and 1 a nephrectomy; 3 patients had a hip replacement; and 1 patient received a facial bone reconstruction. Haemodynamic and echocardigraphic results are summarized in Table 1. Stepwise acute hypervolaemic haemodilution, with a change in PCV from 36.9 (3.1) to 26.3 (2.4), resulted in a 29.3% decrease in the mean systemic vascular resistance index. The increase in the mean cardiac index of 27.5% (2.45 [0.65] *vs* 3.10 [0.68]) correlated with a 27.6% increase in the mean end-diastolic area of the left ventricle. Increases in the mean PWP and PAP from 5.3 mmHg (3.2) to 20.8 mmHg (4.2) and from 12.3 mmHg (3.9) to 31.0 mmHg (5.2) respectively, were recorded. Other haemodynamic variables did not change, except for a slight increase in MAP and a slight decrease in heart rate. 2 hours postoperatively all haemodynamic variables had returned to pre-anaesthetic values except for the systemic vascular resistance index. The increase in cardiac output was associated with an increase in end-diastolic area. With further volume loading, end-diastolic area no longer increased, and the rise in cardiac output was associated with a decrease in end-systolic area. In no patient did an

increase in end-diastolic area lead to a significant decrease in cardiac output.

The results of systemic oxygenation are shown in Table 2. Stepwise hypervolaemic haemodilution did not lead to changes in arterial or mixed venous blood gases. Oxygen flux was constant over the study period because cardiac output compensated for the decreased oxygen transport capacity that took place with haemodilution and blood loss. The constant oxygen flux and decreased consumption resulted in a decreased extraction ratio.

The changes in PCV in patients with a blood loss < 20% of their calculated initial blood volume (14.2 [4.1]%; n=8) and in patients with a blood loss > 20% of the baseline blood volume (42.4 [17.7]%; n=8) are shown in the figure. 2 h postoperatively the difference in PCV was not statistically significant (32.2 [2.7] *vs* 30.8 [4.1]). Only at the end of surgery was a significant difference in PCV seen between the two groups (27.8 [1.6] *vs* 24.8 [3.9]). Blood loss in all patients was 28.2 [18.3]% of the calculated initial blood volume.

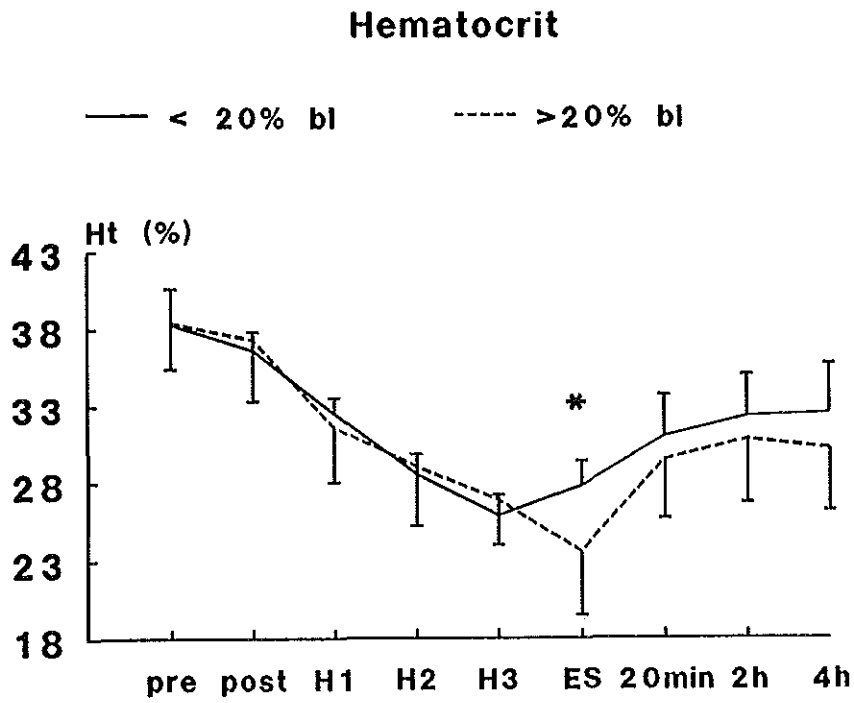

Fig 1. *Change in PCV pre and post anesthetic induction.*
———, *< 20% blood loss;* ---------, *> 20% blood loss.* * *P < 0.05.*

Table 1 *Systemic haemodynamic measurements before and after induction of anaesthesia*

	HR (bpm)	MAP (mmHg)	PAP (mmHg)	PWP (mmHg)	CI (l/min/m²)	EDA (cm²)	ESA (cm²)	PCV (%)
Pre-induction	85 (15)	104 (28)	14.3 (3.1)	4.9 (2.9)	3.06 (0.85)			38.3 (2.8)
Post-induction	95 +(16)	81 + (15)	12.3 + (3.9)	5.3 (3.2)	2.43 +(0.65)	12.3 (3.7)	6.0 (2.7)	36.9 (3.2)
H1	84 * (15)	87 + (15)	19.4 +* (4.3)	10.8 +* (4.4)	2.94 * (0.78)	14.4 * (3.9)	6.6 (2.9)	32.1 +* (2.8)
H2	83 * (14)	87 + (15)	24.9 +* (3.6)	16.6 +* (4.1)	3.07 * (0.74)	15.7 * (3.5)	6.2 (2.5)	28.8 +* (2.9)
H3	85 * (15)	91 +* (15)	31.0 +* (5.2)	20.8 +* (4.2)	3.10 * (0.68)	15.7 * (3.9)	5.8 (2.3)	26.3 +* (2.4)
ES	89 (20)	83 + (15)	19.8 +* (7.8)	11.4 +* (6.6)	3.19 * (0.89)			26.6 + (3.2)
20 min post-op	89 (17)	92 * (15)	17.0 +* (4.0)	6.5 (4.6)	3.53 (1.19)			30.6 +* (3.4)
2 h post-op	87 * (13)	86 + (16)	14.9 (3.1)	4.3 (2.8)	3.43 (1.24)			31.6 +* (3.6)
4 h post-op	88 * (15)	84 + (15)	15.0 (3.2)	4.4 (3.3)	3.51 (0.91)			31.6 +* (3.8)

H1, H2, and H3 show data for each step of hypervolaemic haemodilution up to the end of surgery (ES).
HR = heart rate; CI = cardiac index; ESA = end systolic area.
* $p<0.05$ compared with post-induction values. + $p<0.05$ compared with pre-anaesthetic values.

Table 2 *Systemic oxygenation before and after induction of anaesthesia*

	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	PvO_2 (mmHg)	$PvCO_2$ (mmHg)	O_2flux (l/min/m²)	VO_2 (l/min/m²)	ER (%)	FiO_2
Pre-induction	87 (15)	36 (3)	41 (4)	40 (3)	505 (144)	102 (21)	0.21 (0.04)	0.21
Post-induction	168 + (29)	32 (3)	44 + (4)	37 * (4)	418 +(127)	91 + (21)	0.23 +(0.05)	0.32
H1	166 + (33)	33 (3)	46 + (4)	36 * (3)	431 +(122)	84 + (17)	0.20 * (0.04)	0.32
H2	167 + (29)	33 (3)	46 + (4)	36 * (3)	404 +(103)	80 +* (16)	0.21 * (0.05)	0.32
H3	170 + (27)	32 (4)	47 + (4)	35 * (3)	378 +(97)	73 +* (15)	0.20 * (0.06)	0.32
ES	135 + (38)	36 * (4)	45 + (6)	39 (4)	399 +(123)	82 +* (21)	0.22 (0.07)	0.32
20 min post-op	88 * (19)	42 +* (4)	43 (6)	45 +* (4)	477 (151)	112 * (35)	0.24 +(0.05)	0.21
2 h post-op	102 * (24)	39 (5)	42 (6)	44 +* (6)	492 (164)	119 +* (33)	0.26 +(0.07)	0.21
4 h post-op	96 * (24) *	39 * (4)	42 (6)	43 * (4)	500 (138)	123 * (30)	0.25 (0.06)	0.21

* $p<0.05$ compared with post-induction values. + $p<0.05$ compared with pre-anaesthetic values.

Discussion

Hypervolaemic haemodilution improves cerebral circulation [8] and may be a useful treatment for haemorrhagic disorders in pre-eclampsia [9]. In these reports, haemodilution was induced slowly over 24 h or more. Apart from one case-report of an anaemic Jehovah's Witness [10], the effect of rapid volume loading have not been documented in man.

We found significant increases in PWP and PAP. This result may be because of an increased venous return to the heart after a reduction of viscous resistance of blood by haemodilution [11]. Excessive volume loading is also likely to have contributed to an increased PWP, but in no patient was there any clinical evidence of pulmonary oedema. Intermittent positive pressure ventilation may have avoided such a complication. Extubation of the patients' lungs was possible directly after surgery because, when the forced infusion was stopped, PWP and PAP returned quickly to normal.

Although the end-diastolic diameter of the left ventricle increased, there was no reduction in left ventricular performance because end-systolic diameter remained the same.

A small but significant reduction of oxygen consumption and extraction ratio was observed. Postoperatively the extraction ratio increased to a value above that seen before induction of anaesthesia and was due to an increase in oxygen consumption that confirms the findings of others [12].

Acute preoperative isovolaemic haemodilution gives a supply of the patients' blood and results in fewer red cells being lost in an episode of haemorrhage. This technique is time consuming and needs special arrangements - eg, collection and storage of patients' blood. This technique of hypervolaemic haemodilution allowed major surgery without blood transfusion and was tolerated safely by all patients. However, this study applies only to surgical patients with no associated medical illness and cannot be recommended in patients with a compromised cardiovascular system. Furthermore, it is uncertain whether hypervolaemic haemodilution can influence the total amount of blood loss during surgery.

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TRANSESOPHAGEAL ECHOCARDIOGRAPHIC MONITORING OF PREOPERATIVE ACUTE HYPERVOLEMIC HEMODILUTION

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Summary

Preoperative acute hypervolemic hemodilution is used in anesthesia to reduce the loss of blood cells during intraoperative bloodloss. Indications for use of the technique might be broadened if it can be shown to be safe in older as well as younger patients. Few data are available describing heart function in humans subjected to hypervolemic hemodilution.

Methods: Nineteen anesthetized Jehovah's Witnesses (ages 22-70 yr) without evidence of heart disease had hypervolemic hemodilution before surgery in three stages, each consisting of an infusion of 500 ml dextran 40 (50 g/l) and 500 ml Ringer's lactate over a 10-min period. After each stage, the size and function of the left ventricle were recorded by transesophageal cross-sectional echocardiography in the short-axis view. Simultaneously heart rate, arterial blood pressure, pulmonary arterial and wedge pressures and cardiac output were recorded, to compare the echocardiographic and hemodynamic data.

Results: No complications occurred. Hypervolemic hemodilution resulted in an increased cardiac output by increasing the stroke volume from 48 ml in basal conditions to 67, 71, and 72 ml over the three stages, whereas heart rate did not increase. There was an initial increase in end-diastolic volume of the left ventricle, as assessed from the cross-sectional end diastolic area from 12.9 to 15.5, 16.6, and 16.9 cm^2 followed by a decrease in the in cross-sectional end-systolic area from 6.3 to 6.8, 6.0, and 5.7 cm^2. The increase in wedge pressures (from 5.9 to 12.4,17.9, and 22.6 mmHg) did not lead to progressive cardiac dilatation. There was a curvilinear relation between wedge pressure and cross-sectional end-diastolic area. Stroke volume did not decrease, nor did cross-sectional end-systolic area increase; instead, a decrease in end-systolic area was a common observation.

Conclusions: The described regimen of acute hypervolemic hemodilution is well tolerated during anesthesia by patients without heart disease and does not lead to cardiac failure. It leads to an increase in stroke volume that is generated initially from an increase in end-diastolic volume, followed in many patients by a decrease in end-systolic volume, the mechanism of which is as yet unclear.

Key words: Blood: transfusion. Measurement techniques: transesophageal echocardiography. Transfusion, hemodilution: hypervolemic.

Introduction

Preoperative acute hypervolemic hemodilution is used to reduce the loss of blood cells during intraoperative bleeding and thus avoid the need for blood transfusion. After surgery the hematocrit is partially restored by administering diuretics to remove the excess of intravascular fluid. To date, hypervolemic hemodilution usually has been used in patients who need major surgery but refuse (often for religious reasons) all blood transfusion, including autologous. The indications, however, could be expanded to include any major surgery if the potential risks (especially the risks of acute cardiac failure and pulmonary congestion) can be proven to be low. Our initial experience showed that the procedure is clinically safe [1,2]. In this study we describe in greater detail the effects of acute hypervolemic hemodilution on cardiac size and function and the relation of this echocardiographic information to hemodynamic information obtained through pulmonary artery catheterization and systemic pressure monitoring.

Material and methods

Nineteen patients (3 men and 16 women) undergoing preoperative acute hypervolemic hemodilution were studied. Their ages were 22-70 yr (mean 48 yr) and their weights 48-99 kg (mean 70 kg). All patients were Jehovah's Witnesses who refused any blood transfusion. All had to undergo procedures with an expected significant blood loss. Four were scheduled for orthopedic surgery, the remainder for oncologic surgery. All were informed in detail on the procedure and gave written informed consent before surgery. The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam-Dijkzigt.

Any evidence of heart disease was an exclusion criterion for hypervolemic hemodilution. Eligible patients were referred to our hospital after screening for heart disease. None of the referred patients was subsequently excluded. One patient had a history of mild hypertension, and one had a history of hypertension and chest discomfort without documented ischemia. The others had no evidence of cardiovascular disease in the history or physical examination or on the

preoperative electrocardiogram or chest x-ray.

After receiving 2.5 mg midazolam intravenouslyy, two venous cannulae, an arterial cannula (radial artery), and a pulmonary artery thermodilution catheter (Swan-Ganz, American Edwards Laboratories) were inserted and calibrated to room air for the zero-level of the pressure. Heart rate, arterial blood pressure, right atrial pressure and pulmonary artery pressure were recorded continuously (Horizon, Mennen Medical). The pulmonary capillary wedge pressure (PCWP) was measured intermittently, as a mean pulmonary occlusion pressure at end-expiration. Cardiac output was determined by thermodilution as a mean of three consecutive measurements. A five-lead electrocardiogram (leads X, Y, Z, V2, and V5) was monitored continuously in combination with automated ST-segment analysis. Standard 12-lead electrocardiograms were obtained in all patients 1 day preoperatively, 1 day postoperatively, and 5-8 days postoperatively.

Anesthesia was induced with fentanyl 5 μg/kg, thiopental 5 mg/kg, and pancuronium 0.1 mg/kg. After tracheal intubation the lungs were ventilated with 70% nitrous oxide in oxygen, and tidal volume was adjusted to achieve normocapnia. Anesthesia was maintained with enflurane (end-tidal 0.4 vol%). No additional fentanyl was administered during the hypervolemic hemodilution. After induction of anesthesia a transesophageal ultrasound probe (5-MHZ transducer connected to a Toshiba SSH 160 ultrasound machine) was introduced for continuous and real-time imaging of the heart. The transducer was positioned in the stomach to obtain a two-dimensional short-axis view of the left ventricle at the level of the papillary muscles. After the optimum view had been obtained, the steering mechanisms of the probe were locked and the probe was carefully secured to maintain the identical cross-sectional view throughout the preoperative hypervolemic hemodilution. After a stabilization period of 15 min after induction of anesthesia, baseline hemodynamic data were recorded; blood gas samples were drawn from the arterial and pulmonary arterial catheters; and for 1 min the echocardiographic short-axis view of the left ventricle was recorded on videotape for subsequent analysis.

Hypervolemic hemodilution was then undertaken in three equal stages. Each stage consisted of the infusion of 500 ml dextran 40 (50 g/l) and 500 ml Ringer's lactate over a 1 0-min period. After each stage, all measurements and a recording of the echocardiogram were repeated. The whole procedure took 45-50 min in all patients. Surgery did not start until the hypervolemic hemodilution and all the measurements had been completed.

The echocardiographic two-dimensional images were analyzed off-line from the videotape recordings. Adequate echocardiographic recordings were available for 17 of 19 patients; for 1, the images were lost after a technical error, and for another the image quality was inadequate for analysis. Of three consecutive cardiac cycles, the end-diastolic and the end-systolic echoframes were selected. The end-systolic frame was defined as the one with the smallest enclosed area of the left ventricular cavity. (In case of doubt, several were measured to find the smallest.) The end-diastolic frame was defined as the one with the largest enclosed area, and this always happened to be the first frame on which the QRS complex was visible on the synchronously recorded electrocardiogram. The endocardial borders of the left ventricle were traced with a hand-held input device (a "mouse") and a digitizing tablet connected to a microcomputer-based analysis system, used to calculate the enclosed area of the left ventricular cavity. Data of three cardiac cycles were averaged, and if two measurements differed by more than 10% the data were rejected and the tracing was repeated using three other cardiac cycles.

Analysis of variance with subsequent *t* tests were used for all hemodynamic and echocardiographic variables to identify any significant changes during hypervolemic hemodilution and to determine the stages between which the changes were significant. Level of significance was defined as $P < 0.05$.

Results

Preoperative acute hypervolemic hemodilution was completed in all patients according to the protocol without complications, and all patients subsequently underwent uneventful surgery without blood transfusions. The mean values for the whole group are summarized in Table 1.

Hypervolemic hemodilution resulted in an increase in cardiac output by 36%, solely the result of an increase in stroke volume because heart rate, after an initial decrease, was unchanged. This was a consistent finding in all individuals (Figures 1 and 2).

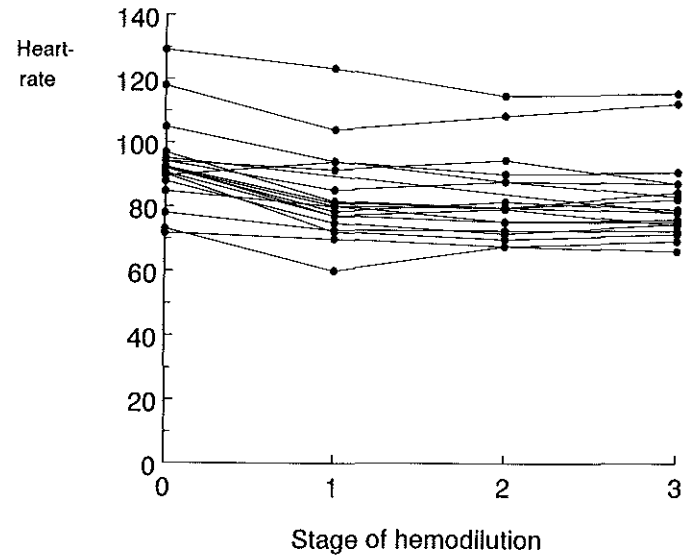

Figure 1. *Heart rate of individual patients during hypervolemic hemodilution.*

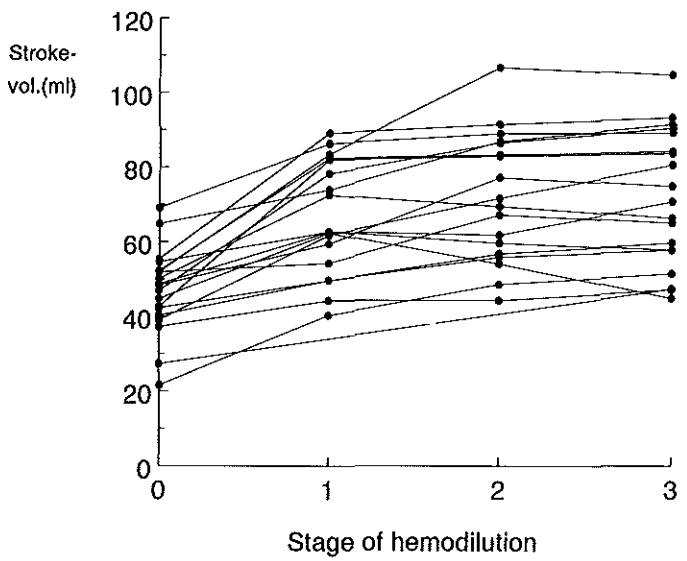

Figure 2. *Stroke volume of individual patients during hypervolemic hemodilution.*

The cross-sectional end-diastolic area (EDA) initially increased in all patients. However, in most patients the EDA reached a maximum at some point in time during the volume loading, beyond which there was no further increase in EDA despite a further increase in PCWP. The relation between EDA and PCWP was curvilinear for the mean values (Table 1) as well as for most individual patients (Figure 3). There was a wide range in the volume of fluid infused before the maximum EDA was reached; in 5 of 17 patients the EDA did not increase after the first liter, in 5 of 17 the maximal EDA was reached after 2 liters infusion and in 7 patients the largest EDA was present after infusion of 3 liters. In these 7 patients, however, increases from the previous recording were minimal. The maximal EDA was usually reached at PCWPs between 15 and 18 mmHg.

