Models of venous return and their application to estimate the mean systemic filling pressure

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Modellen van de veneuze toevoer en hun toepassing om de gemiddelde systemische vullingsdruk te schatten

PROEFSCHRIFT

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CONTENTS

INTRODUCTION

Mean systemic filling pressure is the equilibrium pressure in the systemic circulation when the heart is arrested and there is no flow. This pressure is a measure of the stressed volume of the systemic circulation and regarded as the driving pressure for the venous return during steady states [1-3]. In this thesis the terms stationary level and steady state refer to a state in which the mean pressure and flow, averaged over a heart cycle, do not change. Dynamic conditions refer to changes in averaged pressure and flow between heart beats. The property of mean systemic filling pressure as driving pressure for venous return has been explained by Guyton [1] and others [2,3].

Most methods that are used to determine mean systemic filling pressure require a total stop of the circulation by inflating a balloon in the right atrium [4] or arresting the heart by fibrillation [5-9]. In 1985 Versprille & Jansen developed a method to determine mean systemic filling pressure in the intact circulation [10]. Their method required seven different steady states of central venous pressure and cardiac output. The total procedure lasted approximately 45 min. If circulatory conditions are nor stable for such a time span, this method is not useful. A main purpose of the research described in this thesis was to develop faster methods to determine the mean systemic filling pressure in the intact circulation.

In the next part of this introductory chapter the relevant concepts are introduced to elucidate the significance of mean systemic filling pressure and related circulatory parameters.

INTRODUCTION TO BASIC CONCEPTS

The total volume (Q) of a blood vessel or system of blood vessels can be divided in two distinct components. Firstly, if the pressure difference over the vessel wall (transmural pressure) is zero, the volume within the vessel is not necessarily zero. The maximal volume at zero transmural pressure is called the unstressed volume (Q_0, fig.1). Secondly, to generate pressure in the circulation the vessels must be filled further and this extra volume is called the stressed volume. The change in (stressed) volume for a change in transmural pressure (P_{tm}) of a vessel is defined as its compliance (C): $C = dQ/dP_{tm}$.

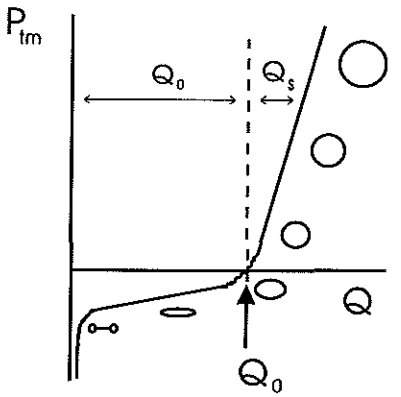


Fig.1: Pressure volume relationship of vessels. P_{tm} is transmural pressure, Q is vessel volume. Q_0 is the unstressed volume, the volume in a vessel at zero transmural pressure. At positive transmural pressure the volume increases with pressure, the difference between total volume and unstressed volume (Q-Q_0) denotes the stressed volume. At negative transmural pressure the vessel collapses. Figure derived from [25 and 26 (review paper)].

If the pressure-volume relationship is linear for positive transmural pressures, this can also be written as [11]:

$$C = \frac{(Q - Q_0)}{P_{tm}} \quad (1)$$

in which Q_0 is the unstressed volume. Normally the circulation is filled up to a transmural arterial pressure of about 80 to 120 mmHg and a transmural central venous pressure of about 0 to 5 mmHg, with the heart as the pump to maintain the pressure difference, necessary for blood flow.

If the heart is arrested and the cardiac output is zero, the pressures in the circulation will tend to equalize. The theoretical equilibrium pressure is called the mean systemic filling pressure. It is the mean pressure in the circulation, weighed by the compliances of each part of the vascular system:

$$P_{sf} = \frac{\sum_i C_i \cdot P_{tm_i}}{\sum_i C_i} \quad (2)$$

If all compliances are constant for different transmural pressures the product $C_i \cdot P_{tm_i}$ denotes the stressed volume of a vascular segment according to eq.(1), and eq.(2) can also be written as:

$$(3) \qquad P_{sf} = \frac{\sum_i (Q - Q_0)_i}{\sum_i C_i} = \frac{Q_{T,s}}{C_T}$$

Where $Q_{T,s}$ is the total stressed volume of the circulation and C_T the total vascular compliance. In eq.(2) and (3) the summations indicate that all parts of the vascular system contribute to the stressed volume and the compliance. Thus, mean systemic filling pressure is an indicator of the total stressed volume in the circulation. If the compliance of the vessels were constant at all transmural pressures, throughout the vascular bed, mean systemic filling pressure would be the mean of aortic and central venous pressure. Because venous compliance is larger than arterial compliance the value of mean systemic filling pressure is in the range of venous pressures [2,3].

THEORY OF VENOUS RETURN

In 1955, Guyton and co-workers studied systemic venous blood flow to the heart (venous return) [1,12]. They found that the venous return ($\dot{Q}_v$) was linearly related to the central venous (or right atrial) pressure (P_{cv}). This linear relationship was formulated as:

$$(4) \qquad \dot{Q}_v = a - b \cdot P_{cv}$$

With this linear relationship the mean systemic filling pressure can be derived as follows: If the flow is zero ($\dot{Q}_v = 0$) the pressure in the circulation is equal to P_{sf} by definition. As a result equation (4) can be rewritten:

$$\dot{Q}_v = 0 \Rightarrow a - b \cdot P_{cv} = 0 \Leftrightarrow P_{cv} = \frac{a}{b} \equiv P_{sf}$$

Substituting this in eq.(4) gives:

$$\dot{Q}_v = b \cdot (P_{sf} - P_{cv})$$

Since 1/b has the dimension of resistance, the equation can be rearranged to [1,3]:

$$(5) \qquad \dot{Q}_v = \frac{(P_{sf} - P_{cv})}{R_{sd}}$$

The value of P_{sf}, determined in vivo, ranges from 7 to 15 mmHg [1,2,4,13,14], which is lower than arterial pressure and higher than central venous pressure. Thus, there will be sites in the circulation where the pressure is equal to P_{sf}, even though the circulation is not arrested. R_{sd} in eq.(5) is defined as the flow resistance between the sites in the circulation where the pressure is equal to P_{sf} and the central veins. If, for a given hemodynamic condition, the stressed volume and the compliance do not change, P_{sf} is constant, according to eq.(3). Then, because eq.(4) and (5) are linear, R_{sd} will be constant also.

There will be many sites in the circulation where the pressure is equal to P_{sf}, because the circulation consists of numerous parallel blood vessels. If all vessels are connected to each other at the arterial and the venous ends of the circulation, P_{sf} is the same for all vessels, according to eq.(2) and (3). Then, the central venous pressure is the downstream pressure for all vessels, and all vessels can be lumped into a model of one tube. For example, if N parallel systems of vessels would exist, venous return would be determined by:

$$(6) \quad \dot{Q}_v = \dot{Q}_{v,1} + \ldots + \dot{Q}_{v,N} = \frac{(P_{sf} - P_{cv})}{R_{sd,1}} + \ldots + \frac{(P_{sf} - P_{cv})}{R_{sd,N}} = \frac{(P_{sf} - P_{cv})}{R_{sd}}$$

Eq.(5) represents a lumped model downstream from the sites in the circulation where the pressure is equal to the mean systemic filling pressure. Because R_{sd} is constant in eq.(5), it is assumed that the parallel resistances $R_{sd,1}$ to $R_{sd,N}$ in eq.(6) are also constant.

A consequence of this theory is that mean systemic filling pressure is a determinant of cardiac output, as has been demonstrated by Guyton [1] and discussed by Rothe [2] and Green [3]. Since the cardiovascular system can be considered as a closed system, the amount of volume pumped out of the heart (cardiac output) must be equal to the amount that flows into the heart (venous return). In figure 2, the balance between the venous return curve and the heart function curve is schematically presented. The intersection of the two curves (point A) represents the equilibrium point of venous return and cardiac output. If, somehow, only the heart function would increase, the cardiac output would increase also, and the equilibrium point would shift. This shift would go along the venous return curve, because no change in circulatory parameters (P_{sf}, resistance, compliance, stressed volume)

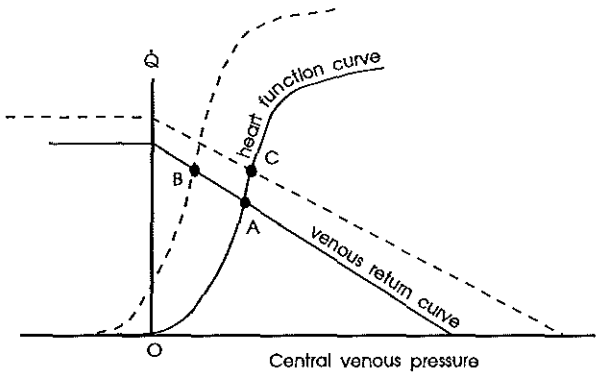


Fig.2: *Equilibrium of venous return and cardiac output. X-axis: central venous pressure, y-axis: $\dot{Q}$ = flow (cardiac output and venous return). Solid lines: venous return curve and heart function curve as indicated in the figure, point A represents the equilibrium. Dashed lines: changes in both curves from the equilibrium. A new equilibrium (B) is obtained if only the heart function is increased, point C is obtained if the venous return is changed by changes in the circulatory parameters (resistance, compliance, vessel volume or blood volume). The graph is derived from Guyton [1] and Green [3].*

has occurred. Consequently, central venous pressure will decrease and a new equilibrium will be set (point B, fig.2). Analogous, if a change in the circulatory parameters occurs, with constant heart function, the venous return curve might shift as in fig.2 (e.g. an increase in R_{sd} or blood volume, or a decrease in compliance or unstressed volume). The central venous pressure will increase and the equilibrium point is shifted towards C (fig.2).

In clinical practice, interventions with drugs can affect the circulatory parameters, by changing resistances, unstressed blood volume, compliance, and thus P_{sf}. Such interventions may change the venous return curve but not the heart function curve, thus changing venous return and thereby the cardiac output [3]. Under these circumstances venous return and cardiac output are determined by eq.(5). In eq.(3) the relationship between mean systemic filling pressure and stressed blood volume was shown for a constant compliance. The combination of both equations gives:

$$(7) \qquad \dot{Q}_v = \frac{(Q - Q_0)}{R_{sd} \cdot C_T} - \frac{P_{cv}}{R_{sd}}$$

This equation indicates that venous return ($\dot{Q}_v$) depends on the central venous pressure (P_{cv}), the stressed blood volume (Q-Q_0), the total vascular compliance (C_T) and the resistance downstream from the sites in the circulation where the pressure is equal to P_{sf}. Under normal steady state conditions the stressed blood volume, vascular compliance and resistance are constant and venous return and cardiac output are strongly dependent on the central venous pressure.