The change in cross-sectional end-systolic area (ESA) was variable. In 12 of 17 patients a decrease in ESA was observed, which had commenced at the stage when EDA had reached its maximum in 10 of these 12, whereas in two patients the ESA had started to decrease one stage earlier. In 5 patients no decrease in ESA was observed, and 4 of these were patients in whom the EDA was still increasing at the final stage of the study. Because there was considerable variation among patients in the amount of fluid infused before a decrease in ESA, the mean changes in ESA (Table 1) are somewhat blunted with a significant decrease only between the second and third stages of hemodilution.

Hypervolemic hemodilution was associated with a steep increase in PCWP (Table 1 and Figure 3). Although the PCWP correlated closely with the amount of fluid infused in the individual patient, the amount of fluid required to reach a certain level of PCWP varied widely among patients, depending also on the PCWP at baseline. In 4 of 19 patients PCWP had exceeded 15 mmHg already after infusion of 1,000 ml, in 10 of 19 patients after the infusion of 2,000 ml, in 3 patients after 3,000 ml, whereas in 2 patients PCWP was still less than 15 mmHg after the infusion of 3,000 ml fluid.

In four of the five patients with the greatest increase in PCWP (ending at 25, 28, 26, 26, and 30 mmHg) EDA had reached its maximum after infusion of 1,000 ml (at PCWPs of 14, 16, 14, and 16 mmHg) and had not increased thereafter.

In one patient in this series, there was a decrease in cardiac output before the completion of hemodilution (from 5.9 to 5.1 l/min during the final stage) associated with an increase in ESA (from 6.2 to 7.0 cm^2), suggesting that cardiac function was depressed. However, these changes were associated with

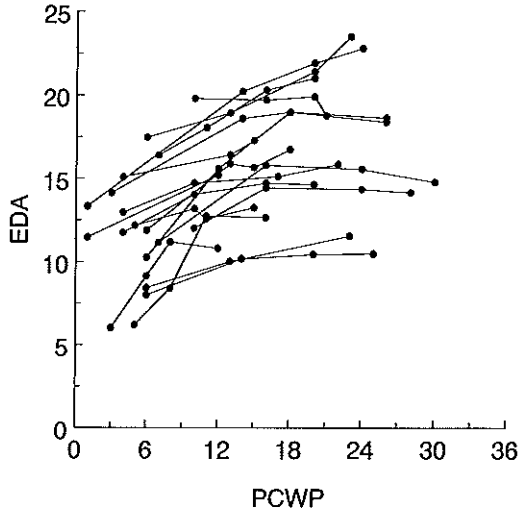

Figure 3. *Changes in echocardiographic end-diastolic area (EDA) during hypervolemic hemodilution in individual patients* versus *simultaneously measured pulmonary wedge pressure (PCWP).*

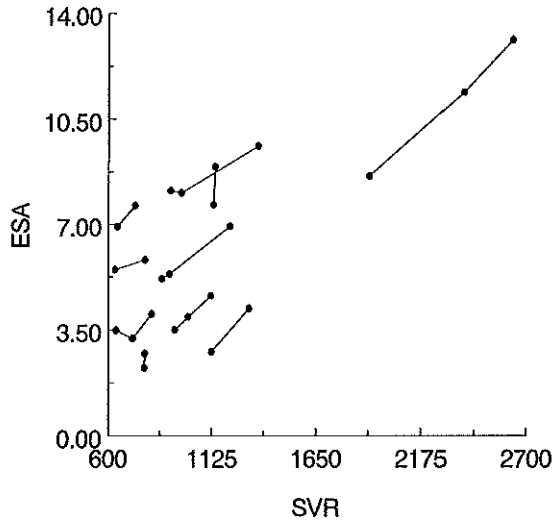

Figure 4. *Changes in echocardiographic end-systolic area after the maximal end-diastolic area had been reached* versus *systemic vascular resistance.*

Table 1 *Hemodynamic data.*

volume load (ml)	Hct %	CO L/min	HR beats/min	BP_{syst} mmHg	BP_{diast} mmHg	BP_{mean} mmHg	PCWP mmHg	SV ml	LVSW g/min	SVR dyne.s.cm^5	EDA cm^2	ESA cm^2	SF %	σES
baseline	37±3	4.4±1.1	93±14	105±21	66±10	81±14	5.9±2.6	48±11	49±14	1,498±626	12.9±3.5	6.3±2.6	6.7±6.5	148±58
1,000	32±3*	5.5±1.3*	83±15*	114±20*	67±10	87±14*	12.4±3.0*	66±15*	67±19*	1,197±461*	15.5±3.3*	6.8±2.6	6.8±6.4	162±61
2,000	29±3*	5.8±1.5*	82±14	117±23	68±11	88±15	17.9±3.8*	71±17*	68±24	1,063±391*	16.6±3.4*	6.0±2.3*	7.1±7.7	163±55
3,000	26±3*	6.0±1.5	83±14	121±21	70±11	92±14	22.6±4.2*	72±18	68±23	1,012±307	16.9±3.7	5.7±2.1	8.0±8.6	162±47

Values are mean ± SD.

Hct = hematocrit; CO = cardiac output; HR = heart rate; BP_{syst} = systolic arterial blood pressure; BP_{diast} = diastolic arterial blood pressure; BP_{mean} = mean arterial blood pressure; PCWP = pulmonary capillary wedge pressure; SV = stroke volume; LVSW = left ventricular stroke work; SVR = systemic vascular resistance; EDA = end-diastolic cross-sectional area of the left ventricular cavity; ESA = end-systolic area; SF = pulmonary shunt fraction; σES = end-systolic wall stress.

* $P < 0.05$ versus the previous measurement.

Table 2 *Distribution of Sex, Age, and Weight of the 19 patients*

patient no	sex	age (yr)	weight (kg)
1	F	43	48
2	F	50	74
3	F	44	61
4	F	42	55
5	F	48	68
6	F	59	64
7	M	22	65
8	F	68	64
9	M	70	70
10	F	49	88
11	M	44	99
12	F	49	90
13	F	41	57
14	F	50	69
15	F	49	70
16	F	54	88
17	F	46	86
18	F	51	55
19	F	38	66

a significant increase in systemic vascular resistance (SVR) and mean arterial blood pressure (from 79 to 101 mmHg) and not by any sign of ischemia. In all other patients, the cardiac output was either increasing or stable throughout hypervolemic hemodilution.

No regional wall motion abnormalities of the left ventricle, indicating myocardial ischemia, [3] were encountered. In one patient, aged 70 yr, ST-segment changes of just less than 0.1 mV developed after induction of anesthesia, resolved during the initial stages of hemodilution, and than returned at maximal infusion. There were no other patients with intraoperative ST-segment changes, nor were the postoperative electrocardiograms different from the preoperative electrocardiogram in any patient.

No pulmonary or ventilatory problems were encountered despite the high PCWPs. No positive end-expiratory pressure ventilation was used in any patient. At an unchanged inspired oxygen fraction of 30% and with tidal volumes adjusted to maintain nommocapnia, the systemic arterial and mixed venous oxygen tensions remained unchanged, in accordance with our previously reported experience [2]. Pulmonary shunt fractions were stable for each

individual patient and at group level (Table 1), despite considerable variation among patients.

Discussion

Hypervolemic hemodilution caused an increase in cardiac output resulting entirely from an increase in stroke volume; heart rate and arterial blood pressure remained unchanged. This observation is in agreement with other studies in which acute hypervolemic hemodilution was used in humans [4-7].

Initially the increase in stroke volume was generated from an increase in the end-diastolic volume of the left ventricle, suggesting a Frank-Starling effect, up to a maximum, which was reached at PCWP of approximately 15-18 mmHg. With further filling there was only an insignificant increase in the end-diastolic volume, even when PCWPs of as much as 28 or 30 mmHg were achieved. This is in agreement with previous animal experiments [8]. It is well known that healthy myocardium has an extremely low distensibility when sarcomere length exceeds 2.2 μm, and it is almost impossible to stretch a strip of cardiac muscle to sarcomere lengths greater than 2.4 μm. This has been explained by the presence of a collagen skeleton that surrounds the cardiac muscle fibers and that constitutes an effective protection against acute dilatation. Also the pericardium has a role in limiting acute cardiac dilatation. More insight into the relative importance of these mechanisms might be obtained from simultaneous measurements of intrapericardial pressure. No clinical experience is available on hypervolemic hemodilution in patients who have had a previous pericardiectomy. Some animal studies suggest that the left ventricle does not need the pericardium as a protective mechanism against acute dilatation, in contrast to the right ventricle [9]. Few data are available in humans. Mangano et al. [10] showed that the muscle of the left ventricle itself, and not the pericardium is the major determinant of diastolic compliance when filling pressures and volumes are moderately increased. However, others do attribute a role to the pericardium in protecting the left ventricle from progressive dilatation in acute increases in volume load in the range our patients received [11]. The clinical implication is that it might be dangerous to apply hypervolemic hemodilution in patients who have undergone a previous pericardiectomy.

The end-systolic volume of the left ventricle decreased with further hypervolemic hemodilution. This change could be due to a decrease in afterload, a Frank-Starling effect, an increase in myocardial inotropic state, or some combination of these effects. Studies in animals undergoing normovolemic hemodilution have shown that a decrease in hematocrit leads to an increased stroke volume that is generated from both a (slight) increase in end-diastolic volume (despite normovolemia in these experiments) and a decrease in end-systolic volume [12]. This decrease in end-systolic volume was then attributed to a decrease in afterload due to the lowered blood viscosity. The identical decrease in end-systolic volume was seen when animals were prevented from increasing their inotropic state by β-adrenergic blockade. In our patients, however, no decrease in arterial pressure was encountered because the decrease in SVR was compensated by the larger stroke volume, resulting in minor changes in systemic arterial pressures. A simplified estimate of end-systolic wall stress, as an index of afterload, remained unchanged (Table 1).#

A possible explanation is that after maximal EDA is achieved, a state of stable optimal performance exists in which ESA is dependent mainly on SVR. When we review the correlation between ESA and SVR in our patients after maximal EDA was achieved, the limited number of data do suggest such a direct correlation (Figure 4).

Our results are different from those of a study in humans by Mangano et al., [13] who reported an increase in end-systolic volume and a decrease in ejection fraction when increasing the preload. There are, however, several differences in study design that may explain these opposite findings. First, they infused 1,500 ml whole blood rather than plasma-expanders. Their decrease in SVR was small compared to ours, and arterial blood pressure increased considerably. Second, they studied patients immediately after coronary bypass surgery, and 13 of 15 patients had one or more previous myocardial infarctions.

#

The end systolic walls tress (table 1) was calculated using a simplification of Laplace's Law:

$$stress\ \sigma = P \times \frac{r}{2h'}$$

where P = pressure; r = radius; and h = wall thickness. r was calculated from the area, making the assumption that the short-axis of the left ventricle is a circle. Wall thickness was not considered because changes in end-systolic wall thickness throughout hemodilution were within the margin of error of M-mode echocardiographic measurements.

Hearts damaged by ischemic heart disease might respond differently to volume loading. Third, because PCWP in their study increased from 2 to 7 mmHg, their patients shifted from hypovolemia to normovolemia. The tendency to decrease end-systolic volume in our patients was observed only during hypervolemia. Indeed in our patients as well, the initial change in ESA often was an increase, especially in those who had a PCWP < 7 mmHg at baseline.

The decrease in SVR in this series cannot be explained by rheologic changes alone. Because of the nonlinear relation between hematocrit and blood viscosity**, the decrease in hematocrit from 37% to 25% would result in decrease in viscosity by 19%, presuming that the infused fluid has the same viscosity as plasma. Based on the viscosity of dextran 40 and Ringer's, this assumption is valid within a reasonable margin of error. Others have measured viscosity during hemodilution with combined Dextran 40 and crystalloid and could not demonstrate a change in plasma viscosity. But even if dilution had been performed with water, the predicted decrease in blood viscosity would be less than 30%. Because SVR decreased by 33% and because viscosity has a linear relation with SVR (Hagen-Poiseuille law), a net vasodilation must have occurred during hemodilution. This may be the result of the sum of the autoregulatory organ redistributions of circulating volume that occur in hemodilution [14,15]). Vasodilation may also have been caused by atrial natriuretic factor, the concentration of which rises steeply with acute hypervolemic hemodilution [16]. Other mechanisms that might in theory have decreased arteriolar tone include local tissue hypoxia, lactic acidosis or vasodilating metabolites such as adenosine. Unfortunately no measurements of atrial natriuretic factor, catecholamines or other neurohumoral factors were included in the study protocol. Another explanation might be the activation of vagal or nonmedullated receptors in the left ventricle, responding to ventricular distension and causing reflex arteriolar vasodilation [17]. This might also explain why the decrease in ESA started usually only after a maximal EDA had been reached, rather than running parallel with hemodilution.

This study did not include patients with a history of ischemic heart disease, and it is unknown whether hypervolemic hemodilution can be performed safely

** Predicted change in blood viscosity (see discussion) are based on the emperical van equation $v = v_p(1 + 0.025H + 0.000735\ H^2)$, where v = blood viscosity; V_p = viscosity of plasma; and H = hematocrit (percentage).

in such patients. In animal experiments, coronary blood flow increased out of proportion to the increased cardiac output during hemodilution, and this was due not only to rheologic changes but also to autoregulatory coronary vasodilation [14,18,19]. It is not known to what extent vasodilation occurs in atherosclerotic coronary arteries. A lower viscosity may improve flow across a stenosis, but in addition steal effects may occur after coronary vasodilation.

As an alternative to hypervolemic hemodilution, isovolemic hemodilution has been used in patients who accept the reinfusion of their own blood during or after surgery. It is not known, from the current literature, whether the apparently more physiologic condition of normovolemia is beneficial to the hemodiluted patient. Withdrawal of blood results in a decrease in maximum oxygen transport capacity, which is unaffected in hypervolemic hemodilution. When hypervolemic hemodilution was compared to normovolemic hemodilution, the former was shown to result in a higher oxygen transport, peripheral oxygen delivery and aerobic exercise capacity [20,21]. In an animal study, Messmer et al. [22] demonstrated that acute hemodilution to a hematocrit of 0.07 was survived by all animals if they were kept normovolemic, but by none that was hypovolemic, thus stressing the importance of volume status for the compensatory mechanisms for acute hemodilution.

In conclusion, preoperative acute hypervolemic hemodilution was well tolerated in patients without evidence of heart disease. No adverse cardiac events were encountered. At unchanged heart rates, the stroke volume increased significantly. This increase was the result of both an increase in end-diastolic volume, as was to be expected on the basis of the Frank-Starling mechanism, and of a decrease in end-systolic volume. The mechanism of these changes is partially explained by the Frank-Starling effect and the decreased blood viscosity, but additional factors cannot be excluded. Further studies are required on the neurohumoral changes, the rheologic and arteriolar changes, the consequences of coronary artery stenosis and the effects of inotropic and, β-blocker drugs in hypervolemic hemodilution.

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Chapter 7

PROFOUND HEMODILUTION: WHAT IS THE CRITICAL LEVEL OF HEMODILUTION AT WHICH OXYGEN DELIVERY-DEPENDENT OXYGEN CONSUMPTION STARTS IN AN ANESTHETIZED HUMAN ?

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Introduction

The risks of homologous blood transfusions are well known, and some patients may refuse blood transfusions on religious grounds. Transfusion requirements may be diminished by hemodilution techniques. The critical level of hemodilution in humans, defined as the critical point at which oxygen consumption (VO_2) starts to decrease because of insufficient oxygen delivery (DO_2), is not known. With the permission of the family, the case history of a Jehovah's Witness patient with a critical level of hemodilution and DO_2-dependent VO_2, due to excessive blood loss during surgery, is presented.

Case report

An otherwise healthy 84-yr-old, 60-kg, male Jehovah's Witness had bleeding from the stomach. At admission, the bleeding stopped spontaneously with a hemoglobin concentration of 7.7 g/dL. Examination revealed a malignant tumour of the stomach. Five weeks after admission, the hemoglobin concentration was 10.1 g/dL (hematocrit 33%). Because of the danger of massive and lethal bleeding from the ulcerative tumour, it was decided to perform a total gastrectomy. The patient refused homologous blood products and any form of autologous blood transfusion. Fully informed consent was obtained for invasive monitoring and for the use of the technique of acute hypervolemic hemodilution [1,2]. Because of the adhesions between the stomach and spleen, the spleen ruptured during surgery and mobilization of the stomach and massive bleeding followed. At the end of surgery, blood loss was 4500 mL. Twelve hours postoperatively, the patient died. In accordance with medico ethical law in The Netherlands, it was forbidden in this case to administer any blood transfusion.

We now describe the methods and results of our investigations during this case. On the day of surgery, two intravenous cannulas were inserted. The radial artery was cannulated and a thermodilution catheter introduced into a pulmonary artery via the internal jugular vein. Midazolam (2.5 mg IV) was administered before catheter insertion. Heart rate, mean arterial blood pressure, pulmonary artery pressure, and right atrial pressure were monitored continuously. After 30 min of stable cardiovascular status, baseline cardiovascular values were

obtained. In addition, arterial and mixed venous blood samples were obtained for measurements of hemoglobin, hemoglobin oxygen saturation, hematocrit, and analysis of blood gases. Systemic vascular resistance, pulmonary vascular resistance, DO_2, VO_2, and P_{50} (PO_2 at which hemoglobin is 50% saturated with oxygen) were calculated from these acquired data. The oxygen extraction ratio was calculated by dividing VO_2 by DO_2. P_{50}, corrected to 37°C and pH = 7.40, was calculated (and not measured by an in vitro biotonometric technique) from a single measurement of venous pH, PO_2, and oxygen saturation of hemoglobin [3]. Anesthesia was induced with fentanyl (5 μg/kg IV), thiopental (5 mg/kg IV), and pancuronium (0.1 mg/kg IV). After tracheal intubation, the lungs were ventilated with 70% nitrous oxide in oxygen, and tidal volume was adjusted to achieve normocapnia. Anesthesia was maintained with fentanyl and enflurane (end-tidal 0.4 vol% throughout the whole surgical procedure) and muscle relaxation maintained with pancuronium (2 mg/h). The bladder was catheterized. Before surgery began, hypervolemic hemodilution was undertaken in three equal steps. Per step, 500 mL dextran 40 (50 g/dL) and 500 mL of lactated Ringer's solution were infused over 10 min. All measurements were repeated after each step. The same variables were recorded after 1500- and 3500-mL blood loss. Peroperatively, lactated Ringer's solution was infused in a volume equal to urine output plus 8 $mL.kg^{-1}.h^{-1}$ (to compensate for fluid loss from the wound). Blood loss was replaced by an equal volume of gelatin solution. Measurements were repeated at the end of surgery (blood loss 4500 mL) and at 1, 2, 4 and 8 h thereafter.

Postoperatively, anesthesia was maintained with continuously intravenous midazolam (0.1 $mg.kg^{-1}.h^{-1}$), and muscle relaxation was achieved with pancuronium (2 $mg.h^{-1}$). The lungs were ventilated with 40% oxygen in air, and body temperature was kept normal. Postoperatively, lactated Ringer's solution was infused at 110 ml/h.

The critical level of hemodilution was determined from a plot of VO_2 against DO_2. The critical point was defined as the point at which VO_2 became dependent on DO_2 with further hemodilution. To avoid the investigator bias of selecting this point by eye, the critical point was analytically chosen from the intersection of the two best-fit regression lines determined by a least sum of squares technique, as described previously by Schumacker et al.

The resultant hemodynamic data are summarized in Table 1. Stepwise acute hypervolemic hemodilution, with a change in hematocrit from 31% to

20%, resulted in a decrease in systemic vascular resistance of 53% and an increase in cardiac output of 54%. At a hematocrit of 8%, cardiac output was slightly decreased but still maintained compared with the postinduction of anesthesia value before hemodilution was induced. Mean arterial pressure decreased at hematocrit values of < 10% because of slightly decreased cardiac output and further decreased systemic vascular resistance. During extreme hemodilution, heart rate increased only slightly.

The results of systemic oxygenation are shown in Table 2. The critical point of DO_2 after which VO_2 gradually decreased was analytically chosen from the intersection of the two best-fit regression lines (Figure 1). The DO_2 at this critical point was 184 $ml.m^{-2}.min^{-1}$ (4.9 $ml.kg^{-1}.min^{-1}$). The hemoglobin content at this critical point was 4.0 g/dL (Figure 2), with the oxygen extraction ratio 0.44, the mixed venous PO_2 34 mmHg, and the mixed venous oxygen hemoglobin saturation 56%. The position of the oxy-hemoglobin dissociation curve (ODC), corrected for changes in pH and PCO_2, shifted to the right, but not before hematocrit was 8%. At a hematocrit of 8%, the mixed venous pH decreased, but the arterial pH did not. Twelve hours postoperatively, the patient died at a hemoglobin concentration of 1.6 g/dL.

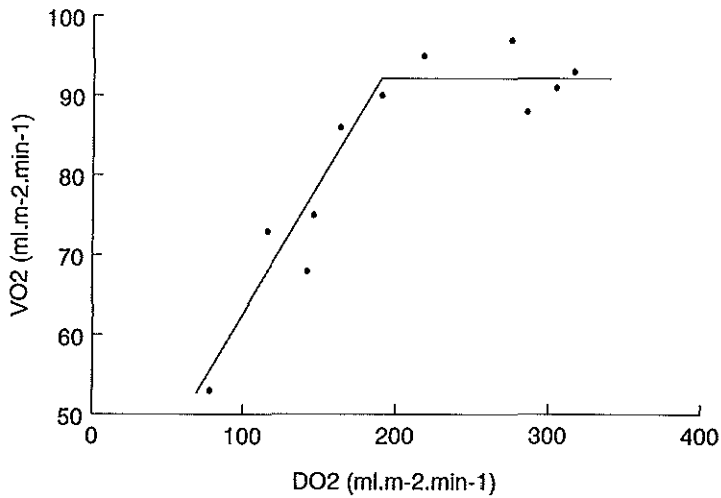

Fig 1. *Relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2) during increasing hemodilution.*

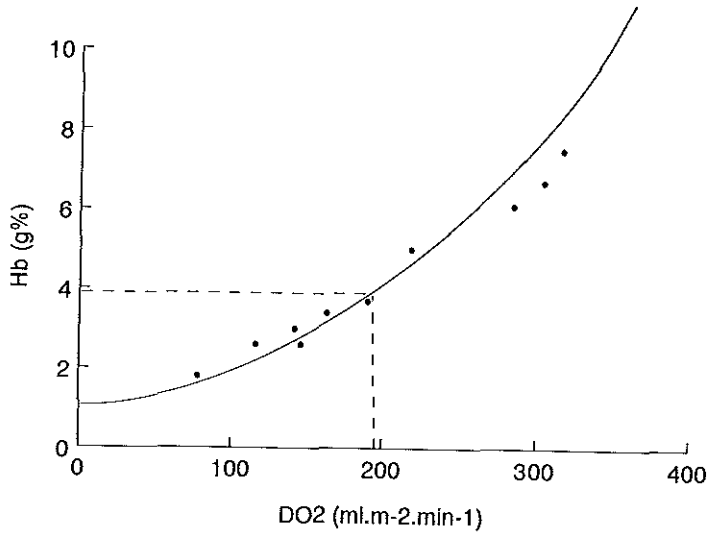

Fig 2. *Relationship between oxygen delivery (DO_2) and hemoglobin (Hb) concentration with critical point of DO_2.*

Discussion

In the present case, values of several variables at the critical point of hemodilution at which DO_2-dependent VO_2 starts could be recorded. There are no reports in the literature on the systemic oxygenation in humans at such a critical point of hemodilution. The point at which VO_2 becomes dependent on DO_2 during hemodilution is not established in humans. In our anesthetized patient, VO_2 started to decline at a DO_2 of 184 $mL.m^{-2}.min^{-1}$ (4.9 $mL.kg^{-1}.min^{-1}$). There are only a few reports concerning critical DO_2 in anesthetized cardiac patients in whom DO_2 was limited, not because of decreased arterial oxygen content but because of decreased cardiac output [5,6]. In one study, VO_2 decreased at $DO_2 < 330$ $mL.m^{-2}.min^{-1}$ and in the other study at $DO_2 < 300$ $mL.m^{-2}.min^{-1}$. The difference in critical DO_2 between our patient and those of the other reports can be easily explained. A decrease in DO_2 by decreased cardiac

output of blood with a normal hemoglobin content is often accompanied by an even more decreased blood flow through the micro circulation, whereas during hemodilution, flows in the micro circulation are accelerated, owing to improved rheologic properties of blood [7]. In animal studies, Cain and Chaplet [8,9] found a critical DO_2 of 10 $ml.kg^{-1}.min^{-1}$ in anesthetized dogs during anemic hypoxia and when oxygen-supply dependency of VO_2 started at a hematocrit of 10%. In another study in anesthetized dogs, a critical DO_2 of 7.9 $mL.kg^{-1}.min^{-1}$ was established [10]. However, in anesthetized pigs, which are more closely related to humans anatomically and physiologically [11], during hemodilution at a DO_2 of 7.8 $mL.kg^{-1}.min^{-1}$ (the final step of hemodilution in the study protocol), we found that VO_2 was still well maintained [12]. In another pig study, in which the critical DO_2 was not discussed, a critical hemoglobin content (where oxygen-supply dependent VO_2 started) of 3.9 ± 0.7 g/dL, similar to the present case was found [13]. In other pig studies we also found a critical hemoglobin concentration of 4.0 g/dL [14]. In our patient, as in another study using the same anesthesia technique [1], VO_2 and DO_2 decreased with the induction of anesthesia. Therefore, the values of DO_2 and VO_2 before induction of anesthesia were not used in Figure 1 to establish the critical point of hemodilution. It is possible that if the patient had been conscious, a different critical level of hemodilution would have been found.

The position of the ODC, corrected for changes in pH and PCO_2, shifted to the right, but not before the hematocrit was 8%. There are no reports concerning the position of the ODC in humans during acute hemodilution, except reports of the ODC during chronic anemia. In two studies in humans, chronically reduced hemoglobin concentration is compensated by improved oxygen unloading, afforded by the shift to the right of the ODC [15,16]. In one study in dogs, an acute change in ODC during acute hemodilution occurred but not before the hematocrit decreased below 10% [17], whereas in sedated pigs at every step of hemodilution, the ODC shifted to the right [11,18]. In these pig studies, a close relationship was found between the shift in ODC and the decreased mixed venous PO_2 for corrected pH 7.4. Therefore, just as in our case, changes in ODC may play a role in oxygen delivery during acute hemodilution and especially, as stated previously [18,19], when oxygen reserves are minimal.

Table 1. *Systemic hemodynamic measurements before and after induction of anesthesia in an 84-year-old male patient.*

	HR (beats/min)	MAP (mmHg)	PAP (mmHg)	PWP (mmHg)	CO (L/min)	SVR (dyne.s.cm^{-5})	Hct (%)	Hb (g/dL)
Preinduction	85	103	23	12	4.4	1818	31	10.1
Postinduction	81	66	14	12	3.5	1440	30	9.6
H1	77	71	21	15	5.0	1040	24	7.5
H2	81	76	28	15	5.2	969	21	6.7
H3	84	73	32	16	5.4	844	20	6.1
1500-ml blood loss	103	82	35	17	5.3	1072	16	5.0
3500-ml blood loss	95	70	31	17	5.5	887	10	3.4
ES	92	56	24	15	5.8	648	9	2.6
1 h postop	117	89	22	5	5.7	1179	12	2.7
2 h postop	104	80	25	10	5.0	1120	12	3.0
4 h postop	92	58	26	13	4.5	800	9	2.6
8 h postop	105	47	25	15	3.8	653	8	1.8

HR, heart rate; MAP, mean arterial pressure; PAP, mean pulmonary artery pressure; PWP, pulmonary wedge pressure; CO, cardiac output; SVR, systemic vascular resistance; Hct, hematocrit; Hb, hemoglobin; H1, H2, H3, data for each step of hypervolemic hemodilution; ES, end of surgery; postop, postoperatively.

Table 2. *Systemic oxygenation before and after induction of anesthesia.*

	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	PvO_2 (mmHg)	$PvCO_2$ (mmHg)	pH art	pH ven	DO_2 (L.m^{-2}.min^{-1})	VO_2 (L.m^{-2}.min^{-1})	ER (%)	P_{50}act (mmHg)	P_{50}c (mmHg)
Preinduction	75	37	31	40	7.46	7.44	339	126	37	26.2	27.3
Postinduction	250	36	37	39	7.45	7.43	275	97	35	27.9	29.0
H1	220	35	42	39	7.45	7.42	326	93	30	28.1	29.2
H2	225	36	41	38	7.44	7.41	304	91	30	27.9	28.8
H3	215	36	42	38	7.43	7.40	285	88	31	28.3	29.0
1500-ml blood loss	92	34	33	36	7.40	7.38	218	95	44	28.6	29.1
3500-ml blood loss	170	36	30	39	7.37	7.34	163	86	53	29.3	28.5
ES	226	37	32	39	7.37	7.33	146	75	51	28.7	27.7
1 h postop	230	44	33	46	7.37	7.34	190	90	48	28.7	27.7
2 h postop	262	34	33	40	7.46	7.38	142	68	48	27.5	27.3
4 h postop	293	30	26	38	7.48	7.40	116	73	63	27.5	27.6
8 h postop	345	30	31	38	7.39	7.26	78	53	68	34.6	30.1

Art, arterial; ven, venous; DO_2, oxygen delivery; VO_2, oxygen consumption; ER, oxygen extraction ratio; P_{50}act, PO_2 at oxyhemoglobin saturation of 50% measured in mixed venous blood; P_{50}c, P_{50} of mixed venous blood corrected at pH = 7.40 and PCO_2 = 40 mmHg; H1, H2, H3, data for each step of hypervolemic hemodilution; ES, end of surgery; postop, postoperatively.

One might argue that from a single case no meaningful conclusions can be made. However, during the same stages of hemodilution (at the same hematocrit level), the cardiovascular responses to hemodilution of this patient were similar to those in another report on anesthetized humans [1], and this case might therefore be representative for anesthetized humans. Furthermore, the advanced age of the patient could have influenced the critical point of hemodilution. However, in a clinical study there were no differences found between young and elderly patient in hemodynamic compensatory mechanisms during hemodilution [20]. Finally, it has been suggested that by calculating VO_2, rather than measuring VO_2, and using the same variable (e.g., cardiac output) for calculating VO_2 and DO_2, the relationship between DO_2 and VO_2 might be based on mathematic coupling. However, it has been stated that by keeping the range of independent variables as large as possible (as in our patient), the effect of coupled error are excluded [21].

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SEVERE ACUTE NORMOVOLEMIC HEMODILUTION AND SURVIVAL

Chaney MA, Aasen MK.

Anesth Analg 1993; **76**: 369-378.

To the editor:

We read with great interest the case report by van Woerkens et al. [1] and the accompanying editorial by Leone and Spahn [2], because we recently treated a patient who survived an episode of severe acute normovolemic hemodilution. Our patient was otherwise healthy 22-yr-old, 50-kg, female who underwent bilateral maxillectomies, bilateral ethmoidectomies, sphenoidectomy, and resection of a midline skull-based chondroblastoma. During the preoperative interview the patient rejected the use of homologous blood products and any from of autologous transfusion because she was a Jehovah's Witness. The preoperative hemoglobin level was 12.7 g/dL and the first postoperative hemoglobin level was 2.3 g/dL. Unfortunately, we did not have the benefit of central venous access. To minimize oxygen consumption and maximize oxygen delivery in the postoperative period, we continued paralysis and sedation, actively cooled the patient to 30°C, and maintained the FiO_2 at 1.0. Erythropoietin and iron supplementation were also initiated. By the 14th postoperative day the hemoglobin level was 4.8 g/dL and on the 28th postoperative day it had increased to 9.1 g/dL. At this point, after 28 days, the patient was actively rewarmed, and the paralysis and sedation were discontinued. She quickly regained consciousness and was weaned promptly from mechanical ventilation. No neurologic deficits were identified and no obvious organ damage occurred. Our patient is living proof that acute normovolemic hemodilution to extremely low hemoglobin levels can be well tolerated in selected patients for extended periods of time.

We are curious as to why van Woerkens et al. chose not to utilize moderate hypothermia and an FiO_2 of 1.0 in the treatment of their patient. Certainly, their use of muscle paralysis [3] and sedation [4] decreased oxygen consumption. The utilization of moderate hypothermia to 30°C will not only decrease oxygen consumption 48% below basal levels [5], but will also increase the amount of dissolved oxygen in the blood by 10% [6], therefore increasing oxygen delivery. At extremely low hemoglobin values, dissolved oxygen in the blood plays an

integral role in oxygen delivery. Indeed, Lichtenstein et al. [7] discuss a case involving a Jehovah's Witness who experienced severe acute normovolemic hemodilution for 4 h before a Massachusetts Superior Court-ordered blood transfusion. At a hematocrit of 4%, an FiO_2 of 1.0, and a body temperature of 30°C, they calculated via invasive hemodynamic monitoring that 51% of the patients oxygen delivery was accounted for by dissolved oxygen in the blood and that this dissolved oxygen provided for 90% of the patient's oxygen consumption. This situation differs markedly from the ordinary scenario of breathing room air, at normal body temperature with a normal hematocrit, where only 2% of the oxygen delivery is accounted for by dissolved oxygen, thus providing for only 5% of the oxygen consumption.

We believe that utilization of moderate hypothermia to 30°C and maintenance of an FiO_2 of 1.0 are vital to successful management of severe acute normovolemic hemodilution. Oxygen consumption is decreased and the increased amount of dissolved oxygen may provide important additional oxygen delivery to these patients who are surviving almost exclusively on dissolved oxygen in the blood.

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IN RESPONSE

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We appreciate the interest that Drs. Chaney and Aasen have shown in our case report and that they have raised fundamental questions about utilization of moderate hypothermia to 30°C and maintenance of an FiO_2 of 1.0 during severe normovolemic hemodilution.

We also considered the use of moderate hypothermia because of the decrease in oxygen consumption, the increase in the amount of dissolved oxygen in plasma, and the increase in the affinity of tissue for oxygen during hypothermia. However, hypothermia also has negative effects on tissue oxygenation. During hypothermia the oxyhemoglobin dissociation curve (ODC) is shifted to the left, increasing hemoglobin affinity for oxygen and thereby decreasing the release of oxygen from the hemoglobin molecule. Decreasing body temperature from 37°C to 30°C decreases the P_{50} value (PO_2 at which hemoglobin is 50% saturated with oxygen) from 26.9 to about 18.7 mmHg [1].

It is concluded that, in several clinical situations, the leftward shift of the ODC during hypothermia may be detrimental to oxygen delivery to tissue [1,2], especially when oxygen reserves are minimal, such as during hemodilution [2-4]. Therefore, more research is needed to determine whether the positive effects of hypothermia during severe anemia (e.g., decreased oxygen demand, increased amount of dissolved oxygen, and increased tissue affinity for oxygen) play a more important role on tissue oxygenation than the negative effect (leftward shift of ODC) of hypothermia.

Furthermore Drs. Chaney and Aasen, presenting their case, discuss the issue of an FiO_2 of 1.0 during a long period, thereby increasing the amount of dissolved oxygen in plasma. However, inspired oxygen in concentrations of 50%-100% during long periods carries the risk of lung damage [5]. Increased ratios of dead space to tidal volume and increased arteriovenous shunting have been reported in patients (with irreversible brain damage) after ventilation with an FiO_2 of 1.0 for 40 h [6]. Using a bronchoalveolar lavage technique in volunteers exposed to more than 95% oxygen for 17 h, a significant alveolar-capillary leak expressed by the presence of increased plasma albumin and transferrin in lavage fluid was detected [7]. Another study in healthy human subjects indicates increased lung epithelial permeability, in a dose-dependent manner, with increa-

sing FiO_2 [8]. Furthermore, it is suggested that increased FiO_2 during a long period induces ongoing free radical formation in the lung with consequent lung tissue damage [5].

Another argument against use of an FiO_2 of 1.0 during a critical level of hemodilution is our observation in pigs (unpublished data) that FiO_2 acutely increased to 1.0 at this critical point of hemodilution induced, despite a recovery of hemodynamics, an acute decrease in brain tissue PO_2, probably because of the vasoconstrictive action of high arterial PO_2 on the cerebrovasculature.

Nevertheless comparison of the case of Drs. Chaney and Aasen with our case suggests that hypothermia and hyperoxia may decrease mortality during severe normovolemic hemodilution. However, we have to note that our patient died, but not before the hemoglobin level dropped to less than 1.6 g/dL, whereas the lowest hemoglobin level measured in their patient was 2.3 g/dL.

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Chapter 8

ACCURACY OF A MIXED VENOUS SATURATION CATHETER DURING ACUTELY INDUCED CHANGES IN HEMATOCRIT IN HUMANS

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Summary

Objective: To determine the accuracy of in vivo mixed venous hemoglobin saturation (SvO_2) measurements with a fiberoptic thermodilution catheter during acute changes in hematocrit.
Design: Comparison of fiberoptic in vivo SvO_2 values with in vitro SvO_2 values obtained with a multi wavelength spectrophotometer.
Setting: Operating room in an university hospital.
Patients: Six consecutive patients who are Jehovah's Witnesses.
Measurements and main results: Before and after each step of hypervolemic hemodilution and after 500 mL of blood loss, blood gases were analysed and hemodynamic, hemoglobin, hematocrit, and in vitro and in vivo SvO_2 measurements were made. Hematocrit values were measured in the range of 40% to 18%. Plotting all in vivo SvO_2 values ($n = 74$) against the in vitro SvO_2 measurements obtained during the entire study period gives $r^2 = .86$. The accuracy of in vivo SvO_2 measurements was not affected by changes in hematocrit or cardiac output. The SvO_2 catheter value at the beginning of the study differed from the in vitro SvO_2 value by -0.86 ± 2.56 % and at the end of the study period of 8 to 10 hours by 0.71 ± 3.04%.
Conclusions: The accuracy of the studied fiberoptic continuous measuring SvO_2 system was not affected by changes in hematocrit or cardiac output. No significant drift in the in vitro SvO_2 measurements was observed.

Introduction

The mixed venous oxygen saturation of hemoglobin (SvO_2) reflects, under certain circumstances, the state of tissue oxygenation. Changes in cardiac output, arterial oxygen content, and oxygen uptake influence these variables [1,2]. Therefore, continuous monitoring of SvO_2 has been developed and is used as an indicator of the effects of various therapeutic manoeuvres in critically ill patients, and for measurement of oxygen transport patterns [3-5]. However, due to scattering of the erythrocyte wall itself, sudden changes in hematocrit might influence the reliability of SvO_2 values, measured by such fiber optic systems [6]. Situations leading to sudden changes in hematocrit are not uncommon

during surgery and intensive care due to, for example, hemorrhage, infusion regimes, and blood transfusions.

A two-wavelength, fiber optic, balloon-tip thermodilution catheter (Spectracath®, Viggo-Spectramed, Oxnard, CA) has been developed, with a third fiber (the far fiber) ending two fiber diameters from the source fiber, which also receives backscattered light. The manufacturer claims that with this system, the reliability of SvO_2 measurement is not affected by sudden changes in hematocrit and that any change in hematocrit will not entail the need to update or recalibrate the device. To our knowledge, no reports exist concerning the reliability of in vivo measurements with this system during sudden changes in hematocrit. Therefore, this study was designed in which, during acutely induced hypervolemic hemodilution followed by surgical blood loss (with no recalibration of the system during the study period), we compared the in vivo SvO_2 values measured with the fiber optic device with in vitro SvO_2 values obtained by multiwavelenght spectrophotometer (OSM3, Radiometer, Copenhagen, Denmark).

Materials and methods

The catheter type studied has three fibers ending in the plane of the tip of the balloon-tip 7.5-Fr thermodilution catheter. A light-emitting fiber directs infrared light (805 nm) and red light (660 nm) into the blood. A second fiber (the near fiber) ends adjacent to the emitting fiber and receives backscattered light from RBC's. A third fiber (the far fiber) is terminated two fiber diameters (500 μ) from the source fiber and also receives backscattered light. The ratio of the infrared (IR) and red (R) light signals from the near fiber is designed as x = IR near/R near. The variable "x" was found by the manufacturer to be highly dependent on saturation, but also dependent on hematocrit. However, they found the ratio R = IR near fiber/IR far fiber directly related to hematocrit but independent of saturation because 805 nm is an isosbestic wavelength. The manufacturer of the fiber optic device claims that algorithms, which are incorporated in the SvO_2 measuring device and based on these observations, give reliable SvO_2 values in the range of 20% to 50%, independent of hematocrit changes.