A few examples serve to illustrate the duality of cardiac output control [1]. Increasing the heart rate in a normal heart by an electrical pacemaker [23] greatly increases cardiac activity, but increases cardiac output relatively little. Replacing the heart with a mechanical pump, capable of pumping far more blood than could possibly return to the heart, will not increase cardiac output above its normal range, despite intense pump activity [24]. These experiments suggest that cardiac output is determined by venous return if the heart functions normally. When heart function is impaired, cardiac output will also be determined by heart function. Then, cardiac output will decrease and venous return will decrease also due to an increase in central venous pressure.

REVIEW OF METHODS TO DETERMINE MEAN SYSTEMIC FILLING PRESSURE (P_{sf})

A commonly used method to determine P_{sf} requires a state of zero flow according to its definition (stop flow method). Several authors have performed such determinations. They stopped the heart beat by fibrillating the heart [5-9] or stopped the flow by inflating a balloon in the right atrium [4,16]. During such stop of flow an increase in central venous pressure and a decrease in aortic pressure were observed. According to the theory of mean systemic filling pressure the pressures at all sites in the circulation should become equal to P_{sf} when the flow is zero. However, in such experiments the aortic pressure often remains higher than the central venous pressure (about 20 mmHg to 6 mmHg respectively) after the flow has stopped and both pressures have reached a steady state. Thus, P_{sf} is not obtained by stopping the flow only [3,4,8,13-15]. To determine P_{sf} nevertheless, a corrective

[1] *This paragraph is adapted from Green [3].*

calculation is performed, based on the assumption that an increase in venous stressed blood volume should correspond to a decrease in arterial stressed blood volume, because the total volume should be constant:

$$(8) \qquad \Delta Q_v = -\Delta Q_a \Leftrightarrow C_v \cdot \Delta P_{cv} = -C_a \cdot \Delta P_{ao} \Leftrightarrow \Delta P_{ao} = -\frac{C_v}{C_a} \Delta P_{cv}$$

Since the venous to arterial compliance ratio (C_v/C_a) is assumed to be about 30 to 75 [2-5,14,15], a small increase in central venous pressure should correspond to a large decrease in aortic pressure. Thus, according to the authors who performed such stop flow studies, P_{sf} is slightly higher than the steady state value of the central venous pressure that is obtained after stopping the flow [2-5,14,15]. For example, if the plateau values of aortic pressure and central venous pressure are 20 and 5 mmHg respectively, and C_v/C_a is 49, the calculated value of P_{sf} is: 5 + (20 - 5)/(49 + 1) = 5.3 mmHg.

Cheng & Rankin [16] reported that such a corrective calculation to determine P_{sf} was not valid, because the pressure in the portal vein remained higher than the central venous pressure and higher than the calculated values of P_{sf} after the flow had been stopped in their experiments.

The corrective calculation to determine P_{sf}, used above, was avoided in experiments with an artificial arterio-venous shunt with a pump [6,9,20]. Any arterial to venous pressure differences were rapidly eliminated by opening the arterio-venous shunt and pumping blood through it, to equalize all pressures fast and obtain P_{sf} directly.

Another method to estimate P_{sf} made use of a right heart bypass with a pump. Rapid (step) changes in central venous pressure were applied and the corresponding value of the venous return, when it had reached a steady state, were measured. From the linear relationship between the venous return and the central venous pressure (eq.(5)), P_{sf} and R_{sd} could be determined. Guyton et al. compared both methods [1,12] and found no difference between the values of P_{sf}.

An important condition for all methods to determine the P_{sf} is that the measurements should be performed in the absence of changes in the activity of the neuro-humoral controls. Such changes affect the vessel volume (stressed or unstressed), resistance and

compliance, and thus, P_{sf}. In most studies a steady state is reached and a determination of P_{sf} is obtained within 15 s after the flow has been stopped [4-9,12-14].

DETERMINATION OF P_{SF} IN THE INTACT CIRCULATION

In the experiments of Guyton and others mentioned above, P_{sf} was determined under artificial conditions of the circulation. Versprille & Jansen tested the validity of the linear relationship between central venous pressure and venous return in the intact circulation in pigs [10]. They used a computer-controlled ventilator that was developed in their laboratory [17]. Their method was based on the variations of pressure and flow that were caused by mechanical ventilation [18].

During inflation air was forced into the lung by the ventilator, causing an increase in intrathoracic pressure. Intrathoracic pressure was the extravascular pressure of the central veins in the thorax. Therefore, an increase in intrathoracic pressure caused an increase in central venous pressure [18,19]. As a result the venous return was decreased (eq.(2) and (6)).

Versprille & Jansen studied the relationship, between central venous pressure and venous return, by applying inspiratory pause procedures at different tidal volumes. In their experiments an inspiratory pause procedure (IPP) consisted of an inflation of the lung (1.2 s), an inspiratory pause (7.2 s) and an expiration (3.6 s) [10]. They observed an increase in central venous pressure and a decrease in venous return during inflation. During the first 2 s of the pause the venous return partly recovered and then reached a steady state during the rest of the pause at a level that was lower than at end expiration (fig.3). If a larger volume (tidal volume) was inflated the increase in central venous pressure was larger and venous return was lower during the pause.

Seven IPPs were performed, at different tidal volumes from 0 to 30 ml/kg in steps of 5 ml/kg, obtaining different steady states of central venous pressure and venous return (fig.3). They showed that the linear relationship between the different steady states of central venous pressure and venous return also existed under these circumstances [10]. P_{sf} was obtained by extrapolation of a linear regression through the seven points to zero flow (fig.3, right). They found no evidence for a non-linear relationship between central venous

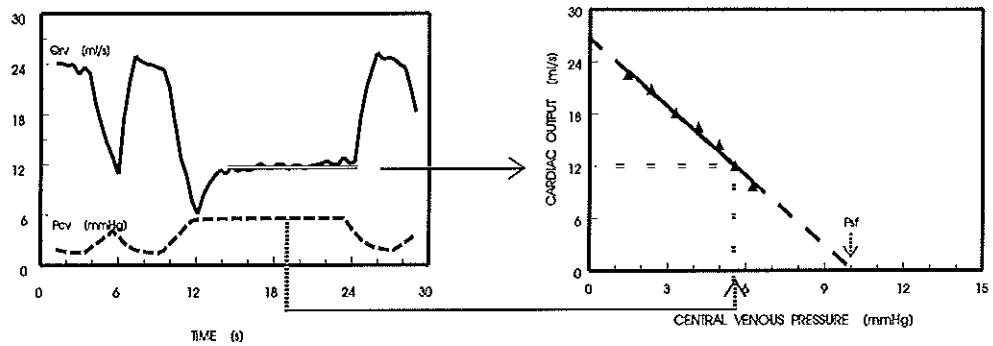


Fig.3: In the left panel the course of venous return and the central venous pressure, averaged per heart beat, during an Inspiratory Pause Procedure (IPP) are shown. During inflation (in this experiment 2.4 s) the central venous pressure rose (dashed line) and the venous return was depressed (solid line). During the pause (in this exp. 12 s) the venous return partly recovered and reached a steady state. The values of venous return and central venous pressure at this steady state were determined and those values produced one point in the right panel. In the right panel the venous return (y-axis) is plotted against the central venous pressure (x-axis). This procedure was repeated at six other volumes of the IPP and a linear regression through these seven points was determined. Mean systemic filling pressure was defined as the intersection of the linear regression with the x-axis, as the flow was zero at that point. The data were taken from an animal experiment in this thesis (Chap.3).

pressure and venous return [10], and argued that their linear curve was equivalent to the venous return curve, described by Guyton et al. [12] in experiments with a right heart bypass.

During the IPPs no changes in control mechanisms were observed during the pause of the IPPs, in which the steady state was reached [10]. Therefore, P_{sf} was assumed to be constant, and R_{sd}, the resistance downstream from the sites in the circulation where the pressure is equal to P_{sf}, was also constant.

In contrast with the stop flow method, this method did not involve a total stop of the circulation. Although pressure and flow were much depressed during IPPs at tidal volumes of 20 to 30 ml/kg, the circulation remained intact, which might facilitate application in

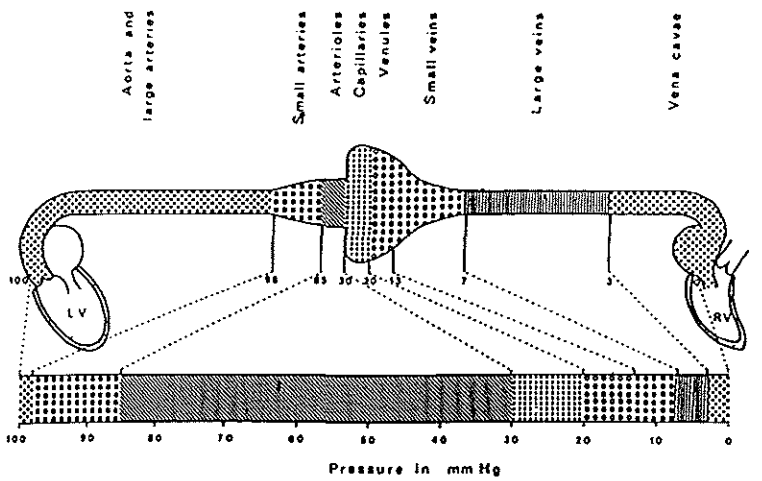
clinical practice. This method to determine P_{sf} is the starting-point of this thesis and will be used as the reference method if other methods to determine P_{sf} are described.

There is a snake in the grass. During the inflation period of the IPPs, the decrease in left ventricular output was delayed with a few heart beats, compared to right ventricular output. Thus, blood volume shifted during inflation from the pulmonary circulation into the systemic circulation [10,18]. For the IPPs at the largest tidal volume (30 ml/kg) the amount of blood that is shifted is about 1.5 to 2.5 ml/kg [18,22]. The total vascular compliance is about 2 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ [2-4,8,15], therefore P_{sf} seems to be overestimated by about 1 mmHg with this method.