The study compromised 74 measurements in six consecutive patients who were Jehovah's Witnesses and were scheduled for major surgery. All patients were American Society of Anesthesiologist class 1 or 2, with an age range of 38 to 84 years (mean 51 ± 10 [SD]). No patient was excluded during the study period. In accordance with rules and regulations observed and enforced by the Medical Ethical Committee of our institution, all patients were fully familiarized with the objectives of the study and signed an informed consent. On the day of surgery, two iv cannulas were inserted and the radial artery was cannulated. Using the Seldinger technique, an introducer sheath was placed in the internal jugular vein. After in vitro calibration according to the manufacturers's specifications, the SvO_2 catheter with three optical fibers was inserted. Catheters were positioned in the pulmonary artery by observing the characteristic pressure waveforms.

Before cannulation of the internal jugular vein, 2.5 mg midazolam iv was given. The fasting period was compensated with 500 mL of lactated Ringer's solution. Heart rate, arterial BP measurements, pulmonary artery pressures, and right atrium pressure were monitored continuously (Horizon 2000, Mennen Medical, Israel). After a stabilization period of 30 mins, baseline values were obtained for mean arterial pressure, mean pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP), and cardiac output.

In addition, arterial and mixed venous blood samples were taken for measurements of hemoglobin, hemoglobin oxygen saturation (spectrophotometer OSM3, Radiometer), hematocrit, PO_2, and PCO_2 and pH (ABL330, Radiometer). All arterial and mixed venous samples were collected anaerobically into heparinized syringes and analyzed immediately. Just before blood collection, the in vivo SvO_2 value was obtained. Anesthesia was then induced with fentanyl 5 μg/kg, thiopental sodium 5 mg/kg, and pancuronium 0.1 mg/kg. After tracheal intubation, the lungs were ventilated with 70% nitrous oxide in oxygen and tidal volume was adjusted to maintain normocapnia. Anesthesia was maintained with fentanyl and enflurane (end tidal 0.4 vol%), while muscle relaxation was obtained with pancuronium. The bladder was catheterized. After a 15-min stabilization period, blood gases were analyzed and hemodynamic, hemoglobin, hematocrit, and in vitro and in vivo SvO_2 measurements were made. Hypervolemic hemodilution was induced in three equal steps.

At each step, the patients received 500 mL of dextran-40 (50 g/L) with 500 ml of lactated Ringer's solution over 10 mins. The same measurements that

were taken before and after induction of anesthesia were repeated after each step. Surgery was performed and the same variables were again recorded after every 500 mL of blood loss. During surgery, lactated Ringer's solution was infused in a volume equal to the urine output plus 8 $mL.kg^{-1}.hr^{-1}$ to compensate for loss of fluid from the open wound. Blood loss was replaced by an equal volume of gelatin solution (Geloplasma®, Roger Bellon, Neuilly-sur-Seine, France). Just before the end of surgery, the forced infusion was stopped. Directly after surgery, the patient's trachea was extubated. Measurements were repeated at the end of surgery, and at 20 mins, 2 hrs, and 4 hrs after surgery. Throughout the study period, the in vivo SvO_2 system was not recalibrated or updated for hematocrit changes. The baseline blood volume values are calculated values [7]. All values are reported as mean ± SD. Statistical analysis was performed by the paired Student's *t*-test and the Wilcoxon signed-rank test. Furthermore, the correlation value, coefficient of determination, and regression line were determined [8]. These relations were also tested by means of Fisher's Z transformation (correlation coefficient) and by means of the test of the regression slope [9]. The accepted probability for a statistical difference between means was $p < 0.05$.

Results

All patients underwent a laparotomy. Each patient study varied between 8 to 10 hours, depending on the duration of the surgical procedure. The in vitro calibration of the SvO_2 catheter at the beginning of the study approximated the spectrophotometer SvO_2 , differing by -0.9 ± 2.6%. At the end of the study period the catheter SvO_2 value differed from the spectrophotometer SvO_2 value by 0.7 ± 3.0% (Table 1). Throughout the study period no significant drift in the in vivo SvO_2 measurements was observed because the difference between the SvO_2 catheter value and the spectrophotometer SvO_2 value at the beginning of the study period was not significantly different from the difference in SvO_2 values at the end of the experimental procedure.

Hypervolemic hemodilution changed the hematocrit from 36 ± 2% to 26 ± 2%. During the study period, hematocrit values in the range of 40% to 18% were measured. Plotting the hematocrit against the difference between in vivo

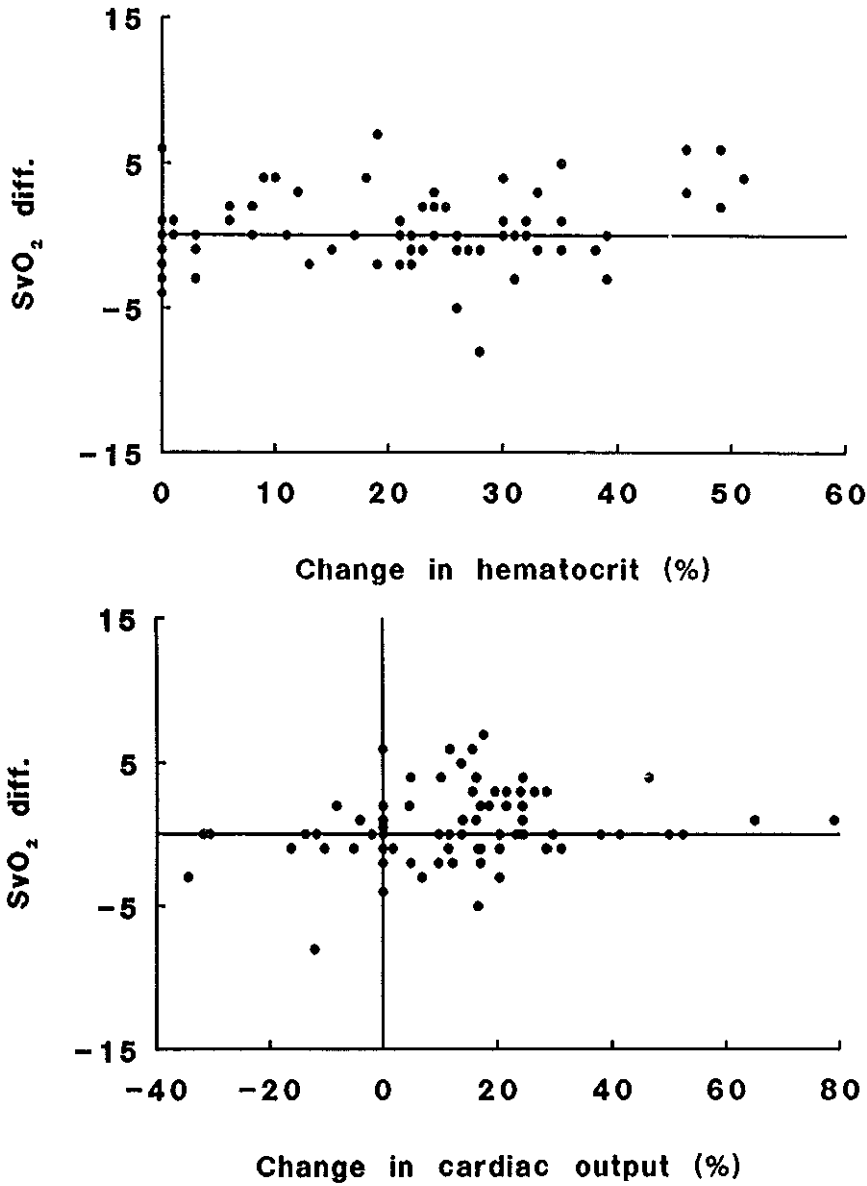

Figure 1. *Scatterplot of the difference between in vivo mixed venous hemoglobin saturation (Svo_2) and in vitro reference Svo_2* (Svo_2 diff.) *against the decerase in hematocrit* (top) *and cardiac output* (bottom). *Testing both the correlation and regression coefficient hypotheses (H) (H_0: $r = 0$, $\beta = 0$ vs. alternate hypotheses H_1: $r > 0$, $\beta > 0$ [$\alpha = 0.025$]) demonstrated that we could not reject the null hypotheses, proving that the catheter was not dependent on changes in hematocrit or in cardiac output in the measured range ($r^2 = .057$, $y = -0.04x - 0.51$* [top]; *$r^2 = .036$, $y = 0.02x + 0.15$* [bottom]).

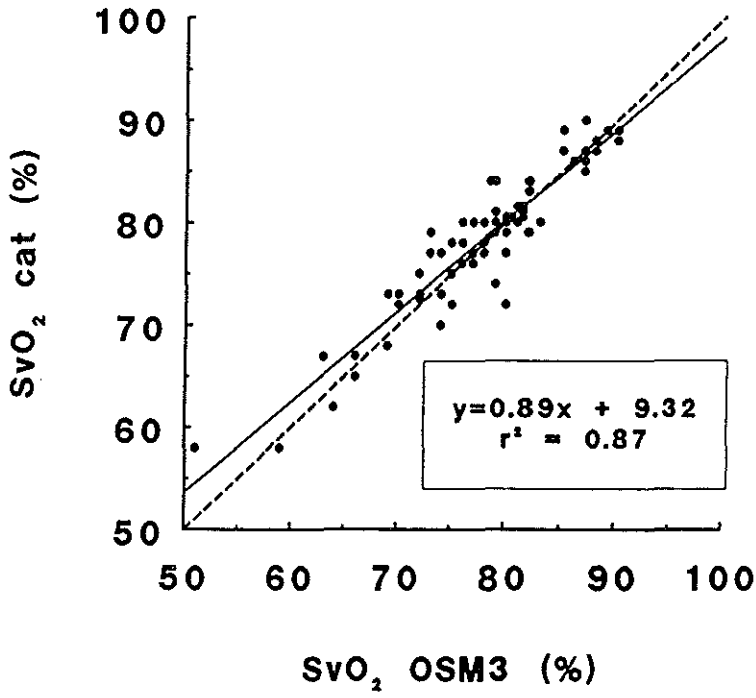

Figure 2. *Scatterplot of all fiberoptic mixed venous hemoglobin saturation (Svo_2) data* (Svo_2 cat) *against the in vitro reference spectrophotometer values* (Svo_2 OSM3). *The* dotted line *represents the line of identity (x = y) and the* solid line *represents the linear regression line (y = 0.89x + 9.32). The coefficient of determination is r^2 = .87. Testing both the correlation and regression coefficient hypotheses (H) (H_0: r = 1, ß = 1 vs. alternate hypotheses H_1: r < 1, ß < 1 [a = 0.025]) demonstrated that we could not reject the null hypotheses.*

SvO_2 and in vitro SvO_2 (catheter SvO_2 minus spectrophotometer SvO_2 values) showed that the catheter gave reliable SvO_2 values independent of changes in hematocrit (Figure 1, *top*). Similarly, changes in cardiac output did not influence the accuracy of the fiber system (Figure 1, *bottom*). Plotting in vivo determination of SvO_2 by the fiber optic system against the in vitro reference

Table 1 *Selected data on systemic hemodynamics and oxygenation before and after induction of anesthesia, after each step of hypervolemic hemodilution (H1, H2, H3), at the end of surgery (ES), and 20 mins, 2 hrs, and 4 hrs postoperatively (postop) (mean ± SD).*

	Hgb (g/dL)	Hct (%)	CI (L/min/m^2)	PAOP (mmHg)	SaO_2 (%)	PaO_2 (torr)	SvO_2 (OSM3) (%)	SvO_2 (Cath) (%)	SvO_2 (Cath)-SvO_2 (OSM3) (%)
Before induction	11.6 ± 0.8	36 ±2	3.0 ±0.5	6 ±2	97 ±1	95 ±14	76 ±3	75 ±4	-0.86 ±2.56
After induction	11.5 ± 1.1	35 ±3	2.4 ±0.5[a]	6 ±2	99 ±1[a]	183 ±28[a]	79 ±3	78 ±2	-0.71 ±0.95
H1	9.7 ± 0.7[a,b]	29 ±3[a,b]	3.4 ±0.8[b]	16 ±2[a,b]	99 ±1[a]	188 ±32[a]	84 ±3[a,b]	83 ±2[a,b]	-0.57 ±1.10
H2	9.2 ± 0.6[a,b]	27 ±2[a,b]	3.6 ±0.8[b]	22 ±3[a,b]	99 ±1[a]	188 ±20[a]	85 ±5[a,b]	84 ±4[a,b]	-0.57 ±0.67
H3	8.7 ± 0.4[a,b]	26 ±2[a,b]	3.5 ±0.8[b]	26 ±2[a,b]	99 ±1[a]	188 ±25[a]	84 ±4[a]	84 ±5[a,b]	-0.57 ±0.96
ES	8.3 ± 1.2[a,b]	24 ±3[a,b]	3.5 ±0.8[b]	18 ±6[a,b]	99 ±1	146 ±35[a]	81 ±5[a]	82 ±5[a]	0.71 ±2.38
20 mins postop	9.8 ± 0.8[a,b]	29 ±3[a,b]	3.9 ±0.6[a,b]	8 ±3	97 ±2[b]	101 ±21[b]	66 ±9[a,b]	67 ±8[b]	0.14 ±2.57
2 hrs postop	9.9 ± 0.9[a]	29 ±3[a,b]	3.4 ±0.4[a,b]	5 ±2	97 ±2[b]	111 ±32[b]	73 ±5[b]	74 ±4	0.43 ±2.98
4 hrs postop	9.5 ± 1.0[a,b]	29 ±3[a,b]	3.6 ±0.4[a,b]	4 ±1	97 ±2[b]	109 ±29	72 ±4[b]	72 ±4[b]	0.71 ±3.04

Hgb, hemoglobin; Hct, hematocrit; CI, cardiac index; PAOP, pulmonary arterial occlusion pressure; SaO_2, arterial hemoglobin saturation; SvO_2, mixed venous hemoglobin saturation; OSM3, spectrophotometer; Cath, catheter.

[a] $p < .05$ compared with preanesthetic values.

[b] $p < .05$ compared with postinduction values.

SI conversion factor for hemoglobin (g/dL to g/L) is 10.0, and for PaO_2 (torr to kPa) is 0.133.

spectrophotometer value of all data points obtained during the entire study period gives r^2 = .87 (y = 0.89x + 9.32) (Figure 2). All values (n = 74) of SvO_2 catheter minus spectrophotometer SvO_2 (SvO_2 diff) have a mean of 0.5 ± 2.6% with median of 0%, minimum value of -8%, and maximum value of 7%. Between -5% and +5% are 69 (93%) of all measured pairs during the whole study period measured pairs.

During surgery, there was a blood loss of 30.6 ± 19.2% of the calculated initial blood volume. No patient required a blood transfusion. Other relevant data selected during the study are presented in Table 1.

Discussion

The value of continuous determination of SvO_2 depends on how accurately in vivo SvO_2 approximates the reference spectrophotometric-measured saturations under different physiologic conditions. Specific obstacles might be vessel wall artifact and confounding effects of varying hematocrit. In vivo measurements of blood oxygen saturation using optical fibers is based on differences in light reflection between oxygenated and reduced hemoglobin. However, saturation measurement is influenced by secondary effect including blood flow, erythrocyte shape, and hematocrit [10]. The hematocrit of the blood floating along the tip of the catheter might be influenced by flow properties (linear flow vs. turbulent flow), and by the systemic hematocrit value. A balloon-tip thermodilution catheter with three optical fibers for measurement of SvO_2 is available (Spectracath®, Viggo-Spectramed). Infrared light and red light are delivered to the blood through a source fiber. Backscattered light from erythrocytes is received by two fibers: one is adjacent to the source fiber; the other is two fiber diameters away (far fiber). The manufacturer claims that the ratio between the intensity of infrared light from the near fiber to the intensity of the far fiber varies as a function of hematocrit and, therefore, can be used to validate in vivo oxygen saturation measurements, independent of hematocrit changes. However, to our knowledge, there are no reports about the accuracy of SvO_2 measurements with this device during in vivo sudden changes in hematocrit.

Because many situations during surgery and intensive care lead to sudden

changes in hematocrit, such a device must produce reliable continuous in vivo SvO_2 measurements, independent of changes in hematocrit. Furthermore, SvO_2 itself is an indicator of the critical point of hemodilution; continuous registration of in vivo SvO_2 , if accurate, might be used as an extra variable to asses oxygen transport capacity of the blood. In a previous study [1] in pigs during stepwise-induced isovolemic hemodilution, a gradual decrease in SvO_2 was observed while the oxygen extraction ratio increased. A direct and strong correlation was found between SvO_2 and oxygen extraction ratio, confirming that SvO_2 during hemodilution reflects the overall balance between oxygen uptake and oxygen delivery. Furthermore, a critical SvO_2 value was found at which oxygen uptake started to decrease during further hemodilution [1]. In this study in humans, the reliability of the test catheter (Spectracath®) continuous SvO_2 device was tested during sudden changes in hematocrit, cardiac output , and PAOP. Acute hypervolemic hemodilution was induced in patients who are Jehovah's Witnesses before major surgery because hypervolemic hemodilution results in fewer RBC's being lost per volume of blood loss [11-13].

The results of this study demonstrate that the fiberoptic device can be calibrated in vitro before insertion. Furthermore, the reliability of the device was not affected by changes in hematocrit, cardiac output, or PAOP, even though no recalibration was performed after in vitro calibration before insertion. The fiberoptic device was able to accurately track measured SvO_2 over the time course of this study. The system did not drift; thus, no more statistically significant deviations were found from the reference-measured SvO_2 at the conclusion of the study period compared with the deviations at the beginning of the experimental procedure. We cannot conclude that the system is more accurate than other continuous SvO_2-measuring devices because of the difference in study protocol between our study and studies of other devices (e.g. three-wavelength catheter with two fibers) [3]. To answer this question, a randomized-designed study is needed to measure SvO_2 values concurrently with changes in the same physiologic variables. However it is concluded that the test device accurately reflects measured SvO_2 over a wide range of time, and also during abrupt changes in hematocrit, cardiac output, and PAOP. Therefore the continuously displayed in vivo SvO_2 value derived with this system can also be used during acute hemorrhage as an extra variable to asses the oxygen transport capacity of the blood.

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COMPARATIVE STUDY OF THE ACCURACY OF TWO FIBEROPTIC VENOUS SATURATION CATHETERS (SPECTRACATH® VS OPTICATH®) DURING ACUTE CHANGES IN HEMATOCRIT AND CARDIAC OUTPUT IN HUMANS

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Introduction

The mixed venous saturation of hemoglobin (SvO_2) reflects, under many circumstances, the state of tissue oxygenation. Changes in cardiac output (CO), arterial oxygen content, and oxygen uptake by the tissue influence this parameter [1,2]. Therefore continuous fiber optic monitoring of SvO_2 has been developed. Due to scattering of the erythrocyte wall itself, however, sudden changes in hematocrit (hct) might influence the reliability of SvO_2 values, measured by such fiber optic systems [3]. Two manufacturers claim that their system overcome this problem, one because of using three wavelengths (Opticath®) and the other using two wavelengths via one fiber but receiving backscattered light by two other fibers (Spectracath®). The manufacturers claim that with their systems the reliability of SvO_2 measurements are not affected by sudden changes in Hct and that any change in Hct will not entail the need to update or recalibrate the device. In this study, during acutely induced hypervolemic hemodilution [4] followed by surgical blood loss and with no recalibration of the systems during the study period, the in vivo SvO_2 values measured with the fiber optic devices were compared with the in vitro SvO_2 values obtained with a multiwave length spectrophotometer.

Patient and methods

One of the studied catheters (Spectracath®, Viggo-Spectramed, Oxnard, USA) has three fibers terminated in the plane of the tip of a balloon-tipped, 7.5 F thermodilution catheter. A light emitting fiber directs infrared (IR: 805 nm) light and red (R: 660 nm) light into the blood. A second fiber (the near fiber) is terminated adjacent to the emitting fiber and receives backscattered light from red blood cells. A third fiber (the far fiber) is terminated two fiber diameters (500 microns) from that source fiber and also receives backscattered light. The ratio of the IR and R signals from the near fiber is designed as X = IR near/R near. X was found to be highly dependent on saturation, but also dependent on Hct. However the ratio R = IR near/IR far directly relates to Hct, but is independent of saturation because 805 nm is an isobestic wavelenght. Using incorporated algorithms based on these observations should give reliable SvO_2 values

independent from Hct changes in the range 20% to 50%. The other studied catheter (Opticath®, Oximetrix, Mt View; CA, USA) has two fibers terminated at the tip of a balloon-tipped, 7.5 F thermodilution catheter. Light emitting diodes generate alternating pulses of three different wavelengths (between 600 and 1000 nm), 244 times per second via a light emitting fiber. A second fiber receives backscattered light from red blood cells and conducts this light to a photodetector. The oxygen saturation of hemoglobin (Hb) is derived by a computer from the relative intensities corresponding to three different wavelength. The study compromised measurements (Opticath®: n = 52; Spectracath®: n = 54) in 12 consecutive Jehovah's Witness patients scheduled for major surgery. Randomly divided between the patients, either a Spectracath® or Opticath® SvO_2 catheter was inserted via the internal jugular vein into the pulmonary artery. Before insertion, according to the manufacturer's specifications, the SvO_2 catheters were calibrated in vitro and no recalibration was performed during the entire study period. The design of the study was the same as in a previously reported study [5].

In brief: values of Hct, blood gases, hemodynamics, and oxygenation were obtained before and after induction of anesthesia, after each step of hypervolemic hemodilution, after every 500 ml of blood loss, at the end of surgery, 20 min, 2 h and 4 h postoperatively. The in vivo SvO_2 values of the devices were compared with the in vitro SvO_2 values obtained with a multiwave length Spectrophotometer (OSM3, Radiometer, Copenhagen).

Statistical analysis was performed by the paired students T-test and the Wilcoxon signed rank test. Furthermore the correlation values, coefficients of determination and regression lines were determined [6]. These relations were also tested by means of a Fisher's Z transformation (correlation coefficient) and by means of the test of the regression slope [7]. The accepted probability for a statistical difference between means was $P < 0.05$.

Results

The study of each patient varied between 9-12 hours depending on the duration of the surgical procedure. Directly after the in vitro calibration of the

SvO_2 gives differences in SvO_2 values compared to the OSM-3 SvO_2 of 1.33 ± 2.87% for the Opticath® and -0.83 ± 3.60 % for the Spectracath® (Table 1). At the end of the study period the catheter SvO_2 values differed from the OSM-3 SvO_2 by 2.67 ± 4.21 for the Opticath® and by 1.00 ± 3.39 for the Spectracath®. Throughout the study period at the same levels of the study, no significant difference between Opticath® and Spectracath® SvO_2 values could be observed, while for both catheters the difference between SvO_2 catheter value and the Spectrophotometer SvO_2 value at the beginning of the study period was not significantly different from the differences in SvO_2 values at the end of the experimental procedure. Plotting Hct against the difference between in vivo SvO_2

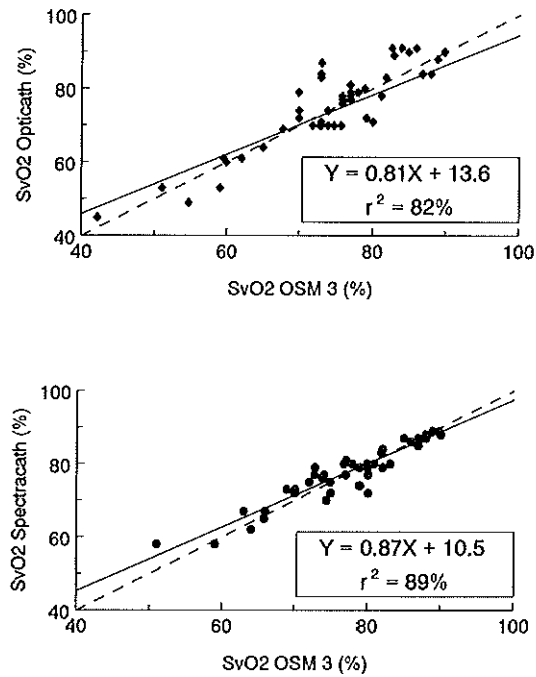

Figure 1. *Scatterplot of all fiberoptic mixed venous hemoglobin saturation (Svo_2) data of both catheters- Opticath® top and Spectracath® bottom- against the in vitro reference spectrophotometer values (OSM3). The dotted line represents the line of identity (x = y) and the solid line represents the lineair regression lines with their respective coefficient of determinant (r^2).*

Table 1. *Selected data on systemic haemodynamics and oxygenation before and after induction of anesthesia; after each step of hypervolemic hemodilution (H1, H2, H3); at the end of surgery (ES); 20 min, 2 and 4 hours postoperatively (PO).*

	Ht (O) %	Ht (S) %	CO (O) l/min	CO (S) l/min	PWP (O) mmHg	PWP (S) mmHg	PaO_2 (O) mmHg	PaO_2 (S) mmHg	Opt®-OSM3 %	Spec®-OSM3 %
pre	38.3	36.0	5.1	5.2	6.8	6.4	89	92	1.33	-0.83
induction	4.1	3.0	0.8	0.7	3.1	2.3	5	13	2.87	3.60
post	36.5	35.0	4.3+	4.2+	5.8	5.8	179+	183+	0.50	-0.67
induction	4.2	3.4	0.9	1.0	3.3	2.9	30	31	5.11	1.20
H1	29.3+*	29.5+*	5.5*	5.8*	10.0+*	16.0+*	165+	182+	0.33	-0.67
	3.1	3.0	1.3	1.3	3.1	3.0	45	42	3.90	1.21
H2	25.7+*	27.5+*	5.7*	6.2*	15.3+*	21.8+*	149+	187+	-0.67	-0.67
	2.5	2.4	1.4	1.5	1.8	3.0	49	28	4.29	0.82
H3	24+*	26.0+*	6.1*	6.2*	19.3+*	26.4+*	149+	186+	-0.67	-0.83
	2.2	1.5	1.7	1.4	1.9	2.7	44	28	5.31	1.16
ES	22.3+*	24.3+*	5.4*	6.3*	18.2+*	19.0+*	143+	139+	-0.17	1.17
	6.7	3.1	1.5	1.7	2.1	7.0	44	35	5.33	2.28
20 min PO	29.8+*	30.0+*	6.3*	6.5*	13.0+*	7.4	98*	111+	3.67	1.33
	2.6	3.2	2.8	1.1	5.6	2.3	45	44	5.30	3.37
2 h PO	30.2+*	30.0	6.7*	5.6*	8.3	4.8	122+	122+	1.00	0.67
	3.7	3.3	2.3	0.5	3.3	2.2	55	45	5.10	4.31
4h PO	30.2+*	29.5+	7.3*	6.0*	7.4	3.2	79*	113+	2.67	1.00
	2.5	3.0	2.8	0.5	3.2	0.4	6	33	4.21	3.39

(O) concerns the Opticath®, (S) concerns the Spectracath®. Ht = hematocrit; CO = cardiac output; PWP = pulmonary wedge pressure; PaO_2 = arterial oxygen pressure. The last columns represent the difference in mixed venous saturation between catheter minus OSM3. + = $P < 5\%$ compared to preanesthetic values; * = $P < 5\%$ compared to post anesthetic values; No difference with $P < 5\%$ between Spectracath® and Opticath® values at the same level were observed.

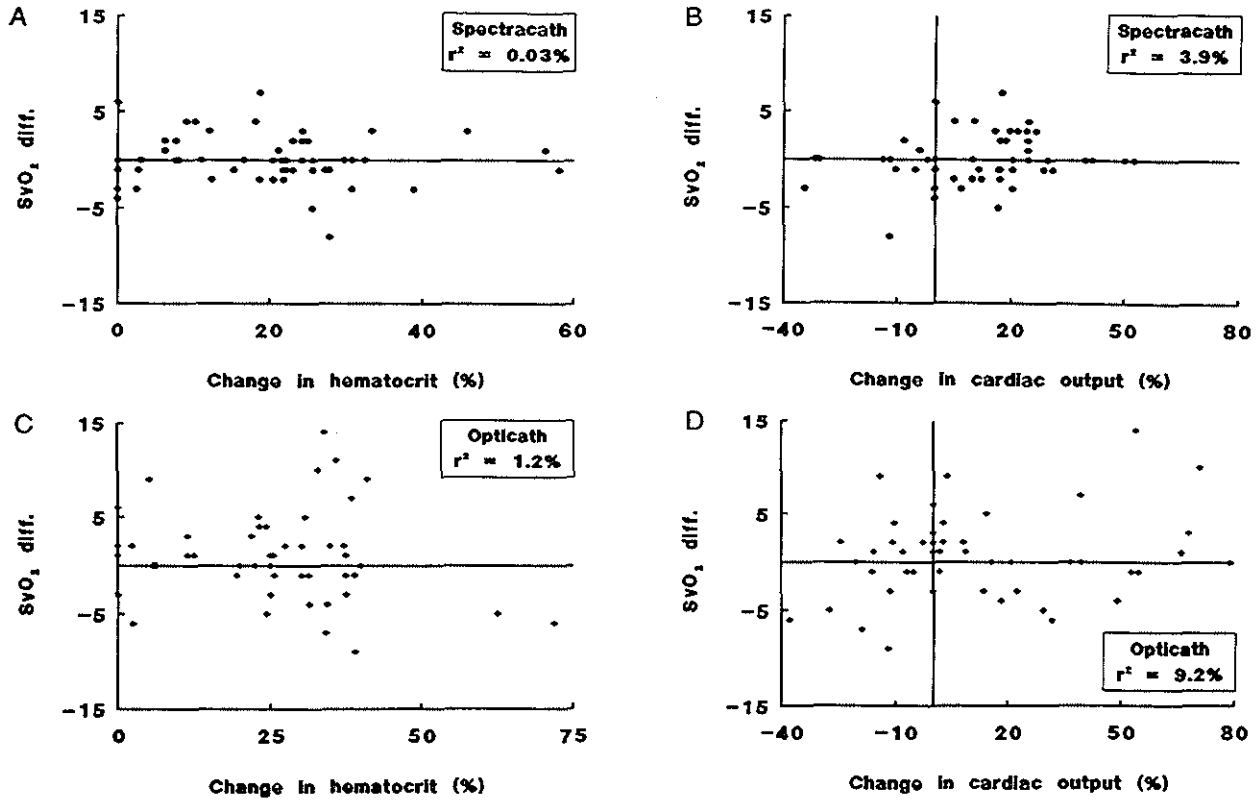

Fig 2. *Scatterplot of the difference between in vivo mixed venous hemoglobin saturation (Svo_2) and in vitro reference Svo_2 (Svo_2 diff) against the change in hematocrit (a: Spectracath® ; c: Opticath®) and cardiac output (b: Spectracath® ; d: Opticath®). Testing both the correlation and regression coefficient proved that both catheters were neither dependent on changes in hematocrit nor cardiac output in the measured range.*

and in vitro SvO_2 of both systems showed that both catheter systems gave SvO_2 values with an accuracy independent from changes in Hct (Figures 2a and c). Changes in CO slightly influenced the accuracy of the Opticath® (r^2 = 3.2%) (Figures 2b and d). Plotting in vivo determinations of SvO_2 by the fiberoptic system against the in vitro reference value of all data points obtained during the entire study gives a correlation coefficient r^2 = 91% (Y = 0.81 X + 13.6) for the Opticath® and r^2 = 94% (Y = 0.87 X + 10.5) for the Spectracath®.

Between -5% and +5% of SvO_2 catheter minus OSM-3 SvO_2 values are 42 (81%) of the Opticath® and 51 (94%) of the Spectracath® of all measured pairs during the whole study period. Other relevant data selected during the study are presented in Table 1.

Discussion

The value of continuous fiberoptical determinations of SvO_2 depends on how accurately in vivo SvO_2 approximates the reference spectrophotometric measured saturations under different physiologic conditions. Specific obstacles as vessel wall artifact and confounding effects of varying Hct and secondary effects including blood flow, erythrocyte shape might influence the saturation measurements [8]. The Hct of the blood floating along the tip of the catheter might be influenced by flow properties (linear flow vs turbulent flow), and by systemic Hct value. Because many situations during surgery and intensive care lead to sudden changes in Hct, devices must produce reliable continuous registration of in vivo SvO_2. In vivo SvO_2 if accurate, might be used as an extra parameter during hemorrhage to assess the oxygen transport capacity of the blood [2]. During stepwise-induced isovolemic hemodilution a gradual decline in SvO_2 was observed while the oxygen extraction (ER) increased. A direct and strong correlation was found between SvO_2 and ER confirming that the SvO_2 during hemodilution reflects the overall balance between VO_2 and oxygen delivery [2,4,9].

In the present study in humans the reliability of the Spectracath® and Opticath® continuous SvO_2 devices was tested during sudden changes in Hct, cardiac output, and pulmonary wedge pressure (PWP). The results of the study, demonstrate that both systems are able to be calibrated in vitro prior to

insertion. Furthermore, the reliability of both devices was not affected by changes in Hct or PWP. Cardiac output changes had a slight influence on the reliability of the Opticath® but not on the accuracy of the Spectracath®. No drift was observed in either system during the course of the study. The Spectracath® was slightly, but not statistically significant, more accurate than the Opticath® system. It is concluded that both devices reflect measured SvO_2 over a wide range of time, also during abrupt changes in Hct. Therefore the continuous displayed in vivo SvO_2 values derived with both systems can also be used during acute hemorrhage as extra parameter to assess the oxygen transport capacity of the blood.

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Chapter 9

S_{35}: A NEW PARAMETER IN BLOOD GAS ANALYSIS FOR MONITORING THE SYSTEMIC OXYGENATION

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Summary

In the estimation of oxygen transport the term oxygen availability is used as the product of cardiac output and the arterial oxygen content (CaO_2). Attempts can be made to modify the concept of oxygen availability by subtracting from the CaO_2 the venous content at a critical PO_2 as measured in mixed venous blood (PvO_2), where oxygen diffusion into tissue becomes compromised and oxygen uptake (VO_2) may decrease. The real arterial available oxygen content ($CavIO_2$) can be calculated by estimating the saturation at the critical PvO_2. For our concept S_{35} was chosen as such a dynamic baseline. Similar modification of oxygen extraction ratio (ERav) defined as VO_2 divided by the real oxygen availability (O_2av) should give, more than the classic ER, a realistic indices of oxygen availability in relation to oxygen consumption. It can be hypothesized that VO_2 starts to decline when ERav is around 1.0. During isovolemic hemodilution VO_2 started to drop when ERav reached 1.08 ± 0.09. The S_{35} changed from 55.0 ± 2.1% to 41.5 ± 4.1%, correlated with changes in PvO_2. A direct correlation was also found between the increase of the classic ER and the change in S_{35}.

We conclude that the S_{35}, the $CavIO_2$ and the ERav can be of value in monitoring the systemic oxygenation and that the concept also includes the effect of changes in oxyhemoglobin characteristics on oxygen delivery.

Key words: arterial available oxygen content; ERav; extraction ratio; hemodilution; hypoxia; isovolemic; oxygen consumption; oxyhemoglobin dissociation curve; P_{50}.

Introduction

In the estimation of oxygen transport the term oxygen availability is used as the product of cardiac output (CO) and the arterial oxygen content. Attempts can be made to modify the concept of oxygen availability by subtracting from the arterial oxygen content (CaO_2) the venous content at a critical PO_2, at pH, PCO_2 and hemoglobin concentration as measured in mixed venous blood (critical PvO_2), where oxygen diffusion into tissue becomes compromised and oxygen

uptake (VO_2) may decrease. Assuming oxygenation of the tissue is also a function of capillary PO_2, the concept of unavailable arterial oxygen content, calculated by estimating the saturation at the critical PvO_2, emphasizes that changes in PvO_2, when no significant arterial admixture exists, reflect changes in mean capillary PO_2.

In former studies we found that during stepwise induced isovolemic hemodilution, the VO_2 started to decline at a PvO_2 of around 35 torr (4.67 kPa) [1]. Therefore, for our concept S_{35} (saturation of hemoglobin at PO_2 = 35 torr) was chosen as dynamic baseline for oxygen delivery and for calculating the unavailable arterial oxygen content. The term oxygen availability (O_2av) should be reserved for the product of CO and the arterial available oxygen content ($CavIO_2$) while the product of CO and total arterial oxygen content (CaO_2) should be called oxygen flux (O_2 flux). Similar modification of the oxygen extraction ratio (ERav) defined as VO_2 divided by O_2av, should give, more than the classic ER (defined as VO_2 divided by O_2flux), a realistic indices of oxygen availability in relation to oxygen consumption.

The concept also includes the effects of changes in oxyhemoglobin dissociation curve (ODC) on oxygen delivery. For example, a shift to the right of the ODC decreases the S_{35} and therefore increases $CavIO_2$ (Figure 1) with, at fixed VO_2 consequent lowering of ERav, indicating that more oxygen should be available to be delivered before oxygen supply dependence of oxygen uptake is initiated. It can be hypothesized that for instance during isovolemic hemodilution VO_2 starts to decline when ERav is around 1.0 (O_2av becomes equal to VO_2).

The aim of the present study was to test this hypothesis and to determine the S_{35} after each step of normoxic acute isovolemic hemodilution.

Material and methods

This protocol was approved by the Animal Care and Use Committee of the Erasmus University, Rotterdam, The Netherlands.

Six male Yorkshire pigs (10.2 - 12.0 kg) were used. After giving 0.3 mg/kg midazolam i.m. a catheter was introduced into one of the ear veins and the trachea was intubated. Throughout the experimental procedure sedation was maintained with a continuous i.v. infusion of 0.2 mg/kg/h midazolam.

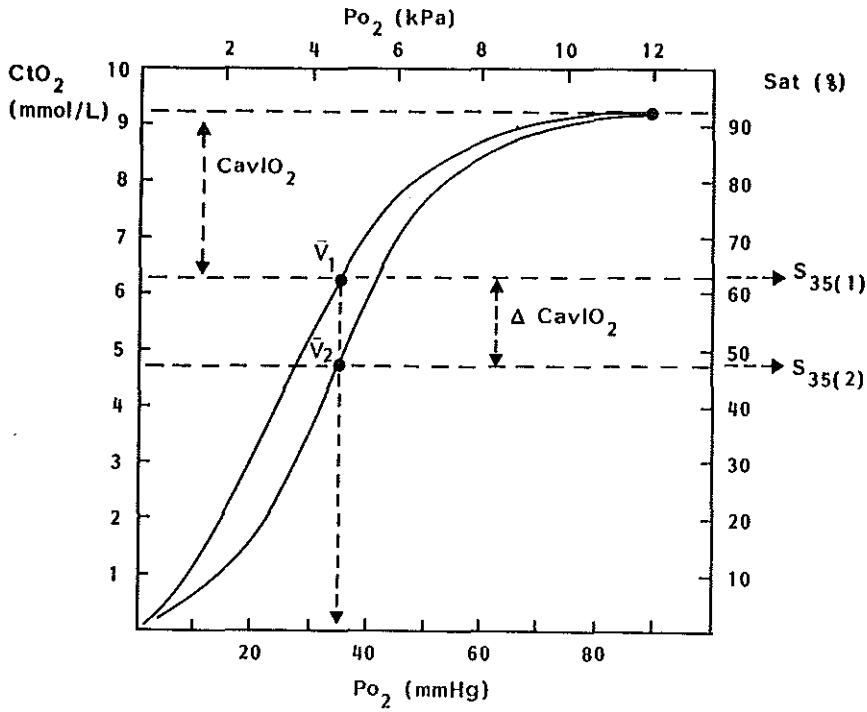

Figure 1. *The effect of changes in P_{50} and slope of ODC on S_{35} and the arterial available oxygen content ($CavIO_2$). V1 indicates the critical mixed venous blood values before changes in ODC. V2 indicates the critical mixed venous blood values after changes in ODC.*

After intubation of the trachea 0.1 mg/kg pancuronium i.v. was given with an additional continuous i.v. infusion of 0.3 mg/kg/h. The pigs' lungs were ventilated with air and tidal volume was adjusted to keep end-tidal CO_2 between 33.8 and 37.5 torr (4.5 and 5.0 kPa). Catheters (Cook Europe, BP8) were placed in the left femoral artery, the right femoral vein and the right femoral artery (the latter for arterial blood pressure monitoring). Via the left femoral vein a thermodilution catheter (Swan Ganz® 93A-095-7F, Am. Edwards Lab., USA) was introduced into a pulmonary artery. In all animals the injectate port was located in the right atrium as was proven on *postmortem* examination. The urine bladder

was cannulated and a urine catheter placed. Body temperature (blood temperature) was measured with the thermistor electrode of the thermodilution catheter and was kept stable throughout the procedure by means of a heating pad. After all preparations were completed, the sedated paralyzed animals were ventilated until blood gas tensions, pH and hemodynamic parameters were stabilized (average time: 30 min). Pulse rate, arterial blood pressures, pulmonary arterial pressures and the right atrium pressure were monitored continuously (Horizon 2000, Mennen Medical, Israel). After the stabilization period baseline measurements were made, including: pulse rate (HRT), mean arterial blood pressure (MAB), systolic pulmonary arterial pressure (sPAP), diastolic pulmonary arterial pressure (dPAP), pulmonary wedge pressure (PWP), right atrial pressure (RAP) and cardiac output (CO). In addition, arterial and mixed venous blood samples were taken for measurements of PO_2, pH and PCO_2 (ABL330, Radiometer A/S, Denmark) and for measurement of hemoglobin (Hb) and oxyhemoglobin content (Spectrophotometer OSM3, Radiometer A/S, Denmark). Oxygen flux (O_2 flux) was calculated as the product of arterial oxygen content and cardiac output. Oxygen uptake by the tissue (VO_2) was defined as the product of CO and the arteriovenous oxygen content difference. The oxygen extraction ratio (ER) was calculated as VO_2 divided by O_2 flux.