Another disadvantage of the method for clinical practice is the time span that is required to determine P_{sf}. Seven IPPs have to be applied, at intervals of at least 5 min for circulatory recovery after the reflexes that follow an IPP, resulting in a period of about 45 min. If the hemodynamic conditions of a patient are not stable for such a period, this method cannot be used. Therefore, we searched for a faster method to determine P_{sf}.

P_{SF} AS TURNING POINT OF THE SYSTEMIC CIRCULATION

The consequence of Guyton's theory of venous return was clarified by Versprille and Jansen using a simple model [10]. A rigid tube with constant flow resistance was used to describe the steady states of the Inspiratory Pause Procedures, during which the compliance of the system had no effect on the flow. In fig.4 a schematical is presented of the contribution to the total systemic flow resistance of the different parts of the circulation, the largest part of the systemic flow resistance being in the arterioles. The advantage of a model with constant resistance is that the pressure drop over the tube is linear and that the slope (dP/dR) represents the flow. In fig.5 the pressure gradient over the resistance is given for seven different IPPs as determined in vivo. During the IPPs P_{sf} was constant as the stressed volume and the vascular compliance were constant and eq.(5) described the venous return. Indeed, when the results of the measurements of aortic pressure and central venous pressure were plotted (fig.5), the different pressure vs. resistance lines, that identified the IPPs, turned around a specific point in the circulation [10]. This turning point was at sites in the circulation where the pressure was equal to P_{sf}.



The systemic circulation modelled as a tube of constant diameter. The numbers give the pressures at the characteristic points of the circulation. They also represent the percentages of total flow resistance over the downstream part of the system

Fig.4: *taken from Versprille & Jansen, 1985 [10]*

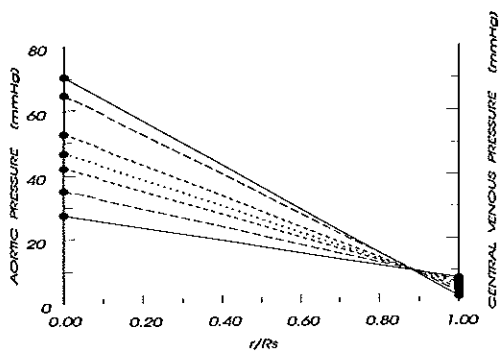


Fig.5: *Plot of the steady states of aortic pressure and central venous pressure during the pauses of different IPPs. On the x-axis the resistance, normalized to total resistance. The resistance was constant over the different IPPs, so the aortic pressure could be plotted on the left y-axis and the central venous pressure at the right y-axis. The slopes of the lines represent the venous return. All lines intersect at one point in the graph, this point is the mean systemic filling pressure (P_{sf}). The figure is adapted from [10], the data were obtained from an animal experiment in this thesis (Chap.3).*

Furthermore, with this method the authors showed that a decrease in aortic pressure was a consequence of the rise in central venous pressure, with a constant P_{sf} and constant flow resistance. The decrease in venous return caused a decrease in right ventricular output, after a delay of 2 to 5 heart beats followed by a decrease in left ventricular output, which in turn caused a decrease in arterial pressure. The total resistance (R_s) did not change over the different IPPs, so that the horizontal axis in fig.5 was the same for all IPPs.

This analysis revealed that the pressure in the circulation, equal to P_{sf}, remained at the same site in the circulation, with respect to the up- and downstream flow resistances, during the different steady states of the IPPs. This constant site of P_{sf} is not necessarily a constant anatomical location in the circulation. Other authors have also mentioned the property of blood pressure equal to P_{sf}, being at a constant site in the circulation [1-3]. It has not been shown that this constant site of P_{sf} is present during dynamic changes of pressure and flow in the intact circulation.

Our first aim was to search for a method to estimate P_{sf} and the other parameters that determine venous return, with use of a method that doesn't require seven steady states of pressure and flow. Furthermore, we aimed to describe the dynamic changes in venous return, caused by mechanical ventilation, by modelling the venous system. With such a model it was investigated whether blood pressure equal to P_{sf} would remain at the same site in the circulation, with respect to the resistances up- and downstream, during inflation and expiration. Finally, it was attempted to explain why the mean systemic filling pressure is a turning point in the circulation for the different IPPs.

OUTLINE OF THIS THESIS

In ***Chapter 2*** the analysis of the relationship between the different steady states of central venous pressure and aortic pressure obtained by inspiratory pause procedures was described. We aimed to determine P_{sf} from the relationship between central venous pressure and aortic pressure, because aortic pressure can be obtained easier in clinical practice than venous return. Furthermore, if the relationship between aortic and central venous pressure was linear, then not only the resistance downstream (R_{sd}), but also the resistance upstream (R_{su}) from the blood pressure equal to P_{sf} was constant. By applying the seven different IPPs and measuring the aortic pressure, the central venous pressure and the

venous return, P_{sf} was estimated on the basis of, firstly, the aortic vs. central venous pressure relationship and, secondly, the venous return vs. central venous pressure relationship. In ***Chapter 3*** a model that represents the circulation downstream from P_{sf} was introduced. The model predicted that P_{sf} would be underestimated if it was determined from a linear regression between central venous pressure and venous return during inflation. This underestimation should decrease if the inflation time was increased. This hypothesis was tested with the use of slow inflation procedures at different inflation times. The model that was adopted in chapter 3 was further analyzed, which was reported in ***Chapter 4***. In this chapter we describe how the venous return was simulated as a function of the central venous pressure. Subsequently, the parameters of the model were adapted to fit the simulated venous return to the venous return, obtained from in vivo experiments. We analyzed whether this model provided reliable estimates of the parameters that determined the venous return, i.e. P_{sf} and R_{sd}, the flow resistance downstream from the blood pressure equal to P_{sf}. A main assumption of this model was that blood pressure equal to P_{sf} remained at the same sites in the circulation with respect to the resistances. In ***Chapter 5*** the test of this assumption is described. The model was extended with an arterial resistance and an additional venous compliance. Again, the venous return was simulated and fitted to the measured venous return by optimizing the model parameters. With this model the transients of the pressures that were approximately equal to P_{sf} were investigated.

The determination of the total systemic vascular compliance remained a problem during the study. In ***Chapter 6*** a first approach was given to estimate the compliance. During the pause of an inspiratory pause procedure an infusion of blood in the right carotid artery was performed. This caused an increase in filling of the systemic circulation, from which the compliance could be estimated. Secondly, the model of Chapter 5 was fitted to the measured venous return during the IPP with infusion. From the fit estimates of the compliance were obtained. In ***Chapter 7*** a summary is given and some sources of possible errors are discussed. Furthermore, the clinical relevance of the determination of P_{sf}, R_{sd} and the compliance is discussed. suggestions for further research of the developed methods to determine mean systemic filling pressure and total systemic compliance are given.

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SYSTEMIC FILLING PRESSURE IN INTACT CIRCULATION, DETERMINED ON THE BASIS OF THE AORTIC VERSUS CENTRAL VENOUS PRESSURE RELATIONSHIPS.

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INTRODUCTION

According to Guytons theory [1,2], venous return ($\dot{Q}_v$) is linearly related to the central venous pressure (P_{cv}): $\dot{Q}_v = a - b \cdot P_{cv}$. This relationship can be used to determine the mean systemic filling pressure (P_{sf}). The P_{sf} is defined as the pressure in the systemic circulation, when flow has stopped and the blood volume distribution has reached equilibrium. The P_{sf} is found from the extrapolated value of P_{cv} at $\dot{Q}_v = 0$, in the $\dot{Q}_v$ versus P_{cv} diagram. Many authors have used this principle to estimate the P_{sf} [3,4,5,6,7]. The relationship was confirmed in conditions of intact circulation [5,7], and found from the stepwise increments of P_{cv} during inspiratory pause procedures [9]. The authors referred to above found that the relationship between P_{cv} and venous return ($\dot{Q}_v$) is linear. This linearity implies a constant flow resistance between the sites in the systemic circulation where pressure is equal to P_{sf} and the right atrium.

If P_{cv} is increased, cardiac output and, consequently, aortic pressure (P_{ao}) will decrease. In that case, the fall in systemic pressure gradient matches the fall in flow [1,2,7]. If systemic flow resistance is constant, the fall in aortic pressure will also be linear. Such linear behavior was hypothesized by Levy [8] in model experiments. We have tested this hypothesis in conditions of intact circulation, in order to find a new method to determine P_{sf} from the change in P_{ao} and P_{cv}, conducting stepwise increments of P_{cv} by inspiratory hold procedures.

THEORY

We consider a stationary hemodynamic condition, with steady laminar flow. We use mean values for flow ($\dot{Q}_s$) and pressures. Then we can apply the basic law of Hagen-Poiseuille for the overall circulation:

$$(1) \qquad \dot{Q}_s = \frac{(P_{ao} - P_{cv})}{R_s}$$

R_s is the total systemic flow-resistance in this formula. Venous return is determined by [1,2]:

$$(2) \qquad \dot{Q}_v = \frac{(P_{sf} - P_{cv})}{R_{sd}}$$

in which R_{sd} is defined as the resistance to flow between the site in the circulation where the blood pressure equals P_{sf} and the entrance of the central veins into the right atrium

(P_{cv}). Thus eq.(2) determines the blood flow downstream of the sites where the pressure equals P_{sf}. For the upstream part of the systemic circulation, we can write:

$$(3) \qquad \dot{Q}_s = \frac{(P_{ao} - P_{sf})}{R_{su}}$$

In this relationship R_{su} is defined as the flow-resistance upstream of the site where the blood pressure equals P_{sf}. In stationary conditions, the venous return ($\dot{Q}_v$) equals the cardiac output ($\dot{Q}_s$), which combines equations (2) and (3) to:

$$(4) \qquad P_{ao} = P_{sf} \cdot (1 + \frac{R_{su}}{R_{sd}}) - \frac{R_{su}}{R_{sd}} \cdot P_{cv}$$

It is assumed that P_{sf} is constant for a given hemodynamic condition. The first term in eq.4 is constant for that condition and this equation becomes linear if the resistances R_{su} and R_{sd} are constant, or if at least their quotient is so. Subsequently, P_{sf} can be determined by measuring the aortic pressure with varying P_{cv}, which we will call the aortic pressure curve. According to eq.(4), P_{ao} versus P_{cv} yields a linear regression. We rewrite eq (4) in general terms as:

$$(5) \qquad P_{ao} = c - d \cdot P_{cv}$$

From equation (4) or (5), it follows that P_{sf} is determined by the direction coefficient (d) and the intersection with the y-axis (c), whereas at zero flow $P_{ao} = P_{cv} = P_{sf}$, according to:

$$(6) \qquad P_{sf} = \frac{c}{(d+1)}$$

Graphically, P_{sf} is determined by the intersection of the aortic pressure curve with the line of identity of P_{cv} (Fig.1).