From the values of PO_2, pH, oxyhemoglobin saturation (SAT) of the mixed venous blood sample the S_{35}, was calculated according to the formula:

$$S_{35} = \frac{e^{f(PO_2)} \cdot 100}{1 + e^{f(PO_2)}}$$

where:

$$f(PO_2) = \ln \frac{SO_{2,o}}{1-SO_{2,o}} + \ln \frac{4.67}{PO_{2,o}} + k \cdot \tanh \frac{(N_o) - 1.\ln \frac{4.67}{PO_{2,o}}}{k}$$

and

	$SO_{2,o}$	=	0.867
	k	=	3.5
	N_0	=	2.87
	$PO_{2,o}$	=	1.955 $(P_{50})_{\text{actual pH}}$

$$(P_{50})_{actual\ pH} = (P_{50})_c \cdot 10^{-(0.48 \cdot (pH-7.4))}$$

and

$$(P_{50})_c = \sqrt[2.6]{\frac{100}{SO_2} - 1} \cdot PO_2 \cdot \left(1 + \frac{0.001.SO_2^2 - 0.1.SO_2 + 2.5}{26.85}\right).10^{-0.48(7.4-pH)}$$

The modified oxygen extraction ratio (ERav) was calculated as VO_2 divided by O_2av (= CaO_2 - CvO_2 divided by $CavIO_2$), whereby the $CavIO_2$ is defined as the arterial oxygen content minus the oxygen content at a PO_2 of 35 torr (4.67 kPa).

The first step of isovolemic hemodilution with iso-oncotic dextran 40, 50 g/L in 0.9 % salt solution (Isodex®, N.P.B.I, Holland) began after baseline measurements were completed. The dextran solution (warmed to 38 °C) was instilled slowly into the right femoral vein at the same time and at the same rate that blood was removed from the left femoral artery. Stepwise isovolemic hemodilution was induced by steps of 10 mL/kg bodyweight until a total exchange of 40 mL/kg bodyweight and afterwards by steps of 5 mL/kg bodyweight. New sets of data were obtained after each step of isovolemic hemodilution when blood gas tension, pH and hemodynamic parameters were stabilized again (average time: 5 min). The time between each step of blood exchange was 15 min.

To establish the mean critical ERav ± SD, VO_2 was plotted against the ERav in each animal. The critical point of ERav after which VO_2 gradually decreased was analytically chosen from the intersection of the two bestfit regression lines, determined by a least sum of squares technique as described by Schumacker et al [2].

All values are expressed as means ± SD The accepted probability for a statistical significance between means was $P < 0.05$. The statistical significance of differences was tested by the Wilcoxon signed-rank test. Regression lines were estimated by methods of least squares. For regression analysis the Spearman rank correlation coefficient was used.

Results

The S_{35} decreased after every reduction in hemoglobin (Table 1). The S_{35} at 100 mL/kg bodyweight blood exchange was nearly 25% lower than the baseline value. The change in S_{35} was not correlated with changes in arterial or mixed venous pH and PCO_2. A direct significant correlation was found with changes in PvO_2 (Figure 2).

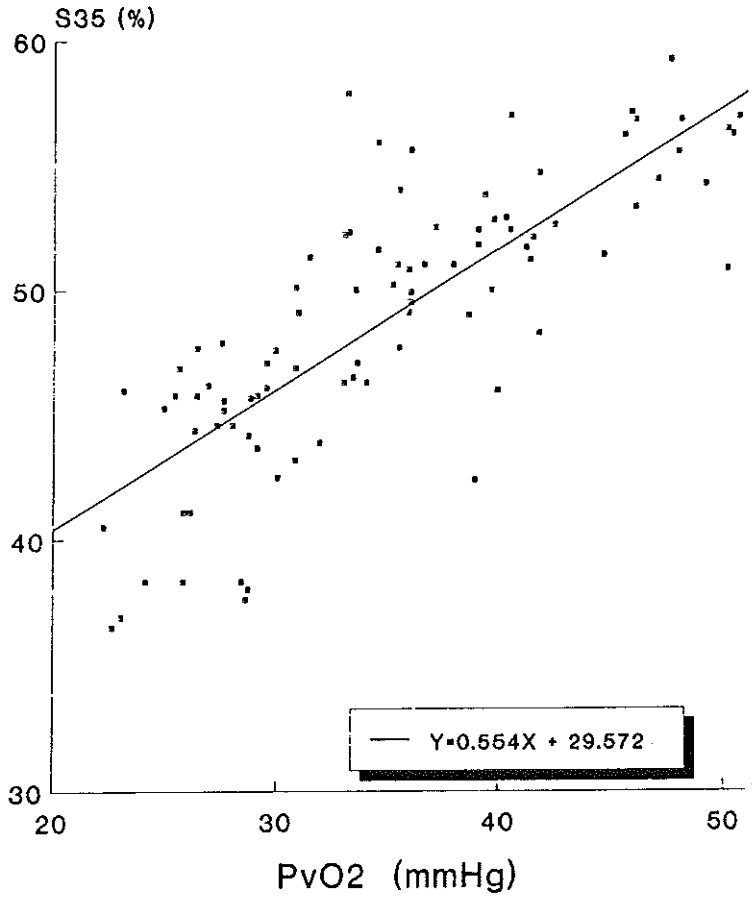

Figure 2. *Scatterplot of S_{35} against PvO_2 (corrected for pH = 7.4). r_s = 0.81. Two-tailed probability of equaling or exceeding Z = 2.4 • 10^{-14}.*

A direct correlation was also found between the increase of the classic ER (defined as VO_2 divided by O_2 flux) with the change in S_{35} (Figure 3). The P_{50} and the modified extraction ratio (ERav) are summarized in Table 1. Plotting ERav against VO_2 in each animal, the mean ERav critical at the point of intersection of best-fit regression lines was 1.08 ± 0.09 (Figure 4). A plot of the mean ERav at each step of hemodilution against the corresponding mean VO_2 gives a critical ERav value of 1.06 (Figure 5).

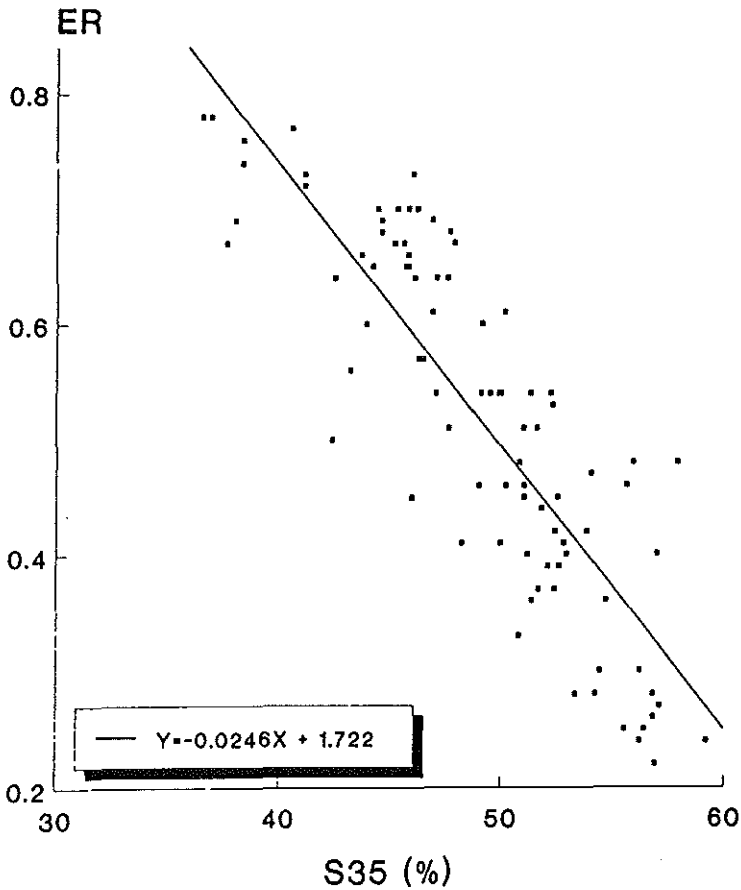

Figure 3. *Scatterplot of S_{35} against ER. r_s = -0.08. Two-tailed probability of equaling or exceeding Z = 2.2 • 10^{-16}.*

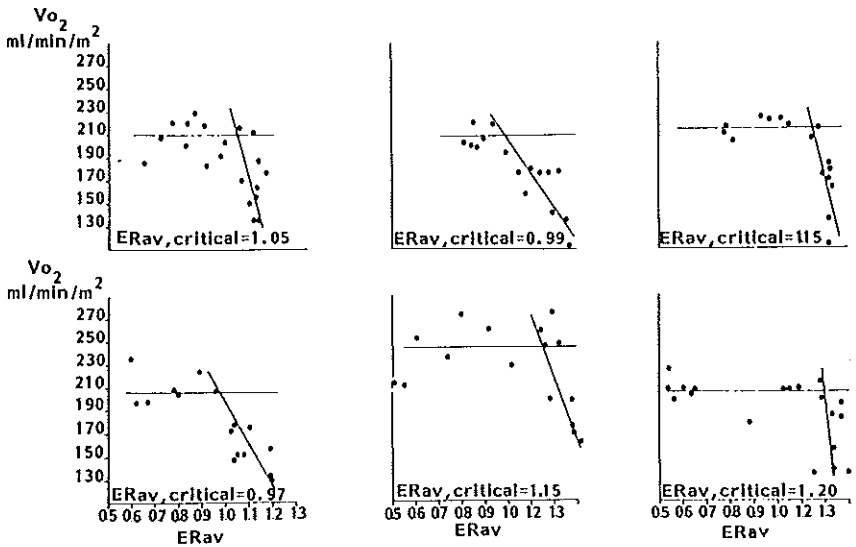

Figure 4. *VO_2 plotted against ERav in each animal. The mean ERav at points of intersection of best-fit regression lines is 1.08 ± 0.09.*

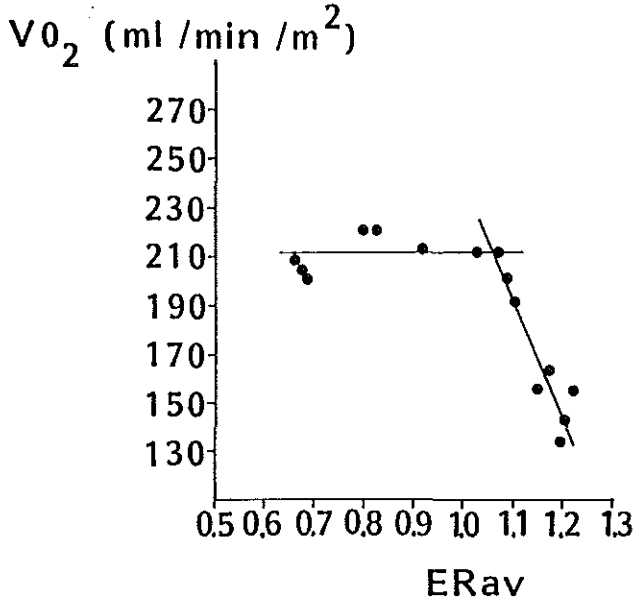

Figure 5. *Mean VO_2 at every step of hemodilution against the corresponding mean ERav. The ERav at the intersection of the two best-fit regression lines is 1.06.*

Table 1 *Some parameters of systemic oxygenation after every step of blood exchange.*

Blood exchange in mL.kg^{-1} body weight	Hb mmol.L^{-1}	S_{35} %	ER	ERav	P_{50} kPa
0 (baseline)	6.3 ± 0.7	55.1 ± 2.1	0.30 ± 0.08	0.66 ± 0.15	4.39 ± 0.20
10	4.9 ± 0.5*	54.2 ± 2.4	0.32 ± 0.07	0.68 ± 0.13	4.41 ± 0.20
20	4.2 ± 0.4*	53.6 ± 3.1	0.33 ± 0.07	0.68 ± 0.16	4.47 ± 0.21
30	3.8 ± 0.5*	52.8 ± 3.2	0.38 ± 0.07	0.80 ± 0.12	4.56 ± 0.17
40	3.3 ± 0.3*	51.0 ± 2.9*	0.42 ± 0.04	0.83 ± 0.11	4.65 ± 0.19
50	2.8 ± 0.2*	50.8 ± 5.6*	0.46 ± 0.06*	0.93 ± 0.10*	4.68 ± 0.28*
60	2.5 ± 0.3*	49.4 ± 2.8*	0.53 ± 0.08*	1.02 ± 0.12*-	4.72 ± 0.25*
65	2.3 ± 0.2*	47.4 ± 5.7*	0.56 ± 0.07*	1.07 ± 0.10*	4.85 ± 0.37*
70	2.1 ± 0.1*	47.8 ± 5.3*	0.59 ± 0.08*	1.09 ± 0.06*	4.80 ± 0.31*
80	1.9 ± 0.3*	47.1 ± 4.4*	0.63 ± 0.06*	1.17 ± 0.07*	4.84 ± 0.20*
85	1.8 ± 0.2*	45.5 ± 4.5*	0.65 ± 0.08*	1.15 ± 0.06*	4.92 ± 0.21*
90	1.6 ± 0.2*	45.7 ± 3.8*	0.67 ± 0.07*	1.20 ± 0.08*	4.85 ± 0.19*
95	1.4 ± 0.2*	43.9 ± 5.8*	0.68 ± 0.08*	1.18 ± 0.10*	4.85 ± 0.25*
100	1.4 ± 0.2*	41.5 ± 4.1*	0.72 ± 0.05*	1.20 ± 0.05*	4.95 ± 0.19*

Abbreviations: Hb = hemoglobin; S_{35} = saturation of hemoglobin at oxygen tension of 4.67 kPa (35 mmHg); ER = extraction ratio of total arterial oxygen content; ERav = oxygen extraction ratio of arterial available oxygen content; P_{50} = oxygen tension at hemoglobin saturation of 50% (corrected to pH = 7.40).

* $P < 0.05$ (in comparison to baseline).

Discussion

In the present study S_{35}, the saturation at an oxygen tension of 35 torr (4.67 kPa), was used as a dynamic baseline for oxygen delivery calculations, assuming that oxygen bound to Hb at a tension of less than 35 torr (4.67 kPa) should be considered relatively unavailable as a decrease of the end capillary PO_2 below 35 torr (4.67 kPa) may be followed in some organs by tissue hypoxia due to limitation of oxygen diffusion into the tissue. Intensive care patients with a consistent PvO_2 of less than 30 torr (4 kPa) did not survive while all survivors had a PvO_2 of more than 35 torr (4.67 kPa). The group of patients with a consistent PvO_2 between 30 and 35 torr included survivors and non-survivors [3,4,5]. Schumacker found during hypovolemia in dogs a critical PvO_2 of 29.0 ± 2.3 torr (SD) (4.0 ± 0.3 kPa) [6].

In dogs during isovolemic hemodilution a critical PvO_2 between 30 and 40 torr (4.0 - 5.3 kPa) has been reported [7], while in pigs during isovolemic hemodilution a critical PvO_2 of 32.0 ± 3.1 torr (SD) (4.27 ± 0.41 kPa) was determined [1].

In the present study a S_{35} of 55 % was found as baseline value. In terms of our definition this means that the arterial available oxygen content ($CavIO_2$) is only 45 % of the total arterial oxygen content (CaO_2) and that when the required VO_2 should exceed the $CavIO_2$, a decrease in VO_2 would be expected. During hemodilution a gradual decrease in S_{35} at pH and PCO_2 as measured in the mixed venous blood, was observed. This means an increase in the amount of the $CavIO_2$ as part of the CaO_2 perhaps diminishing thereby the chance of an oxygen supply dependence of oxygen uptake. In the present study the change in the actual S_{35} was accompanied by an acute shift to the right of the ODC as expressed by a change in the P_{50} (corrected to pH = 7.40). No correlation was found between the change in S_{35} and changes in arterial or mixed venous actual pH, PCO_2 or temperature. A close relationship was found between the actual S_{35} and the for pH corrected PvO_2. Thus alterations in ODC characteristic during normoxic acute normovolemic hemodilution may partly compensate for the reduction in end-capillary PO_2. These alterations are in agreement with the reported acute changes in PO_2 of coronary sinus, venous and arterial blood during signs of hypoxia of the heart in humans [8,9,10]. The concept of S_{35} and ERav includes the effects of changes in ODC on oxygen delivery. In many

studies the role of the ODC on tissue oxygenation has been discussed. In all these studies the P_{50} value of the blood was manipulated. Malmberg et al reported that a left shift of the ODC in rats limits oxygen delivery during hemorrhagic shock [11]. In rats with low P_{50} blood, increased blood flow to brain and heart, probably to compensate for decreased tissue O_2 pressure, has been observed [12]. Increased blood oxygen affinity decreased canine brain oxygen consumption [13], while in dogs reduced blood oxygen affinity after coronary artery occlusion significantly decreased the extent of myocardial necrosis for the same degree of ischemia [14]. Schumacker et al suggested, that low P_{50} confounds oxygen extraction when delivery is very low, but found that in dogs with reduced P_{50}, the critical oxygen flux and critical extraction ratio did not differ from controls [2]. In a review Rand stated that where oxygen reserves are minimal, the position of the ODC may well be a critical factor in the survival of the tissue, and thus the entire organism [15].

In our study we found a direct significant linear relationship between the decrease in S_{35} and the increase in the classic extraction ratio suggesting that the position of the ODC also influences the amount of oxygen extracted in the capillaries from hemoglobin.

In the present study, besides the S_{35} the value of the ERav was calculated after each step of isovolemic hemodilution. We reasoned that the relationship between $CavIO_2$ and VO_2, expressed by us as ERav, should give a more realistic indices of oxygen supply in relation to oxygen consumption. It was assumed that for instance during normoxic normovolemic acute hemodilution VO_2 starts to decline when ERav reaches around 1.0. In this study using the S_{35} as dynamic baseline, VO_2 started to decrease when ERav was 1.08 $\pm$ 0.09. Using a plot of the mean ERav at each step of hemodilution against the corresponding VO_2 a critical ERav of 1.06 was found. We are unaware of any previous studies comparing such modified extraction coefficient with the critical point of VO_2.

We conclude that the S_{35}, the $CavIO_2$ and the ERav can be of value in monitoring the systemic oxygenation and that the concept of arterial available oxygen content also includes the effect of changes in oxyhemoglobin characteristics on oxygen delivery.

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S_{35} AND DERIVED PARAMETERS DURING EXTRACORPOREAL CIRCULATION TOGETHER WITH HEMODILUTION AND HYPOTHERMIA IN HUMANS

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Summary

A new concept in monitoring systemic oxygenation that includes the effect of changes in oxyhemoglobin dissociation curve (ODC) has been introduced. Using the S_{35} (saturation of hemoglobin at PO_2 = 35 mmHg), real arterial oxygen content ($CavIO_2$) can be calculated being the maximum amount of oxygen that can be extracted from hemoglobin before oxygen diffusion into tissues becomes compromised and oxygen uptake (VO_2) may decrease. The relation between VO_2 and $CavIO_2$ expressed by the extraction ratio of the arterial available oxygen content (ERav) gives a realistic indices of oxygen supply in relation to oxygen consumption. In the present study, during extracorporeal circulation (ECC), a severe shift to the left of the ODC could be observed. The classic parameter for monitoring systemic oxygenation as mixed venous oxygen saturation (SvO_2) and extraction ratio (ER) did not change. The S_{35} increased because of the shift to the left of the ODC with consequent decrease in $CavIO_2$. The ERav reached critical values during ECC together with hemodilution and hypothermia. A severe decrease in mixed venous PO_2 (PvO_2) was also observed. The authors conclude that besides the PvO_2, the S_{35}, The $CavIO_2$ and especially the ERav are of value in monitoring the systemic oxygenation during hypothermic ECC.

Key words: blood gases; coronary bypass, ERav, extraction ratio; hypoxia; mixed venous PO_2; mixed venous saturation; oxygen consumption; oxyhemoglobin dissociation curve; pump flow.

Introduction

Release of oxygen at the tissue level is influenced by several factors as blood flow, hemoglobin concentration (Hb) and the affinity of hemoglobin for oxygen as expressed by the position and slope of the oxyhemoglobin dissociation curve (ODC).

A new concept in monitoring systemic oxygenation that includes the effect of changes in ODC on oxygen delivery has been proposed [1]. Using the S_{35} (saturation of hemoglobin at PO_2 = 35 mmHg), the real arterial available oxygen content ($CavIO_2$) can be calculated being the maximum amount of oxygen that

can be extracted from hemoglobin before oxygen diffusion into tissue becomes compromised and oxygen uptake (VO_2) may decrease (Figure 1). The basis of the concept is the observation that when end capillary PO_2 decreases somewhere below 35 mmHg (4.67 kPa) in some organs tissue hypoxia may begin [2].

The relation between VO_2 and $CavIO_2$ expressed by the extraction ratio of the available oxygen content (ERav) gives a realistic indices of oxygen supply in relation to oxygen consumption [1].

During extracorporeal circulation (ECC) for cardiac surgery the ODC is influenced due to alterations in acid-base status, body temperature and erythrocyte 2,3-diphosphoglycerate (2,3-DPG) content. These changes result in a severe increase in affinity of hemoglobin for oxygen [3].

The purpose of this preliminary study was to evaluate S_{35}, $CavIO_2$ and ERav during extracorporeal circulation together with hemodilution and hypothermia.

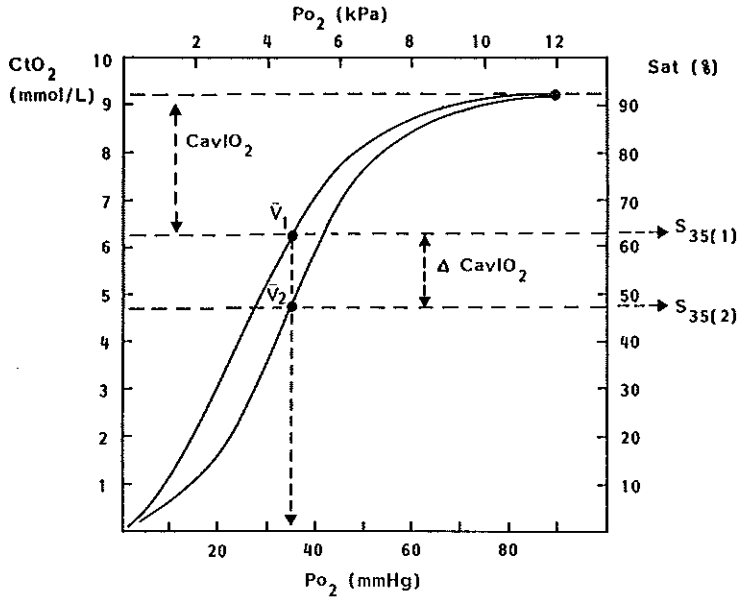

Figure 1. *Effect of changes in ODC on S_{35} and arterial oxygen content ($CavIO_2$). V1 indicates critical mixed venous blood values before changes in ODC. V2 indicates critical mixed venous blood values after a shift of the ODC to the right [from ref. 1].*

Materials and methods

Seven consecutive adult patients scheduled for coronary bypass surgery were included. The evening before surgery premedication was given with oral 15 mg flurazepam (Dalmadorm®) and 90 min preoperatively with oral 2 mg lorazepam (Temesta®). An intravenous cannula was inserted and the radial artery was cannulated. After induction of anesthesia, a central venous catheter was introduced via the right internal jugular vein. Pressures were continuously displayed and recorded throughout the procedure together with ECG, nasopharyngeal and rectal temperature. Anesthesia was induced with fentanyl 15 $\mu g.kg^{-1}$, midazolam (Dormicum®) 0.1 $mg.kg^{-1}$ and pancuronium bromide 0.1 $mg.kg^{-1}$. After tracheal intubation, the lungs were ventilated with 30% oxygen in air, using a servo ventilator 900C (Siemens, Elema, Sweden), with a tidal volume of 10 $mL.kg^{-1}$, frequency of 12 min^{-1} and inspiratory/expiratory ratio 1:2. Anesthesia was maintained with midazolam (Dormicum®) and pancuronium bromide. After a stabilization period baseline values were obtained. Arterial and mixed venous blood samples were taken for measurements of PO_2, pH and PCO_2 (ABL330, Radiometer A/S, Denmark) and for measurements of Hb and Hb oxygen saturation (Spectrophotometer OSM3, Radiometer A/S, Denmark). The actual S_{35} and P_{50} (corrected for pH = 7.4 and body temperature = 37°C) were calculated using formulas as described previously [1]. The classic extraction ratio (ER) was calculated as the arterio-mixed venous oxygen content difference $C(a-v)O_2$ divided by the total arterial oxygen content (CaO_2). The ERav was calculated as $C(a-v)O_2$ divided by $CavIO_2$. Total ECC was then started via atrio-aortic cannulae using a micropores membrane oxygenator (Shiley M2000, Irvine, USA) and a 180° roller pump. The oxygenator and tubes were primed with 1700 mL gelatine solution (Haemacel®), 100 mL albumin (20 %), 200 mL mamitol (20 %) and 50 mL 8.4 % NaHCO3. Anticoagulation was with i.v. heparin 3 $mg\text{-}kg^{-1}$. The patients were cooled using a water-cooled heat exchanger. Pump flow was recorded and baseline measurements and calculations were repeated directly after ECC was started but before cooling, 30 min after cooling just before rewarming and directly after rewarming.

Data are presented as means ± SD. Presented PO_2 measurements are values at the actual body temperature. The accepted probability for a statistical significance between means was $P<0.05$. Differences were tested by the

Wilcoxon Signed-rank test.

Results

The results are summarized in Table 1. The start of ECC was accompanied by a decrease in hematocrit (Hct) from 37 ± 2 % to 24 ± 3 %. The Hct did not significantly change throughout the following studied period. During ECC the patients were cooled to a body temperature of 26.4 ± 1.5°C (nasopharyngeal temperature) and before getting off from ECC, rewarmed to baseline body temperatures. The classic parameters for monitoring systemic oxygenation as SvO_2 and ER did not change. Due to hemodilution at the start of ECC CaO_2 decreased from 7.76 $mmol.L^{-1}$ to 5.38 $mmol.L^{-1}$; no further statistically significant changes occurred in CaO_2 during the following procedures. The $CavIO_2$ also decreased at the beginning of ECC; not only due to induced hemodilution but also due to the increase in S_{35}. Due to cooling a further statistically significant increase in S_{35} could be observed, together with a decrease in $CavIO_2$. The S_{35} did not return to values observed before cooling started. At the start of ECC, P_{50} (corrected to pH = 7.40 and body temperature = 37°C) decreased and did not change significantly anymore throughout the whole following procedure.

Discussion

In the present study the start of normothermic ECC was accompanied by an acute significant shift of ODC to the left. This shift did not correlate with changes in pH or PCO_2. As expected, during hypothermia a further shift to the left could be observed, demonstrated by the further increase in S_{35} after cooling was induced. However, the P_{50} corrected for temperature to 37°C and corrected to pH = 7.4 did not change in comparison to the corrected P_{50} at the start of ECC before cooling. The initial fall in the corrected P_{50} at the start of ECC cannot be explained by data from the present study. Others found a decrease in 2,3-DPG during cardiopulmonary bypass [3]. This could explain the initial shift in ODC which was not correlated with pH, PCO_2 or body temperature.

Table 1. *Some parameters of systemic oxygenation during extracorporeal circulation (ECC)*

	pump flow L/min.m^{-2}	bodytemp °C	S_{35} %	$P_{50}c$ kPa	Hct %	SvO_2 %	PvO_2 kPa	CaO_2 mmol/L	$CavIO_2$ mmol/L	ER	ERav
before ECC		36.8±0.3	63.8±2.0	3.71±0.07	37±2	78.7±10.3	6.42±1.90	7.76±0.66	2.85±0.09	0.22±0.09	0.61±0.24
on ECC before cooling	2.44±0.21	36.1±0.1	69.0±4.0*	3.49±0.09*	24±3*	79.0±6.0	5.72±0.81	5.38±0.58*	1.88±0.15*	0.26±0.05	0.75±0.15
30 min on ECC	1.55±0.20#	26.4±1.5*#	79.0±2.5*#	3.52±0.15*	25±2*	80.8±4.8	2.76±0.38*#	5.51±0.63*	1.30±0.18*#	0.22±0.03	0.97±0.25*#
on ECC just before rewarming	1.65±0.10#	26.9±1.1*#	79.1±2.5*#	3.49±0.12*	26±2*	78.8±3.5	2.37±0.40*#	5.63±0.71*	1.28±0.24*#	0.24±0.03	1.05±0.20*#
on ECC after rewarming	2.54±0.20	36.7±0.3	73.0±1.5*#	3.52±0.07*	26±2*	77.5±0.4	5.13±0.39	5.75±0.55*	1.81±0.18*	0.27±0.05	0.87±0.12*#

Abbreviations: S_{35} = saturation of hemoglobin at oxygen tension of 4.67 kPa (35 mmHg); $P_{50}c$ = oxygen tension at hemoglobin saturation of 50% (corrected to Ph = 7.40 and body temperature = 37 °C); Hct = hematocrit; SvO_2 = mixed venous saturation of hemoglobin; PvO_2 = mixed venous oxygen tension; CaO_2 = arterial oxygen content; $CavIO_2$ = available oxygen content; ER = extraction ratio; ERav = extraction ratio of the available oxygen.

* $P < 0.05$ (compared to values before ECC); # $P < 0.05$ (compared to values during ECC before cooling).

Table 2 *.Data of blood gas analysis during extracorporeal circulation (ECC)*

	pH(a) 37	pH(a) act	pH(v) 37	pH(v) act	PaO_2 37 kPa	PaO_2 act kPa	$PaCO_2$ 37 kPa	$PaCO_2$ act kPa	$PvCO_2$ 37 kPa	$PvCO_2$ act kPa	SaO_2 %
before ECC	7.42±0.04		7.39±0.03		17.48±9.40		5.09±1.05		5.79±0.32		96±3
on ECC before cooling	7.50±0.06*		7.41±0.04		41.70±8.34*		4.09±0.49*		5.46±0.65		99±0
30 min on ECC	7.48±0.04	7.63±0.04	7.41±0.04	7.56±0.04	31.57±5.56*	24.22±8.72	4.29±0.40	2.66±0.34	5.24±0.55	3.21±0.40	99±0
on ECC just before rewarming	7.48±0.03	7.63±0.05	7.41±0.04	7.56±0.04	30.09±4.63*	24.11±4.42	3.98±0.30*	2.45±0.14	4.80±0.44*	2.95±0.23	99±0
on ECC after rewarming	7.54±0.04*		7.47±0.03*		41.79±2.18*		3.51±0.28*		4.43±0.28*		99±0

Abbreviations: pH(a),37 = pH arterial blood corrected to 37°C; pH(a),act = pH arterial blood at the actual body temperature; pH(v),37 = pH mixed venous blood corrected to 37°C; pH(v),act = pH mixed venous blood at the actual body temperature; $PaCO_2$ = arterial CO_2 tension; $PvCO_2$ = mixed venous CO_2 tension; SaO_2 = arterial hemoglobin saturation.

* $P < 0.05$ (compared to values before ECC).

The increase in oxygen affinity can be thought to be a limiting factor in tissue oxygenation during ECC. The reported decrease in oxygen consumption during hypothermic ECC might be due not only to reduced metabolic requirements, but also to the limited amount of oxygen that can be extracted from Hb because of the severe leftwards shift of the ODC [3]. During hypothermic ECC lactate was found to be increased [3,4] while the lactate/pyruvate ratio was found to be consistently higher during hypothermia than during the rewarming phase, suggesting some degree of tissue hypoxia [3]. The practice of monitoring SvO_2, ER or CaO_2 as parameters for tissue oxygenation is therefore questionable during hypothermic ECC. In the present study SvO_2 and ER did not change during the various stages of the study while CaO_2 did not include the effects of shifts in ODC, but only the changes in Hct. We found PvO_2 more sensitive for changes in several factors influencing oxygenation. Also others suggest that PvO_2 may indeed be the more reliable variable to use [4]. However, it is still impossible to conclude from PvO_2 measurement if the tissue oxygenation is sufficient or not. A new concept in monitoring the systemic oxygenation that includes the effect of changes in ODC on oxygen delivery has been introduced [1]. The concept makes it possible to calculate the real maximum amount of oxygen that can be extracted from the hemoglobin under different circumstances. The relation between this so-called arterial available oxygen content ($CavIO_2$) and the VO_2 (ERav = VO_2 divided by $CavIO_2$) gives an index of the systemic oxygenation.

In the present study $CavIO_2$ was affected by hemodilution as well as by the shift in ODC. The ERav significantly increased with hypothermia indicating that the available oxygen reserve decreased. The value of 1.05 ± 0.20 at the end of the hypothermic period indicates that at this stage of the study hypoxia may have exist in some cases, because in another study an ERav value of 1.08 ± 0.09 was found to be critical where oxygen uptake starts to decrease due to limited oxygen availability [1].

We conclude that strategies to maintain effective oxygen delivery to the tissue during hypothermic ECC have to accommodate the severe shift to the left of the ODC and that S_{35}, $CavIO_2$ and especially ERav are of value in monitoring systemic oxygenation. It is essential that both pump flow and hemoglobin concentrations are kept at adequately high levels to prevent an increase in ERav above 1.0 and thus prevent tissue hypoxia during hypothermic ECC

Acknowledgments

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Chapter 10

SUMMARY AND CONCLUSIONS

Blood transfusions, although sometimes necessary, have several disadvantages including transmission of infectious diseases, transfusion reactions and isosensitization, and immunosuppression. Reducing the amount of homologous blood used perioperatively helps to diminish the risk of one of these complications occurring. The methods which can be employed to try to avoid homologous blood transfusions perioperatively include the use of several hemodilution techniques and the application of preoperative autologous blood donation. During hemodilution the hemoglobin level of the circulating blood is reduced, diminishing the oxygen carrying capacity of the blood. This is compensated for by several mechanisms which are discussed in **chapter 2**, including an increase in cardiac output (in anesthetized subjects mainly due to an increase in stroke volume), a redistribution of the cardiac output to meet the metabolic demands of different organs, possibly a shift of the oxygen dissociation curve, and an increase in oxygen extraction ratio.

Extreme degrees of hemodilution can only be applied in experimental animal studies. As described in **chapter 3**, during extreme normovolemic hemodilution in anesthetized pigs we observed an increase in cardiac output mainly due to an increase in stroke volume (as described previously). Redistribution of the cardiac output occurred, with the heart and brains receiving a relatively large portion. The increase in cardiac output was able to largely compensate for the decrease in oxygen carrying capacity of the blood and total oxygen consumption was maintained. Catecholamines were excluded as a regulatory factor in these changes in this experimental model. The heart is further discussed in part two of **chapter 3**. During hemodilution oxygen delivery to the heart actually increased, resulting in a decrease in the oxygen extraction ratio despite an increase in myocardial oxygen consumption. However, this was accompanied by a redistribution of the intramural blood flow away from the subendocardial layer of the left ventricle indicating an exhaustion of the compensation mechanism (vasodilatation) in this layer. This could cause ischemia of the subendocardial layer during extreme hemodilution.

Changes in mixed venous blood were also studied during normoxic normovolemic hemodilution in pigs and the results are presented in **chapter 4**. The balance between oxygen delivery and oxygen consumption is influenced by hemodilution, causing changes in the mixed venous blood. These changes include a decrease in mixed venous oxygen saturation and mixed venous oxygen

pressure. In this study, oxygen supply dependent oxygen consumption started at a mean mixed venous oxygen pressure of 32.2 mmHg and a mean mixed venous oxygen saturation of 44%. The oxygen extraction ratio at this point was 0.57.

We also studied several aspects of different hemodilution techniques in humans. **Chapter 5** presents the results of a randomized prospective controlled study in which we compared during general anesthesia the effects of acute preoperative normovolemic hemodilution and the more gradual peroperative normovolemic hemodilution with another method of reducing the amount of homologous blood used, namely preoperative autologous blood donation. All hemodynamic changes that have been described previously were also observed in this study. In addition, we found an increase in pulmonary wedge pressure as the hematocrit was reduced. This is probably due to the reduction blood viscosity which is induced by hemodilution causing an increase in venous return. Given the critical value of a mixed venous oxygen pressure of 32.2 mmHg measured during the experimental study described in chapter 4, we tried to evaluate whether during this study some patients reached this critical level. We found such measurements of Pvo_2 in 18 out of 30 hemodilution patients at a mean hemoglobin level of 4.8 ± 0.2 mmol/l. This indicates that at a hemoglobin level of less than 4.8 mmol/l in some patients a deficiency in oxygen delivery may occur. Also 3 out of 10 control patients at some point during the study had Pvo_2 values below 33 mmHg at a ehmoglobin level > 6.0 mmol/l. Further analysis showed that these 3 patients had a large change in P_{50} indicating a significant leftward shift of the oxygen hemoglobin dissociation curve, which was not found in the 18 hemodilution patients. Therefore, we concluded that the low values of Pvo_2 in the hemodilution patients might be due to a decreased oxygen delivery brought about by the decrease in hemoglobin level, while in the control patients the decrease in Pvo_2 might be due to a decreased oxygen availability induced by the leftward shift of the oxygen dissociation curve. The least number of homologous blood transfusions were needed peroperatively in the PABD group (0.5 ± 0.3 U), and the highest number in the control group (5.9 ± 0.8 U). In the ANH and NHD group these numbers were 2.0 ± 0.7 U and 4.3 ± 0.5 U, respectively. There was no significant difference in blood loss between the four groups.

Hypervolemic hemodilution is a more practical and less time consuming method for achieving acute preoperative hemodilution, but introduces the risk of volume overload. The results of a study on the efficacy and safety of

hypervolemic hemodilution in anesthetized Jehovah's Witness patients are presented in **chapter 6**. Hemodynamic consequences of this technique are largely the same as those of normovolemic hemodilution, with the exception of a larger increase in filling pressures (pulmonary wedge pressure and pulmonary artery pressure). Inducing hypervolemia by administration of 1500 ml colloid combined with 1500 ml of lactated Ringer's did not cause any problems in the patients studied, especially no signs of cardiac failure. Furthermore, there was no significant difference in packed cell volume between patients who had lost less than or greater than 20% of their initial blood volume. One of the questions that remains to be answered is whether hypervolemic hemodilution influences the total amount of blood loss during surgery.

Transesophageal echocardiographic evaluation during hypervolemic hemodilution showed that the increased cardiac output was solely due to an increase in stroke volume. This increase in stroke volume was associated with an increase in end-diastolic area of the left ventricle, followed by a decrease in end-systolic area. No progressive cardiac dilatation occurred as wedge pressures increased.

Thus, hypervolemic hemodilution was a safe method that allowed major surgery in patients refusing the use of blood products. Unfortunately, however, one Jehovah's Witness patient with a preoperative anemia died due to a massive hemorrhage peroperatively, despite the application of hypervolemic hemodilution. This case report is presented in **chapter 7**. For this patient during the extreme hemodilution we were able to measure several parameters at the critical point of hemodilution, as we had previously done in an experimental model. Oxygen supply dependent oxygen consumption started at an oxygen delivery of 184 $ml/m^2/min$ at a hemoglobin level of 4.0 g/dl (2.4 mmol/l). Analysis of mixed venous blood gases at this critical point showed a mixed venous oxygen pressure of 34 mmHg and a mixed venous oxygen saturation of 56%, with an oxygen extraction ratio of 0.44.