If we obtain equal values of P_{sf} from the venous return curves and from the aortic pressure curves, the assumption of a constant flow-resistance with changing P_{cv} is acceptable. In that case, the method using the aortic pressure curves will provide an easier way to determine the P_{sf}.

METHODS

As the experimental set-up has been described in previous papers [7,9], we will only mention the essentials here.

SURGERY

Ten piglets (8-10 weeks, mean weight 9.7 ± 0.5 kg) were anesthetized with 30 mg/kg pentobarbital sodium i.p., followed by additional doses of 7.5 mg/kg when necessary. After tracheostomy, the animals were ventilated at a rate of 40-50 per min. and a tidal volume adjusted to an arterial P_{CO_2} of about 40 mmHg, while a positive end expiratory pressure (PEEP) of 2 cm H_2O was given to avoid atelectasis. P_{CO_2}, airway pressure and air flow were measured in the tracheal cannula. The animals were placed in a supine position on a thermo-controlled operation table (38 °C). A catheter was inserted through the right common carotid artery into the aortic arch to measure the aortic pressure (P_{ao}) and sample arterial blood. Two other catheters were inserted through the right external jugular vein: a Swan Ganz catheter into the pulmonary artery to measure pulmonary artery pressure and to sample mixed venous blood, and a four lumen catheter into the superior vena cava to measure central venous pressure (P_{cv}), and to infuse pentobarbital and curare. The lumen for blood pressure measurements were kept patent by an infusion of 3 ml saline per hour.

After thoracotomy, two electromagnetic (EM) flow probes were placed within the pericardium around the ascending part of the aortic arch and the pulmonary artery. Two suction catheters, one dorsal and one ventral, were inserted into the thorax for evacuation of air and recovery of negative intrathoracic pressure [9]. After surgery, the ventilation was set to an inspiration-expiration ratio of 2.4 : 3.6 (total 6 s). The tidal volume was re-adapted to a Pa_{CO_2} of 40 mmHg.

Anesthesia was maintained by means of a continuous i.v. infusion of pentobarbital sodium of 8.0 $mg \cdot kg^{-1} \cdot h^{-1}$. The animals were paralyzed through a continuous i.v. infusion of d-tubocurarine (0.2 $mg \cdot kg^{-1} \cdot h^{-1}$, loading dose 0.1 mg/kg in 3 min.). Maintenance of the pigs' fluid balance was approximated by keeping a record of the in- and output of fluid. There was no information available on evaporation via the skin.

MEASUREMENTS

ECG, aortic pressure (P_{ao}), central venous pressure (P_{cv}), airway pressure, pulmonary artery and aortic flow ($\dot{Q}_v$ and $\dot{Q}_s$) and air flow during inspiration and expiration were recorded. Zero level of blood pressures was chosen at the level of the manubrium. The pressure transducers were calibrated by application of pressure to this reference under guidance of a mercury manometer.

During the special observations, ECG, flow and pressure signals were sampled real-time for periods of 18 s at a rate of 250 Hz. Areas of the flow curves were analyzed off-line. The calibration factors in area units per ml (AU/ml) for both EM signals were determined during the stationary conditions of normal mechanical ventilation, using the Fick method. Mean flow over a cardiac cycle was found by dividing stroke volume by heart interval.

PROTOCOL

To change the central venous pressure we changed the intrathoracic pressure, by applying inspiratory pause procedures (IPP) at different inspiratory volumes. The IPPs were performed at 5 min intervals and consisted of an inflation of 1.2 s, an inspiratory hold of 7.2 s, and a spontaneous expiration of 3.6 s. The tidal volumes were in the range of 0 to 300 ml with increments of 50 ml. Thus, an observation series consisted of 7 IPP's applied in random order.

In eight of the ten animals we performed two series, in one only one series and in the remaining experiment three series, all under normovolemic conditions. In two experiments we performed an additional series under hypovolemic conditions which were induced by bleeding 15 ml/kg body weight. During each IPP, we determined the mean flow from the stroke volumes of a period of five seconds, starting two seconds after peak inflation was obtained. During that period, the right and left ventricular output were equal and stationary.

DATA ANALYSIS

In total, 22 pairs of P_{sf} values were obtained from the venous return curve and the aortic pressure curve. The relations between $\dot{Q}_v$ and P_{cv} (venous return curve) and between P_{ao} and P_{cv} (aortic pressure curve) were analyzed according to the theory based on linear regression. The statistical analyses were done by calculating the mean of the differences (bias), the standard deviation, and the 95% limits of agreement for the comparison of the individual measurements, according to Bland and Altman [10].

We plotted P_{cv} on the X-axis and used two different Y-axes. The left is flow, the usual venous return curve as defined by Guyton (flow-curve); the right is the P_{ao} (aortic pressure curve). The values for P_{sf} obtained with these methods were defined as follows:

$P_{sf}(q)$ = P_{sf} determined from flow-curve;

$P_{sf}(p)$ = P_{sf} determined from aortic pressure curve.

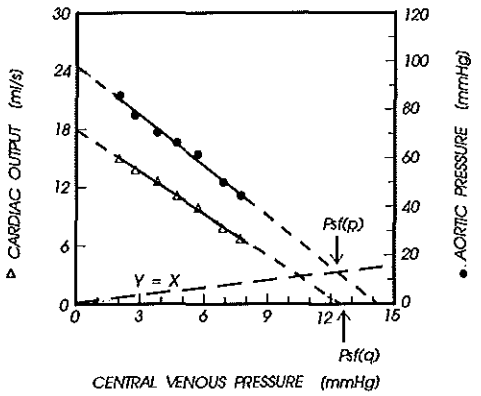

Fig.1: *In this individual example of the determination of P_{sf} P_{CV} is plotted on the X-axis. On the left Y-axis, cardiac output is plotted (triangles), and on the right Y-axis aortic pressure (dots). $P_{sf}(q)$ is found from the extrapolation of the linear regression through the datapoints of cardiac output to zero flow. $P_{sf}(p)$ is found from the intersection of the linear regression through the data of the aortic pressure versus P_{CV}, with the line of identity of P_{CV} (line Y = X).*

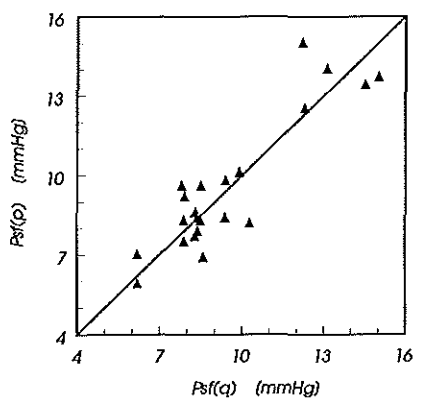

Fig.2: *Each triangle represents the value of $P_{sf}(p)$, obtained from the aortic pressure curve, plotted against the corresponding value of $P_{sf}(q)$, obtained from the venous return curve. The solid line is the line of identity.*

RESULTS

An individual example of the venous return and aortic pressure curves is presented in fig.1. The value of $P_{sf}(q)$ is the central venous pressure at the intersection of the flow curve with the X-axis. $P_{sf}(p)$ can be found as the intersection of the aortic pressure curve with the line of identity of P_{cv}. All results were analyzed in this way. The results of all 22 regressions are presented in Table 1. Almost all correlation coefficients were greater than 0.90. To compare the two methods, we first plotted the raw data of $P_{sf}(p)$ versus $P_{sf}(q)$ for all 22 IPP series in the ten experiments (fig.2). Furthermore, we calculated the difference between $P_{sf}(p)$ and $P_{sf}(q)$ and plotted this against the mean of $P_{sf}(q)$ and $P_{sf}(p)$ for each experiment (fig.3). The bias between $P_{sf}(p)$ and $P_{sf}(q)$ was 0.03 mmHg, so the two methods agree very good, and there is no difference between the two methods on the average.

The standard deviation of the differences (s_{diff}) was 1.16 mmHg, and therefore the 95% limits of agreement are [-2.29 ; 2.35] mmHg.

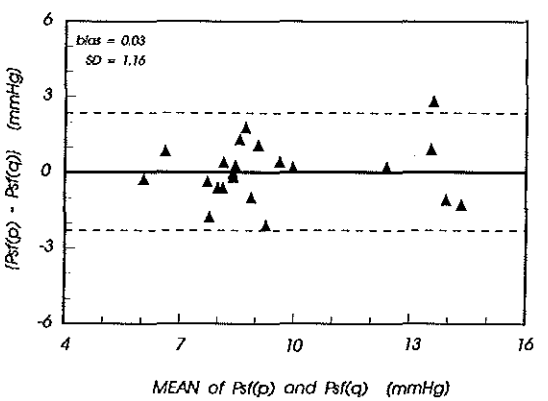

Fig.3: *Each triangle represents a series of IPPs. In the left upper corner, the bias (mean difference) and its standard deviation are given. The dashed-dotted line represents the 95% confidence interval for an individual measurement. The dashed line represents the bias of the two measurements.*

EXP	a	b	r	Psf(q)	c	d	r	Psf(p)
1A	13.6	1.45	0.97	9.4	105.5	11.6	0.95	8.4
1B	11.7	1.48	0.98	7.9	103.1	12.7	0.96	7.5
2A	9.54	0.93	0.98	10.3	70.5	7.61	0.98	8.2
2B	9.00	1.06	0.93	8.5	70.0	7.43	0.99	8.3
3A	11.2	1.35	0.98	8.3	83.9	9.93	0.96	7.7
3B	10.7	1.27	0.99	8.4	76.1	8.74	0.99	7.8
4A	21.2	2.55	0.94	8.3	163	18.0	0.96	8.6
4B	18.1	2.28	0.99	7.9	170	19.4	0.99	8.3
5A	11.0	1.31	0.97	8.4	70.4	7.42	0.98	8.4
5B	8.81	1.02	0.92	8.6	62.3	8.07	0.995	6.9
6A	17.2	1.15	0.88	15.0	128	8.31	0.94	13.7
6B	16.7	1.37	0.98	12.2	115	6.66	0.96	15.0
7A	21.1	1.45	0.89	14.5	107.7	7.02	0.95	13.4
7B	17.9	1.45	0.999	12.3	98.3	6.89	0.994	12.5
8A	28.8	2.20	0.98	13.1	107.2	6.64	0.76	14.0
9A	18.4	2.35	0.995	7.8	77.1	7.04	0.98	9.6
9B	17.4	2.20	0.99	7.9	82.1	7.92	0.97	9.2
9H	9.47	1.53	0.99	6.2	60.1	9.17	0.99	5.9
10A	16.2	1.72	0.99	9.4	100.3	9.22	0.99	9.8
10B	14.7	1.49	0.97	9.9	99.3	8.88	0.98	10.1
10C	13.7	1.61	0.98	8.5	96.5	9.07	0.98	9.6
10H	8.61	1.39	0.996	6.2	62.4	7.89	0.99	7.0

Table 1: *The coefficients of the linear regression of the venous return curves:* $\dot{Q}_V = a - b \cdot P_{CV}$ *and the aortic pressure curves:* $P_{ao} = c - d \cdot P_{CV}$ *are presented together with their respective correlation coefficients and* P_{sf} *values. The numbers in the first column indicate the experiments: A indicates the results of the first series of IPPs and B those of the second series, both under normovolemic conditions. H in experiments 9 and 10 indicates the results during hypovolemic conditions.* $P_{sf}(q)$ *is systemic filling pressure determined from flow curve.* $P_{sf}(p)$ *is systemic filling pressure from aortic pressure curve.* $P_{sf}(q) = a/b$ *and* $P_{sf}(p) = c/(d+1)$.