Monitoring is an important issue during hemodilution. The aim is to prevent any complications caused by a too extreme lowering of the hemoglobin level. Mixed venous blood gas values reflect the balance between oxygen consumption and oxygen delivery and therefore are important parameters during hemodilution. Catheters to measure mixed venous oxygen saturation continuously are available, and might be useful as an on-line monitoring tool during profound

hemodilution. However, their accuracy during acute changes in hematocrit or cardiac output has been questioned. **Chapter 8** presents an evaluation of two different types of catheters. One uses three wavelengths (Opticath®), while the other uses only two wavelengths but receives backscattered light via two other fibers (Spectracath®). Analysis of the accuracy of these two catheters during hypervolemic hemodilution followed by surgical blood loss, and thus during acute changes in hematocrit and cardiac output, showed that reliability was not influenced by changes in hematocrit or pulmonary wedge pressure. Changes in cardiac output, however, did have a slight influence on the accuracy of the Opticath®, but not on the accuracy of the Spectracath®. No drift was observed in either of the two systems. Therefore both catheters can be used to measure mixed venous oxygen saturation to assess the oxygen transport capacity of the blood.

In an attempt to improve the accuracy of predicting when oxygen supply becomes critical during hemodilution a new parameter is introduced in **chapter 9.** The amount of oxygen which the tissues can extract is determined by the amount of oxygen available for extraction. The normal oxygen extraction ratio (ER) is calculated by dividing oxygen consumption by total oxygen delivery. However, not all the oxygen bound to hemoglobin and dissolved in the plasma is available for delivery to the tissues. Therefore, the modified extraction ratio of the available oxygen (ERav) uses the available oxygen content rather than total oxygen content for calculation of available oxygen delivery. The ERav is defined as oxygen consumption divided by the available oxygen delivery. The S_{35} is defined as the saturation at which the oxygen pressure of the blood is 35 mmHg. Using this S_{35} the amount of oxygen actually available in the blood can be calculated and used for calculation of the ERav. The ERav is thus influenced by changes in the position of the oxygen dissociation curve. A leftward shift will reduce the availability of oxygen to be delivered to the tissue and will therefore reduce the amount of available oxygen despite a constant total oxygen delivery. A leftward shift of the oxygen dissociation curve will not influence the normal ER, but will increase the ERav. This theory has been tested during extreme hemodilution in pigs, and during the combination of hemodilution with a decrease in body temperature in humans. During extreme hemodilution in anesthetized pigs a decrease in S_{35}, indicating a rightward shift of the oxygen dissociation curve, with an increase in oxygen availability was observed. Theoretically the critical point of oxygen delivery should start at an ERav of

1.00. Oxygen consumption started to decrease in this study at an ERav of 1.08 ± 0.09, while plotting the mean ERav against the corresponding oxygen consumption resulted in a critical ERav of 1.06.

In anesthetized humans the study on S_{35} and ERav was conducted during extracorporeal circulation. Lowering of the body temperature caused a leftward shift of the oxygen dissociation curve with an increase in the S_{35}. This reduced the available oxygen reserve, which was reflected by an increase in ERav to 1.05 ± 0.20. At this point hypoxia may have existed in some cases. This suggests that the use of S_{35}, available oxygen content and especially ERav are of value in monitoring the systemic oxygenation.

SAMENVATTING EN CONCLUSIES

Bloedtransfusies lijken vaak een levensreddende functie te hebben, maar leveren ook heel wat gezondheidsrisico's op. Deze risico's omvatten transfusie reacties, een verkeerde bloedtransfusie, overdracht van diverse infecties (o.a. HIV, hepatitis, CMV), onderdrukking van het immuunsysteem (met daardoor een grotere kans op postoperatieve ontstekingen en mogelijk ook een grotere kans op terugkeer van kanker). Verder zijn de kosten verbonden aan deze bloedtransfusies niet onaanzienlijk. Redenen genoeg om te proberen deze transfusies zoveel mogelijk te vermijden. Hiertoe staan de anesthesioloog een aantal methoden ter beschikking, waaronder de toepassing van diverse hemodilutie (bloedverdunning) technieken, de intraoperatieve cell saving techniek (waarbij het bloedverlies in een speciaal reservoir opgevangen, daarna gewassen wordt en vervolgens terug gegeven kan worden aan de patiënt) en het gebruik van bloed door de patiënt zelf gedoneerd bij de bloedbank (preoperatieve autologe bloed donatie, PABD).

De besparing op het aantal homologe bloed transfusies door hemodilutie technieken wordt bereikt door het feit dat verdund bloed minder erythrocyten (rode bloed cellen) bevat, zodat er per liter bloedverlies ook minder erythrocyten verloren gaan. In **hoofdstuk 2** wordt ingegaan op de diverse compensatie mechanismen (zoals die ook werden waargenomen bij de diverse studies in dit proefschrift) die in werking treden tijdens de toepassing van hemodilutie. Doordat er per liter bloed minder erythrocyten zijn, kan er ook minder zuurstof vervoerd worden per liter bloed. Het lichaam compenseert hiervoor door een verhoging van het hartminuutvolume (per minuut stromen meer liters bloed door het lichaam); een verhoging van de zuurstof extractie ratio (ER, deze wordt berekend door de zuurstof consumptie te delen door het zuurstof aanbod; een grotere ER betekent dat een groter deel van de hoeveelheid zuurstof in het bloed door de weefsels uit het bloed gehaald wordt); een andere verdeling van het hart minuten volume (waarbij organen met een relatief hoge zuurstof behoefte, zoals hart en hersenen, een relatief groot deel van het hart minuten volume krijgen); een verschuiving van de zuurstof dissociatie curve (waardoor het hemoglobine in de erythrocyten makkelijker zuurstof afgeeft aan de weefsels).

Hoofdstuk 3 beschrijft een studie naar de effecten van hemodilutie in varkens onder algehele anesthesie. In deze studie wordt aangetoond dat de stijging van het hartminuut volume een voldoende compensatie geeft voor de afname van het zuurstof dragend vermogen van het bloed tijdens hemodilutie en

dat deze stijging voornamelijk veroorzaakt wordt door een toename van het slagvolume van het hart en dus niet door een toename van de hartfrequentie. Verder werd er een toename gezien van de doorbloeding van alle organen, met de grootste toename in hart en hersenen (dus een herverdeling van het hart minuut volume). Deze toename was zo groot dat het zuurstof aanbod aan bijna alle organen gehandhaafd werd. In het hart werd zelfs een toename van het zuurstof aanbod gezien. De lichaams zuurstof consumptie werd hierbij volledig gehandhaafd. De zuurstof consumptie door het hart nam iets toe, echter zonder een toename van de zuurstof extractie ratio door het hart. Verder werd er gekeken of circulerende catecholamines ("stress hormonen") een rol speelden bij deze veranderingen: een stijging van deze hormonen werd niet aangetoond. In deel twee van **hoofdstuk 3** worden de veranderingen in het hart tijdens deze varkens experimenten nader belicht. De waargenomen toename van het zuurstof aanbod aan het hart is voldoende om de toename van het zuurstof verbruik door het hart te compenseren. Echter er wordt een herverdeling gezien van de doorbloeding van de linker hartkamer, waarbij de subendocardiale (binnenste) laag de relatief kleinste toename liet zien in doorbloeding. Dit wijst erop dat binnen het hart compensatie mechanismen in werking treden tijdens hemodilutie die bij een te ver doorgevoerde verdunning van het bloed kunnen leiden tot een zuurstofgebrek van de subendocardiale laag van de linker hart kamer. Extra aandacht hiervoor is nodig in situaties waarbij het zuurstof gebruik door het hart verhoogd is of als er beperkingen zijn aan het (maximale) zuurstof aanbod naar het hart.

Hoofdstuk 4 belicht de veranderingen die in de bloedgas waarden optreden tijdens hemodilutie in varkens. Een belangrijk probleem tijdens hemodilutie is dat het zuurstof aanbod naar het lichaam voldoende moet blijven. Dat wil zeggen er moet een balans blijven bestaan tussen zuurstof aanbod en zuurstof verbruik door het lichaam. Deze balans wordt gereflecteerd in bepaalde bloedgas waarden in het gemengd veneuze bloed (dat is het zuurstofarme bloed verzameld uit het hele lichaam, na menging in de rechter harthelft), met name de gemengd veneuze zuurstof saturatie (SvO_2) en de gemengd veneuze zuurstof spanning (PvO_2). Voor deze waarden bestaan kritische grenzen, waarbij er een tekort schieten van het zuurstof aanbod aan het lichaam verondersteld wordt als deze waarden onder die kritische grens dalen. Op dat moment begint de zuurstof consumptie van het lichaam afhankelijk te worden van het zuurstof aanbod en

zal dus gaan dalen. Deze knik in de zuurstof consumptie kan gebruikt worden om het kritische punt te bepalen. Op deze manier werd bepaald dat in varkens de kritische PvO_2 32.2 ± 3.1 mmHg en de kritische SvO_2 44.2 ± 7.9 % waren. De zuurstof extractie ratio (ER) bij dit kritische punt was 0.57 ± 0.08.

In mensen werd gekeken naar de effecten van verschillende technieken om te besparen op het aantal benodigde homologe (dat wil zeggen niet van de patiënt zelf) bloedprodukten rondom een operatie. In **hoofdstuk 5** zijn 3 verschillende methoden (acute normovolemische hemodilutie (ANH), preoperatieve donatie van eigen bloed (PABD) en een meer geleidelijke vorm van hemodilutie tijdens de operatie (NHD) met elkaar en met een controle groep vergeleken. Dit gebeurde bij mannen die onder algehele anesthesie een operatie ondergingen die over het algemeen gepaard gaat met veel bloedverlies. Er werd gekeken naar de effecten van de verschillende technieken op hemodynamiek (onder andere het hartminuutvolume, diverse bloeddrukken, en de zogenaamde vullingsdrukken, waaronder de pulmonale wiggedruk), de zuurstofvoorziening van het lichaam, gebruik van bloedprodukten en bloedverlies. Hierbij werd gevonden dat het minste aantal homologe bloedprodukten van de bloedbank gebruikt werden in de groep met PABD, gevolgd door de groep met ANH. De meeste homologe bloedprodukten werden gebruikt bij de patiënten in de controle groep. Tijdens hemodilutie werden dezelfde compensatie mechanismen gezien als in andere studies (toename hartminuut volume en toename zuurstof extractie ratio). Ondanks het feit dat er sprake was van een streven naar normovolemie (d.w.z. een gelijkhouden van het normale circulerende volume) werd er een toename van de pulmonale wiggedruk ("vullingsdruk") waargenomen naarmate de hematocriet verder daalde. Waarschijnlijk kan dit verklaard worden door een afname van de viscositeit (stroperigheid) van het bloed waardoor het bloed sneller gaat stromen, met name in die delen van het vaatstelsel met een trage stroomsnelheid (d.w.z. het veneuze = zuurstofarme bloed vervoerende deel van de circulatie). Hierdoor neemt de hoeveelheid bloed die per minuut terugkeert naar het hart toe, waardoor de pulmonale wiggedruk zal stijgen. Verder hebben we gekeken of er patiënten waren die ergens tijdens de studie periode een punt bereikten waarbij er een aanwijzing is dat het zuurstof aanbod naar de weefsels in gevaar komt. Als aanwijzing hiervoor gebruikte we het feit dat de PvO_2 daalde onder de waarde van 33 mmHg (dit is de waarde die gevonden was tijdens het al eerder beschreven varkens experiment). Dit gebeurde inderdaad bij achttien

van de dertig hemodilutie patiënten, bij een gemiddeld hemoglobine gehalte van 4.8 ± 0.2 mmol/l. Het is dus mogelijk dat bij een aantal patiënten er een tekortschieten van het zuurstof aanbod kan ontstaan bij een Hb < 4.8 mmol/l. Bij een controle hierop in de controle groep werden er ook drie van de tien patiënten gevonden die onder deze grens zakten met hun PvO_2. Hiervoor kon echter een verklaring gevonden worden in de vorm van een linksverschuiving van de zuurstof dissociatie curve. Dit betekent dat het hemoglobine moeilijker zuurstof kan afstaan aan de weefsels, waardoor ondanks een gelijkblijven van het totale zuurstof aanbod, de hoeveelheid beschikbare zuurstof afneemt, en er via dat mechanisme een relatief tekort aan zuurstof kan ontstaan in de weefsels. Deze linksverschuiving kan onder andere veroorzaakt worden door het geven van een bloedtransfusie met relatief oud bloedbank bloed, waarvan de zuurstof dissociatie curve naar links verschoven is door een afname van het 2,3-DPG gehalte.

In **hoofdstuk 6** is een andere vorm van hemodilutie, namelijk de hypervolemische hemodilutie toegepast in patiënten die tevens Jehova's getuigen zijn. Deze mensen weigeren de toediening van alle vormen van bloedprodukten op religieuze gronden. Bij de techniek van hypervolemische hemodilutie wordt het circulerend volume uitgebreid door toevoeging van plasma vervangende vloeistoffen, en wordt het bloed op deze manier verdund. Hypervolemische hemodilutie heeft het voordeel dat het in de praktijk veel minder arbeidsintensief is dan ANH. Het nadeel van deze methode is dat er een kans bestaat op acute overvulling van de patiënt. We bekeken de efficiëntie en veiligheid van deze methode. Er werd geen verschil gezien in het hemoglobine gehalte na de operatie tussen een groep met een bloedverlies kleiner dan 20% van hun circulerend bloedvolume en een groep met een bloedverlies groter dan 20% van hun circulerend volume. Een toename van het hartminuut volume werd gezien, met een toename van de pulmonale wiggedruk (een maat voor de vulling van het vaatstelsel), echter zonder tekenen van hartfalen of overvulling (bekeken via onder andere transoesofageale echocardiografie). Deze techniek gaf geen complicaties in de bestudeerde patiënten, en maakte in deze groep patiënten ook grotere operaties mogelijk zonder de toediening van bloed transfusies.

Helaas was deze techniek niet in staat alle patiënten veilig door een operatie te krijgen. Eén patiënt overleed ten gevolge van een te sterke daling van het hemoglobine gehalte. Het beloop bij deze patiënt wordt beschreven in

hoofdstuk 7. Het betrof een man met maagkanker en tengevolge daarvan een bloedarmoede. Tijdens de operatie was een onverwacht groot bloedverlies ten gevolge van een scheur in de milt. Met toestemming van de familie werden de verzamelde getallen in een artikel gepubliceerd, omdat uit deze casus iets valt te leren over de kritische grenzen van het zuurstof aanbod, zoals ook beschreven in hoofdstuk 4. Bij deze patiënt lag de kritische grens van het zuurstof aanbod tijdens deze extreme vorm van hemodilutie bij 184 ml/m^2/min (4.9 ml/kg/min) bij een hemoglobine gehalte van 4.0 g/dl (= 2.4 mmol/l). Analyse van het gemengd veneuze bloed liet zien dat op dit kritische punt de PvO_2 34 mmHg, de SvO_2 56%, en de ER 0.44 waren. In hoeverre één patiënt echt iets kan zeggen over toepasbaarheid bij alle mensen is niet goed uit te maken, maar de getallen die gevonden werden kwamen goed overeen met die tijdens de varkens experimenten.

Zo lijkt het er dus op dat de gemengd veneuze zuurstof saturatie een maat is voor de beoordeling van de balans tussen zuurstof aanbod en consumptie tijdens hemodilutie. Deze waarde is tegenwoordig continu te meten met behulp van bepaalde catheters. Het was echter niet duidelijk of deze catheters ook nauwkeurig blijven meten tijdens de snelle en grote veranderingen in hemoglobine gehalte en hart minuut volume, zoals die vaak optreden rondom operaties. Daarom werden 2 catheters getest op hun nauwkeurigheid in patiënten tijdens operaties waarbij gebruik werd gemaakt van hypervolemische hemodilutie en dus snelle veranderingen optraden in hemoglobine gehalte en hart minuutvolume. De resultaten hiervan zijn weergegeven in **hoofdstuk 8.** Beide catheters bleken goed bruikbaar en betrouwbaar, zodat deze catheters toegepast kunnen worden in situaties met groot bloedverlies. De gemeten SvO_2 waarden kunnen dan mede gebruikt worden om het moment dat een transfusie noodzakelijk wordt te bepalen. Een nadeel hiervan is dat het getal niets zegt over individuele organen, maar alleen over het zuurstof aanbod aan het hele lichaam.

Tenslotte hebben we gepoogd een parameter te ontwikkelen die nog nauwkeuriger zou kunnen voorspellen wanneer de kritische grens van hemodilutie bereikt wordt. Dit wordt beschreven in **hoofdstuk 9.** Als uitgangspunt werd hierbij genomen dat het zuurstof aanbod naar de weefsels bepaald wordt door de hoeveelheid zuurstof die daadwerkelijk beschikbaar is om afgegeven te worden vanuit het bloed en dus niet door de totale hoeveelheid zuurstof in het bloed. Als de PvO_2 in het gemengd veneuze bloed onder de al

eerder beschreven waarde van 33 mmHg daalt, bestaat de kans dat er in de weefsels een zuurstof tekort optreedt. Dat wil zeggen dat van alle zuurstof die aanwezig is in het arteriële zuurstof-rijke bloed, alleen de hoeveelheid die als het ware boven deze waarde aanwezig is ook daadwerkelijk beschikbaar is om effectief afgegeven te worden aan de weefsels. Bij een discussie over zuurstof transport wordt er in het algemeen gesproken over de zuurstof extractie ratio (ER). Dit is de zuurstof consumptie gedeeld door het totale zuurstof aanbod. Wij hebben deze ratio gemodificeerd naar de zuurstof extractie ratio van het beschikbare zuurstof (ERav). Dit is de zuurstof consumptie gedeeld niet door het totale zuurstof aanbod, maar gedeeld door de hoeveelheid zuurstof die theoretisch maximaal beschikbaar is (dus de hoeveelheid die afgegeven kan worden tot de zuurstof spanning in het bloed gedaald is onder de 33 mmHg). Om deze waarde te kunnen berekenen wordt er gebruik gemaakt van de S_{35}, dat is de zuurstof saturatie bij een zuurstof spanning van 35 mmHg. Hierdoor wordt de ERav, in tegenstelling tot de ER, mede afhankelijk van de ligging van de zuurstof dissociatie curve. Dit is geëvalueerd in twee verschillende situaties. De eerste in een dier experimenteel model, waarbij extreme hemodilutie toegepast werd. Hierbij werd gezien dat als de zuurstof extractie ratio van het beschikbare zuurstof inderdaad steeg boven de 106% (de theoretisch maximale extractie ratio is 100%) er inderdaad een daling optrad van de zuurstof consumptie. Dit wijst erop dat de weefsels niet meer alle benodigde zuurstof uit het bloed konden halen. Een tweede studie werd uitgevoerd in mensen die een operatie ondergingen waarbij gebruik gemaakt werd van de hart-long machine. Tijdens dergelijke procedures wordt naast een verdunning van het bloed (hemodilutie) de lichaamstemperatuur verlaagd. Een gunstig effect van deze verlaging van de temperatuur is dat de zuurstof consumptie van het lichaam afneemt. Een nadeel hiervan is echter dat de zuurstof dissociatie curve naar links verschuift, wat inhoudt dat het hemoglobine moeilijker zuurstof kan afstaan aan weefsels. Dit houdt dus in dat de hoeveelheid daadwerkelijk beschikbare zuurstof in het bloed afneemt bij een gelijkblijven van de totale hoeveelheid zuurstof in het bloed. Met behulp van de ERav kon dit verschijnsel inderdaad aangetoond worden. Een nadeel van deze meting is wederom dat het alleen een maat is voor het lichaam als geheel en geen antwoord geeft op de vraag of de individuele organen en weefsels voldoende zuurstof aangeboden krijgen.

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CURRICULUM VITAE

De schrijfster van dit proefschrift werd op 19 september 1963 te Rotterdam geboren. In 1981 behaalde zij het diploma VWO aan het Emmaus College te Rotterdam. In 1981 begon zij aan de studie Biologie aan de Rijksuniversiteit van Leiden, alwaar zij in 1982 haar propedeuse Biologie haalde. In 1982 begon zij met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam, alwaar zij op 14 juli 1989 het artsexamen behaalde. Haar werkzaamheden op de afdeling anesthesiologie van het Academisch Ziekenhuis Rotterdam Rotterdam/Sophia begonnen in augustus 1989. Het eerste jaar was dit als AGNIO op een research plaats grotendeels doorgebracht op de afdeling Experimentele Cardiologie van prof. Dr. P.D. Verdouw, gevolgd door een jaar AGNIO anesthesiologie in het Dijkzigt ziekenhuis. Hierna volgde van juli 1991 tot juli 1996 haar opleiding tot anesthesiologe onder leiding van prof. Dr. W. Erdmann. Sinds juli 1996 is zij als anesthesiologe werkzaam in het Academisch Ziekenhuis Rotterdam Dijkzigt en het Sophia Kinder Ziekenhuis.