DISCUSSION

In these experiments, we used the same criteria for stability as were used previously [7,9]; the most important criteria were cardiac output, aortic pressure, central venous pressure and heart rate. Following these criteria, there was no reason to exclude one of the observation series.

In our experiments we showed that there was no significant difference between the determinations of P_{sf} via the aortic pressure curve and the venous return curve. The mean values of P_{sf} for each method in normovolemic conditions was 9.8 ± 2.4(SD) mmHg (n = 20), which is not different (p = 0.44) from the value of 10.5 ± 2.3(SD) mmHg that we found previously [7].

The hypovolemic values of P_{sf} in experiments 9 and 10 were lower than the values obtained during normovolemic conditions. Also, in this range of P_{sf} similar values were obtained with both methods.

A variation in the systemic flow resistance will cause eq.(4) to be non-linear. For a small change the linear regression would have been theoretically not correct, but it would have remained a good approximation. In our results, we did not find any indication that the linear model is not valid.

In 1977, Levy studied pressure-flow diagrams in a physical model with flow as independent variable and P_{cv} and P_{ao} as dependent variables [8]. He started at zero flow, where $P_{ao} = P_{cv} = P_{sf}$. When he raised the flow, an increase in P_{ao} and a decrease in P_{cv} occurred. In our experiments on the intact circulation, P_{cv} was the independent variable. P_{cv} was increased by increasing intrathoracic pressure. Consequently, venous return and therefore also cardiac output diminished, which in its turn, with a delay of a few heart beats, caused P_{ao} to decrease also [7]. The theories of Levy [8] and Guyton [1,2] have the same result for zero flow, implying $P_{ao} = P_{cv} = P_{sf}$. Both theories can be regarded as two different ways of presenting the same mechanisms.

In conclusion, we would like to emphasize that the P_{ao} versus P_{cv} relationship provides a reliable method to determine the mean systemic filling pressure. This new method has the advantage that it does not require estimations of cardiac output, which are more complicated and less accurate than pressure measurements.

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SYSTEMIC FILLING PRESSURE IN THE INTACT CIRCULATION DETERMINED WITH A SLOW INFLATION PROCEDURE.

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INTRODUCTION

During stationary conditions venous return ($\dot{Q}_v$) varies linearly with central venous pressure (P_{cv}) according to [3,4]:

$$(1) \qquad \dot{Q}_v = a - b \cdot P_{cv}$$

According to the law of Hagen-Poiseuille, this can also be written as [2-5,9]:

$$(2) \qquad \dot{Q}_v = \frac{(P_{sf} - P_{cv})}{R_{sd}}$$

in which R_{sd} is defined as the flow resistance between the sites in the circulation where the blood pressure is equal to P_{sf} and the entrance of the central veins into the right atrium (P_{cv}). Eq.(1) and (2) describe the venous system downstream from the sites where blood pressure is equal to P_{sf}. These relationships have been used in the intact circulation during mechanical ventilation to determine the mean systemic filling pressure (P_{sf}), i.e. the pressure in the circulation when flow is zero [5,9]. This method is based on inspiratory pause procedures (IPPs) inserted during normal mechanical ventilation with intervals of 5 min. [9]. To obtain seven different stationary levels of venous return and P_{cv} seven different tidal volumes were inflated. The linearity of eqs.(1) and (2) has been shown under various circumstances [2-4,7,9].

In 1990 Versprille described a windkessel-type model of the venous system, with two resistances and a compliance, to explain the observed responses of the venous return ($\dot{Q}_v$)

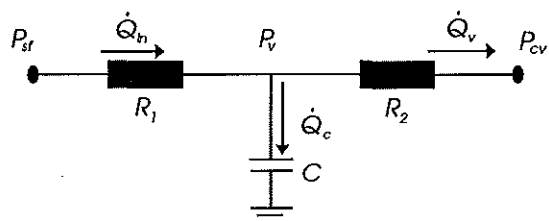

Fig.1: *Model of the venous circulation with two resistances and one capacitor. The sum of the resistances (R_1 and R_2) is equal to R_{sd} as is defined in eq.2. The capacitor (C) is the total compliance downstream from the site in the circulation where the pressure is equal to the mean systemic filling pressure (P_{sf}).*

to mechanical ventilation and inspiratory pause procedures in pigs [8]. During inflation the $\dot{Q}_v$ decreases and in the first two seconds of an inspiratory pause flow increases again towards a new stationary level, lower than the level at end-expiration. In fig.1, an analogy of this model is presented, in which the venous return is determined by:

(3) $\dot{Q}_v = \dot{Q}_{in} - \dot{Q}_c$

in which $\dot{Q}_{in} = (P_{sf} - P_v)/R_1$, $\dot{Q}_v = (P_v - P_{cv})/R_2$, and $\dot{Q}_c = C\, dP_v/dt$.
During stationary conditions the pressures, averaged over a heart cycle, are constant, $\dot{Q}_c$ is zero and $\dot{Q}_v = \dot{Q}_{in}$, fulfilling Guytons equation (2). During mechanical inflation of the lungs, central venous pressure increases. Because P_v in the model is located at a site downstream from P_{sf}, P_v will also rise and the capacitor will be loaded. Thus, $\dot{Q}_c$ will be non-zero and cannot be neglected. As a consequence $\dot{Q}_v$ is lower than predicted by eq.(2) at the same level of P_{cv}. If the inflation time increases, at constant tidal volume, $\dot{Q}_c$ will become smaller and can be neglected if the inflation time is long enough. Then, eq.(3) approximates to eq.(2) and the condition is quasi-stationary.

We studied the effect of slow inflation procedures (SIP) with different inflation times. The right ventricular output ($\dot{Q}_{rv}$) was determined and considered equal to $\dot{Q}_v$. The P_{sf} was determined off-line from the extrapolation of the linear regression of $\dot{Q}_v$ vs. P_{cv} during the inflation to $\dot{Q}_v = 0$. As $\dot{Q}_v$ is lower during inflation than predicted by eq.(2) because the venous capacity is loaded ($\dot{Q}_c$), the P_{sf} will be underestimated with the use of the SIP, compared to the value obtained during stationary conditions, using IPPs. However, this underestimation should decrease when longer inflation times are used.

METHODS

SURGERY

The experimental set-up has been described in detail in previous papers [9,10]. Therefore we have mentioned only the essentials. All experiments were performed according to the "Guide for Care and Use of Laboratory Animals" published by the US National Institutes of Health (NIH, 1985) and under the regulations of the Animal Care Committee of the Erasmus University Rotterdam, the Netherlands.

Nine piglets (8-10 weeks, bodyweight (BW) 10.3 ± 0.8 kg, mean ± SD) were anaesthetized with 30 mg/kg(BW) pentobarbital sodium i.p., followed by a continuous infusion of 9.0 $mg \cdot kg^{-1} \cdot h^{-1}$(BW). After tracheostomy, the animals were ventilated at a rate of 10 breaths per min at an inflation-expiration ratio of 2.4:3.6 and with a tidal volume adjusted to an arterial P_{CO_2} of about 40 mmHg, while a positive end-expiratory pressure of 2 cmH_2O was applied to minimize atelectasis. P_{CO_2}, airway pressure and air flow were measured in the tracheal cannula. The animals were placed in a supine position on a thermo-controlled operation table (38 °C).

A catheter was inserted through the right common carotid artery into the aortic arch to measure the aortic pressure and sample arterial blood. Two other catheters were inserted through the right external jugular vein: 1) a Swan Ganz catheter into the pulmonary artery to measure pulmonary artery pressure and sample mixed venous blood, and 2) a four lumen catheter into the superior vena cava to measure central venous pressure and infuse pentobarbital and pancuronium bromide (Pavulon, Organon Teknika Boxtel, the Netherlands). The catheters for blood pressure measurements were kept patent by an infusion of 3 ml saline per hour.

After an intercostal thoracotomy in the second left intercostal space, an electromagnetic (EM) flow probe was placed within the pericardium around the pulmonary artery. Two suction catheters, one dorsal and one ventral, were inserted into the left pleural space. A pressure catheter was positioned in the pericardium, which was sutured. The thorax was closed airtight. The evacuation of air and fluid was accomplished by applying a negative pressure of 10 cmH_2O to the suction catheters for one or two minutes. After surgery the animals were paralysed with an i.v. infusion of Pavulon (0.3 $mg \cdot h^{-1} \cdot kg^{-1}$), after a loading dose of 0.1 mg/kg in 3 min.

MEASUREMENTS

ECG, aortic pressure, pulmonary artery pressure, central venous pressure (P_{cv}), intrathoracic pressure, airway pressure, pulmonary artery flow ($\dot{Q}_{rv}$), capnogram and air flow were recorded. Zero level of blood pressures was chosen at the level of the tricuspid valves, indicated by the Swan Ganz catheter during lateral to lateral radiography. The pressure

transducers were calibrated by application of pressure to this reference under guidance of a mercury manometer.

During the special observations, ECG, flow and pressure signals were sampled real-time for periods of 30 s at a rate of 250 Hz. Areas of the flow curves were analyzed off-line. The calibration factor in area units per ml (AU/ml) for the EM-flow signal was determined during 72 s of normal mechanical ventilation, using the mean of two cardiac output estimates with the direct Fick method for oxygen as the reference [9]. The calibration factor used during a series of special observations, was the average of two calibration factors, one determined before the series and one determined after the series. Mean flow over a cardiac cycle was found by dividing stroke volume by heart interval.

PROTOCOL

To determine the P_{sf}, two different procedures to change the central venous pressure were used. First we used the method of inspiratory pause procedures (IPP) to obtain a reference value of the P_{sf} [5,9,10]. One procedure consisted of an inflation of 2.4 s, a pause of 12 s, and an expiration of 3.6 s, in total 18 s. The tidal volumes were 0 - 30 ml/kg at steps of 5 ml/kg, in total 7 volumes. The IPPs were randomly applied with intervals of at least 5 min, to maintain haemodynamic stability.

The second method was based on slow inflation procedures (SIP). The total duration of a SIP was the same as that of an IPP, i.e. 18 s. In these experiments we used five inflation times (T_i): 2.4, 4.8, 7.2, 9.6 and 12.0 s. Consequently, the durations of the inspiratory pauses were 12.0, 9.6, 7.2, 4.8 and 2.4 s, respectively. Each SIP was performed at two tidal volumes: 15 ml/kg and 30 ml/kg; in total 10 SIPs were applied in random order with intervals of at least 5 min. After the series of SIPs a second series of IPPs was measured, to obtain a second reference value of the P_{sf}. The IPPs and the SIPs could be applied by our computer controlled ventilator [6].

DATA ANALYSIS

In previous papers [5,9] we have described the determination of the P_{sf} with the use of IPPs. The P_{sf} was obtained as the extrapolated value of P_{cv} at zero flow from the linear regression between the heart-beat values of $\dot{Q}_{rv}$ and the mean P_{cv} values of each previous heart beat because of the delay between $\dot{Q}_v$ and $\dot{Q}_{rv}$ of one beat. We used the same method to

determine P_{sf} from the SIP, neglecting the effect of non-stationary conditions. The average of the two P_{sf} values [P_{sf}(IPP)] was used as the reference value for the P_{sf} determined with use of a SIP [P_{sf}(SIP)], the differences between P_{sf}(SIP) and P_{sf}(IPP) were tested with a one-tailed paired t-test. The differences between the P_{sf}(IPP) values of the first and the second series were also analyzed and tested with a two-tailed paired t-test. $P < 0.05$ was regarded significant.

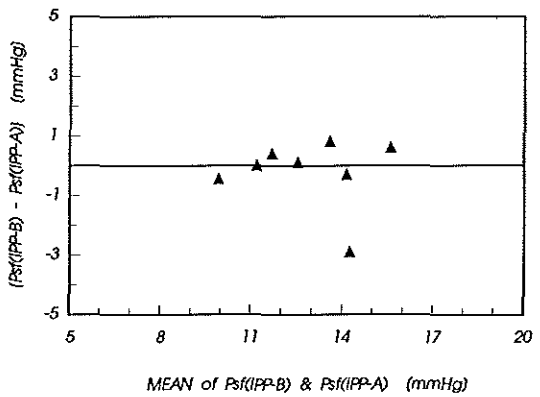

Fig.2: *On the x-axis are the mean values of P_{sf}(IPP-A) and P_{sf}(IPP-B) determined by the IPP-series before and after all SIPs respectively. On the y-axis the differences between the values of both P_{sf}(IPP)-series. The mean ± SD was -0.22 ± 1.16 mmHg, there was no significant difference between both P_{sf}(IPP) determinations in this group. For abbreviations see text.*

RESULTS

P_{sf}(IPP) of the series before the SIPs (A) has been plotted versus the P_{sf}(IPP) of the series after the SIPs (B) in fig.2. There was no significant difference between the values of P_{sf}(IPP) of both series. The mean difference of [P_{sf}(IPP-B)-P_{sf}(IPP-A)] was -0.22 ± 1.16 mmHg (mean ± SD). There was one outlier in these observations (exp.3, [P_{sf}(IPP-B)-P_{sf}(IPP-A)] = -2.9 mmHg). Without the outlier the mean difference of both series was: 0.17 ± 0.46 mmHg. Two individual examples of the determination of the P_{sf} with two SIPs, with inflation times of 4.8 and 12 s and a tidal volume of 30 ml/kg, are presented in fig.3, together with the data of one of the series of IPPs.

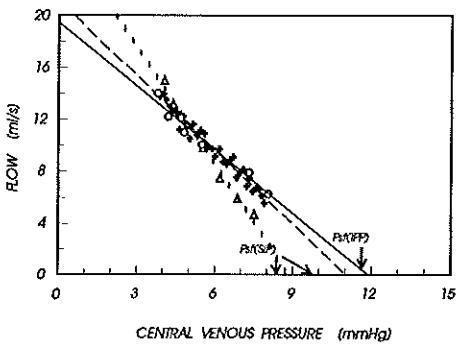

Fig.3: *The open circles are the mean values of venous return and central venous pressure (P_{cv}) determined in the stationary part of the inpiratory pause procedure (IPP). The crosses are the beat-to-beat values of venous return and mean P_{cv} during a slow inflation procedure (SIP) with an inflation time of 12 s. The triangles represent the beat-to-beat values of flow and P_{cv} of a SIP with an inflation time of 4.8 s.*

In accordance with the theory, the P_{sf} was underestimated less during a SIP at larger T_i as compared to the P_{sf}(IPP). Similar results were observed in all animals (Table 1). There was no significant difference between the values of P_{sf}(SIP) obtained at both tidal volumes for T_i = 7.2, 9.6 and 12.0 s (p-values resp.: 0.33, 0.40, 0.76). The P_{sf}(SIP)-values from a series with tidal volume 30 ml/kg, at T_i = 2.4 and 4.8 s, were significantly lower than those from the series with a tidal volume of 15 ml/kg (p-values of 0.004 and 0.01 respectively). We analyzed which T_i would be satisfactory to obtain a reliable estimation of the P_{sf} by fitting an exponential function to the data of each experiment. This exponential function fitted the data best. The inflation time (Θ_{sip}) at which the difference between the exponential function and the P_{sf}(IPP) was less than 0.75 mmHg, was calculated from the fit. The value of 0.75 mmHg was based on the reproducibility of the determinations of the P_{sf}(IPP) in this experiment. Without the outlier the standard deviation of the differences in P_{sf}(IPP) of series A and B was 0.46 mmHg (fig.2). The 95 % coefficient of repeatability (one tailed) was

Exp.	V_T	Inflation time (T_i) in seconds					P_{sf}(IPP)
	(ml/kg)	2.4	4.8	7.2	9.6	12.0	(mmHg)
1	15	9.8	10.1	8.7	12.1	12.2	12.6
	30	8.6	10.3	11.0	12.0	12.3	
2	15	10.0	12.2	14.3	13.7	12.9	15.6
	30	9.5	11.4	12.0	13.5	13.8	
3	15	10.3	12.4	14.6	14.1	14.5	14.3
	30	8.4	10.9	12.9	14.8	14.5	
4	15	8.6	11.2	12.4	12.5	12.4	14.2
	30	8.1	10.1	10.5	10.3	10.8	
5	15	8.9	11.6	12.1	12.6	12.2	13.6
	30	8.9	10.1	11.5	12.6	12.4	
6	15	7.2	8.4	8.9	9.6	9.8	11.2
	30	6.3	7.8	9.0	9.6	10.0	
7	15	9.7	10.1	11.0	12.1	12.1	11.7
	30	8.7	9.9	10.6	11.1	11.2	
8	15	6.9	7.9	8.8	8.8	9.7	9.93
	30	6.1	7.6	9.0	9.3	10.1	

Table 1: *All individual values of mean systemic filling pressure (P_{sf}) determined with use of slow inflation procedures (SIPs) in 8 animals at different inflation times (T_i) and at two tidal volumes (V_T). The last column contains the reference values of P_{sf} determined with the inspiratory pause procedures (IPPs).*

calculated as 1.64·SD = -0.75 mmHg [1]. The individual values of Θ_{sip} are presented in Table 2. Without the outlier the mean value ± SD of Θ_{sip} reduced from 13.3 ± 7.0 mmHg to 11.8 ± 3.9 mmHg. Without the outlier we calculated the 90 % limits of agreement [1] as [11.8 ± 1.64·SD] = [5.4; 18.2] mmHg. The mean values of [P_{sf}(SIP)-P_{sf}(IPP)] of all animals have been plotted against T_i with tidal volume (15 and 30 ml/kg) as a parameter (fig.4). At a T_i of 12 s, P_{sf}(SIP) is still significantly different from the P_{sf}(IPP) ($p = 0.023$, one tailed paired t-test).

Exp.	V_T (ml/kg)	α (s)	ß (mmHg)	Θ_{sip} (s)	P_{sf}(IPP) (mmHg)
1	15	9.15	8.35	15.9	12.6
	30	4.33	5.54	9.71	
2	15	7.00	8.35	15.9	15.6
	30	7.66	7.32	18.4	
3	15	2.21	2.27	6.13	14.3
	30	2.99	0.75	8.65	
4	15	5.78	6.20	13.7	14.2
	30	16.4	7.76	35.3	
5	15	4.78	6.39	10.8	13.6
	30	5.85	6.33	13.3	
6	15	8.32	5.91	16.3	11.2
	30	6.49	4.13	14.6	
7	15	3.40	7.19	6.10	11.7
	30	4.91	6.89	9.12	
8	15	5.50	5.20	10.1	9.93
	30	3.65	2.40	8.42	
MEAN (SD):		6.16 (3.35)	5.69 (2.25)	13.3 (7.0)	12.9
MEAN (SD): (no outlier)		5.47 (2.00)	5.55 (2.25)	11.8 (3.9)	

Table 2: *Individual results to the exponential fits of the form:*

$$P_{sf}(SIP) = (P_{sf}(IPP) - \beta) \cdot (1 + e^{\frac{-T_i}{\alpha}}) + \beta$$

In this formula, T_i is the inflation time, α and ß are fitting parameters, V_T is the tidal volume. Θ_{sip} is the calculated T_i at which the difference between P_{sf}(IPP) and the exponential fit is less than 0.75 mmHg: $\Theta_{sip} = -\alpha \cdot ln[0.75/(P_{sf} - \beta)]$. The range of Θ_{sip}-values was [6 s - 16 s] at V_T = 15 ml/kg, and [8 s - 18 s] at V_T = 30 ml/kg.

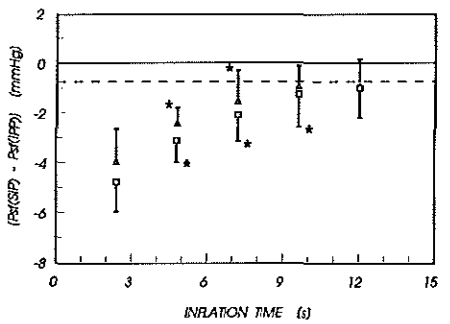

Fig.4: *The mean differences (P_{sf}(SIP)-P_{sf}(IPP)) of all experiments (n=8), versus inflation time at two tidal volumes (V_T), the vertical bars represent the standard deviations. The squares represent the values at V_T = 30 ml/kg, the triangles represent the values at V_T = 15 ml/kg. The dashed line is at -0.75 mmHg to obtain an estimation of the inflation time that produces a reliable estimation of P_{sf} for each experiment. The asterisks indicate that the value is significantly different from the previous value with a shorter inflation time at the same V_T.*

DISCUSSION

In these experiments we used the same criteria for haemodynamic stability as in previous studies [9,10]; the most important criteria were cardiac output, aortic pressure and heart rate. Following these criteria we excluded one of the experiments, because of a large increase in heart rate from 2.5 to 3.5 beats per second. In all other animals (n=8) the conditions were stable. We have no explanation for the outlier in the differences between P_{sf}(IPP-A) and P_{sf}(IPP-B) (fig.2).

We aimed to estimate P_{sf} with one SIP. A T_i of twelve seconds was too short to obtain P_{sf}(SIP) equal to P_{sf}(IPP). The exponential function fitted through the differences between P_{sf}(SIP) and P_{sf}(IPP) of each experiment predicted, without the outlier a mean satisfactory T_i of 11.8 s. The 90 % limits of agreement ranged from 5 s to 18 s, a T_i of 18 s should then be satisfactory for 95 % of all animals. An advantage of a long T_i is that more data points are

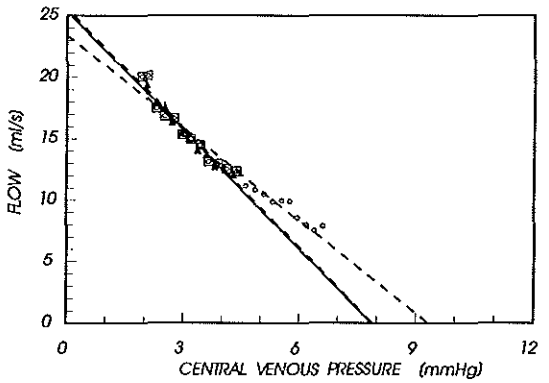

Fig.5: *The triangles represent the values of central venous pressure versus venous return (P_{CV};$\dot{Q}_V$) during a SIP at V_T = 15 ml/kg with an T_i of 4.8 s. The small circles represent the values (P_{CV};$\dot{Q}_V$) during a SIP of 9.6 s at V_T = 30 ml/kg. The first half of this procedure is analyzed separately: the circles within squares. Three values of P_{sf} are thus obtained. The values of V_T = 15 ml/kg and the first half of V_T = 30 ml/kg are equal. All data are beat-to-beat values of pressure and flow during the SIP.*

available to the linear regression. However, during a long T_i the activity of the circulatory control mechanisms could change and affect the measurements. In our experiments we had no indication (from heart rate) that the activity of the control mechanisms changed during the SIP, but we did not apply a SIP of more than 12 s. In these experiments we have used SIPs at V_T = 15 and 30 ml/kg. Therefore, the inflation velocity of a SIP of 2.4 s at low V_T (15 ml/kg) is equal to the inflation velocity of a SIP of 4.8 s at high V_T (30 ml/kg) (group I). Similarly, a SIP of 4.8 s at low V_T and a SIP of 9.6 s at high V_T have equal inflation velocities (group II). As a consequence, the rise in P_{CV} is equal for both procedures in each group. However, the values of P_{sf}(SIP) of these procedures are significantly different (fig.4 and Table 1, group I: p = 0.001, group II: p = 0.01, paired t-tests). This difference is explained by the non-linearity of the model (fig.1 and eq.(3)). Immediately after the start of a SIP, the P_{CV} is increased, whereas the rise in P_V is delayed due to the venous capacity. Thereafter, P_{CV} and P_V rise linearly, but P_V at a slower rate. This initial delay in the rise of P_V

will cause the $\dot{Q}_v$ to fall more rapidly than in the linear part immediately thereafter. As a consequence, a linear regression to the first part of the curve will produce a steeper slope of $\dot{Q}_v$ vs. P_{cv} and, consequently, a lower value of P_{sf} than a regression applied to the total curve (fig.5), which has a larger linear part. If the first part of the longer SIP at the high V_T is compared to the shorter SIP at low V_T the procedures are on average not different (group I: $p = 0.38$; group II: $p = 0.34$). The P_{sf} may be estimated more accurately if it were possible to apply a reliable linear regression through the linear parts of the curves only. However, the exact length of the linear part of the curve is unknown on beforehand.

A disadvantage of the SIP is the necessity of a beat-to-beat determination of the right ventricular output, or at least a signal that is proportional to the right ventricular output. Such technique is not (yet) available in practice, but will become possible if an adequate pulse contour method has been developed for the pulmonary circulation. The advantage of a Slow Inflation Procedure to estimate P_{sf} is that only one special procedure of less than a minute is needed, whereas the method using IPPs takes about 45 minutes. Because in a period of about 12-18 s circulatory control mechanisms might interfere, we think that the applicability of such a procedure will be restricted to conditions where neuro-humoral control mechanisms are suppressed as during intensive care and anaesthesia.

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ESTIMATION OF MEAN SYSTEMIC FILLING PRESSURE DURING MECHANICAL VENTILATION BY MODELLING VENOUS RETURN.

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INTRODUCTION

Mean systemic filling pressure (P_{sf}) is the equilibrium pressure in the systemic circulation if the heart is arrested and blood flow is zero. P_{sf} is a conceptual pressure; it indicates the effective filling state of the circulation, since the product of P_{sf} and total systemic vascular compliance represents the total stressed volume of the systemic circulation. Theoretically, measurement of mean systemic filling pressure requires a total stop of the circulation and equilibration of the arterial and venous pressures. This condition can be obtained by inflating a balloon in the right atrium [2,3,14], or by interrupting the heart beat by acetylcholine or electrical fibrillation [8-10].

Our group has developed different methods to determine the mean systemic filling pressure in the intact circulation [5,6,12]. These methods were based on the linear relationship between central venous pressure (P_{cv}), aortic pressure (P_{ao}) and venous return ($\dot{Q}_v$). Changes in central venous pressure were induced by applying seven inspiratory pause procedures (IPPs) of 18 s each, at tidal volumes of 0 to 30 ml/kg. P_{sf} was derived from the linear relationship between central venous pressure and venous return using the stationary levels of the IPPs [12]. Similarly, it was shown that P_{sf} could be estimated from the linear relationship between central venous pressure and aortic pressure [5]. In both methods the IPPs were performed at intervals of 5 to 10 min, thus, these methods, although reliable, might be too time consuming for clinical application. The latest development was a method to determine the mean systemic filling pressure (P_{sf}) with a slow inflation procedure [6]. A disadvantage of this method was that a large inflation time, of about 15 s, was necessary to obtain an estimation of P_{sf}. In such time span changes in neuro-humoral control might change P_{sf}.

In this study, we aimed to estimate P_{sf} with use of a single IPP. We adopted a model of a main part of the venous system, that has been introduced previously [6,13]. Venous return ($\dot{Q}_v$) was computed by the model and fitted to measurements of venous return in pigs in vivo by estimation of the model parameters, giving P_{sf} directly from the fit.

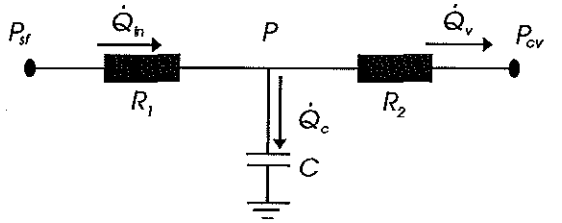

Fig.1: *The venous model, downstream from the sites in the circulation where the pressure equals mean systemic filling pressure (P_{sf}) as described in the text. P_{cv}: central venous pressure, $\dot{Q}_v$: venous return, R_1 and R_2: venous flow resistances, C: effective venous compliance, $\dot{Q}_c$: flow into the capacity and $\dot{Q}_{in}$: the flow into the model.*

METHODS

The model was a lumped representation of a part of the venous system (fig.1). It consisted of two resistances (R_1 and R_2) and a compliance (C). The model can be computed by solving the differential equation, equation (1):

$$(1) \qquad \frac{dP(t)}{dt} = -P(t)\cdot\left(\frac{1}{R_1\cdot C} + \frac{1}{R_2\cdot C}\right) + \frac{P_{sf}}{R_1\cdot C} + \frac{P_{cv}(t)}{R_2\cdot C}$$

P_{sf}, the resistances and the compliance are constant. The model and equation are linear and the pressure P can be calculated if the central venous pressure (P_{cv}) is known. An initial condition, P_0, must be set to solve the differential equation. The output of the model is venous return ($\dot{Q}_v$) which is computed as a function of time from equation (2):

$$(2) \qquad \dot{Q}_v(t) = \frac{P(t) - P_{cv}(t)}{R_2}$$

Venous return was computed for a given set of values of the parameters P_{sf}, R_1, R_2, C and P_0, with $P_{cv}(t)$ as the model input. Subsequently the computed venous return was compared to the measured venous return.

OPTIMIZATIONS

For each set of parameter values, the model was computed with a mixed 2^{nd}-3^{rd} order Runga-Kutta method provided by the software package MATLAB (The MathWorks, USA), at intervals of 0.1 s, starting at t=0. The simulated venous return was then known at 251 time points (25 s at 0.1 s intervals, plus the initial condition). To obtain values of the measured central venous pressure and the venous return at the same instants, we interpolated the beat-to-beat signals by a cubic spline. MATLAB performed the interpolation automatically during the simulation. At each computation instant the absolute difference between the simulated flow and the interpolated measured flow was calculated. The error D_q was defined as the mean of the absolute differences. The Simplex method, provided by MATLAB, was used to find the optimal parameter set, defined as the set having minimal error, min(D_q).

SURGERY & MEASUREMENTS

Observations were made in ten pigs, having body weights of 10.5 ± 0.7 kg (mean ± SD). Surgery, anaesthesia, maintenance of stability and the application of inspiratory pause procedures (IPPs) have been described in previous papers [6,12]. Briefly, the animals were anaesthetized with 9.0 $mg \cdot kg^{-1} \cdot h^{-1}$ pentobarbital-sodium. After surgery they were paralysed with an infusion of 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ pancuronium bromide (Pavulon, Organon, the Netherlands), after a loading dose of 0.1 mg/kg^{-1} in 3 min. Mechanical ventilation was set at 10 breaths per minute with tidal volume adjusted to an arterial P_{CO_2} of 38 to 42 mmHg. These conditions were kept constant.

Two catheters were inserted via the right external jugular vein: a Swan-Ganz catheter was placed into the pulmonary artery for pressure measurements and to sample mixed venous blood, another catheter was inserted to measure central venous pressure (P_{cv}) near the right atrium with a catheter. Aortic pressure (P_{ao}) was measured with a catheter, inserted via the right common carotid artery, this catheter was also used to sample arterial blood.

Cardiac output was estimated with use of the direct Fick method for oxygen [12]. Right ventricular output was measured with an electromagnetic flow probe and calibrated against the cardiac output of the Fick method [12]. The probe was placed around the pulmonary artery after a left intercostal thoracotomy in the second intercostal space. Right ventricular output averaged over a heart beat was taken as mean venous return of the previous heart

cycle. We used the mean values of pressure and flow per heart beat in the model simulations.

INTERVENTIONS

Recordings of central venous pressure (P_{cv}) and venous return ($\dot{Q}_v$) during an Inspiratory Pause Procedure (IPP) and a preceding period of normal ventilation (total 25 s) were used in the simulations. An IPP consisted of an inflation of 2.4 s, an inspiratory pause of 12 s and an expiration of 3.6 s (total 18 s). One series of observations consisted of seven different IPPs at tidal volumes of 0 to 30 ml/kg in steps of 5 ml/kg, randomly applied at intervals of at least 5 min [12]. In each animal two series of IPPs were performed.

SENSITIVITY ANALYSIS

We analyzed the sensitivity of the error function to deviations from the optimal value of the P_{sf} estimates. P_{sf} was set to different fixed values and then the simulated venous return was fitted by adapting the other parameters, R_1, R_2, C and P_0. This procedure was performed at values of P_{sf} that ranged from -30 % to +30 % of the optimal value in all IPPs.

STATISTICS

The reference method to determine P_{sf} required all seven IPPs [12], model estimates of P_{sf} were obtained from all IPPs separately. The data obtained from the IPPs at 0 ml/kg were not used because only stationary values of pressure and flow were present in those signals. The reference values and the model estimates of P_{sf} of the first and the second series were tested with a two way ANOVA for significant differences between the tidal volumes and the series. If no significant trend was found between the series, the P_{sf} model estimates of both series at equal tidal volume within an animal were averaged. They were compared with the mean of both P_{sf} estimates derived from all seven IPPs [12] as the reference. Thus, differences were found between the model estimate and the reference value of P_{sf}, at each tidal volume in each animal. These differences were tested to have a normal distribution by the Kolmogorov-Smirnoff test. If the distributions are normal, the mean difference and standard deviation (SD) for all animals at each tidal volume can be calculated. Then, the corrected standard deviation was calculated as: $SD_c = \sqrt{(SD^2 + (½\cdot s_1)^2 + (½\cdot s_2)^2)}$, in which s_1 and s_2 are the repeatabilities of the model estimates and the reference method respectively, as they are introduced below. The differences between the P_{sf} estimates with the model and the reference method were analyzed with the corrected standard deviation

(SD_c) to account for the effect of the repeated measurement error [1]. The 95% confidence interval was calculated as t times the standard error, with t representing the value of the t-statistic at (n-1) degrees of freedom, with n the number of experiments. The repeatability was calculated as the standard deviation of the differences between the values of the first and the second series [1].

The variance of the reference method was determined by the sum of the variance of the measurement (σ^2(meas)) and the variance between the animals (σ^2(between)). As two determinations of the reference value of P_{sf} were performed in each animal, the variance of the measurement σ^2(meas) was equal to the square of the repeatability. The variance between animals was then calculated by: $\sigma^2(between) = SD^2(P_{sf}(ref)) - \sigma^2(meas)$, in which $SD^2(P_{sf}(ref))$ was the overall variance of the reference method. Then, the intra-class correlation coefficient (R), which is the ratio of the variance between the animals to the total variance was calculated. For the reference method: $R = \sigma^2(between)/SD^2(P_{sf}(ref))$ and for the model estimates: $R = \sigma^2(between)/[\sigma^2(between) + \sigma^2(model)]$, in which σ^2(model) denotes the square of the repeatability of the model estimates of P_{sf} at each tidal volume.

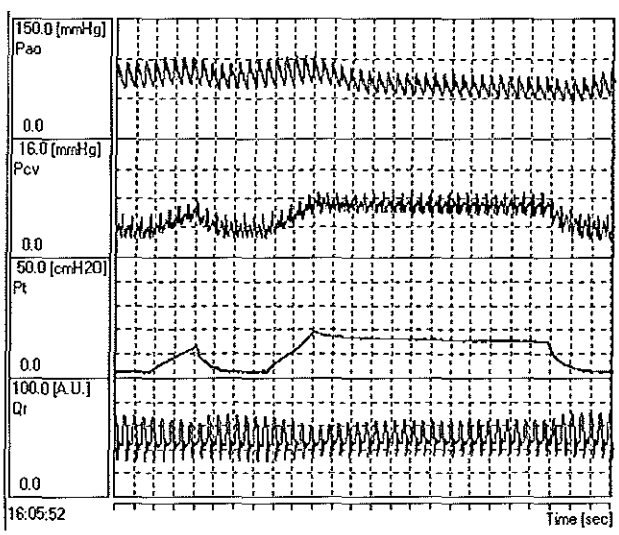

Fig.2: An example of an original recording. From the upper to the lower panel: P_{ao}: aortic pressure, P_{cv}: central venous pressure, P_t: tracheal pressure and $\dot{Q}_{rv}$: right ventricular output, this was taken as the venous return of the previous heart cycle.

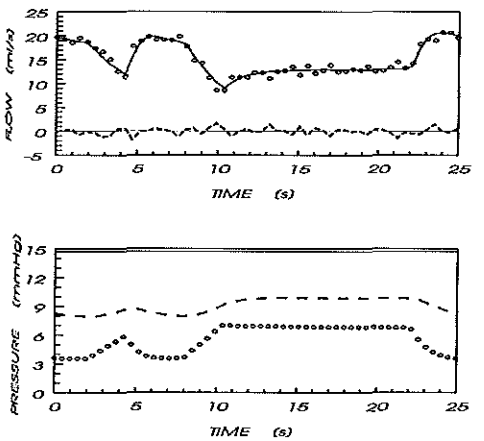

Fig.3: *An example of an optimal fit of the model estimated flow to the measured venous return. Upper panel: the circles represent the measured flow per heart beat, the solid line through the circles is the optimal fit and the dashed line around zero is the residual (difference) between the interpolated data and the fit. Lower panel: the circles represent the central venous pressue (P_{cv}), solid line: P_{sf} estimate, dashed line: simulated pressure (P) at the model compliance, see fig.1 and text for further details.*

RESULTS

Of the ten pigs that were observed, the data of three pigs were not used in the analysis. In those pigs the hemodynamic conditions were not stable within the IPPs (one exp.) or between the IPPs over the duration of the experiment (two exp.), indicated by changes in heart rate (2.5 to 3.5 Hz.) and changes in pressures and flow. The other seven animals remained stable over the experiments. An example of an original recording is shown in fig.2, the fit of the model to the data is shown in fig.3.

The changes in error for changes in P_{sf} at each tidal volume, averaged over all animals ($n=7$), are presented in fig.4. The minimal error ($\min(D_q)$) is most sensitive to deviations from the optimal value of P_{sf} at the highest tidal volumes, reflected by the steepest curve in the figure.

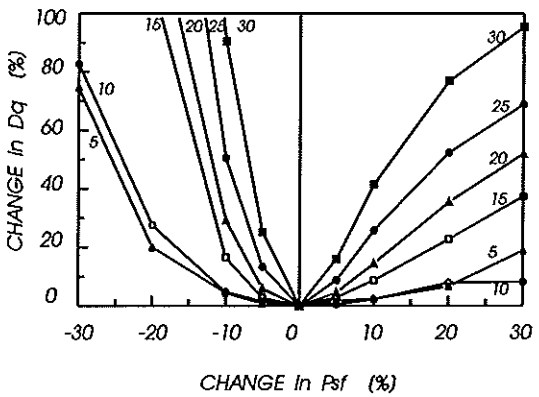

Fig.4: *A plot of the change in error (D_q) for changes in the P_{sf} estimate. X-axis: P_{sf} ranging from -30% to +30% from the optimum. Y-axis: change in the minimal error (min(D_q)). The curves show the average results of all experiments as in all animals qualitatively similar results were obtained. The numbers in the figure indicate the tidal volumes of the IPPs from which the curves are obtained.*

EXP.	5	10	15	20	25	30	P_{sf}(ref.)
1	-0.50	0.25	-1.45	0.45	0.50	0.45	12.6
2	1.4	-1.44	-1.43	-0.27	0.04	0.15	10.1
3	-2.0	1.4	4.8	0.0	0.60	-0.10	15.0
4	0.80	3.65	2.1	1.0	0.30	-0.80	13.4
5	X	4.45	1.7	1.05	0.40	0.0	10.8
6	-1.9	0.45	-0.10	0.80	0.55	1.15	11.7
7	0.55	3.6	1.45	1.30	0.45	-0.44	9.9
mean	-0.5	1.8	1.0	0.62	0.41	0.06	11.9
SD_c	3.0	2.5	2.8	0.86	0.85	0.89	1.9
95% CI	3.0	2.3	2.6	0.80	0.79	0.82	
repeatability	4.2	1.6	2.3	0.82	1.0	0.87	0.29
R	0.17	0.58	0.40	0.84	0.78	0.82	0.98

Table 1: *Differences between estimates of mean systemic filling pressure (P_{sf}) by the model and the reference values. First column: experiment number, last column: reference value of P_{sf}, the mean of two values, obtained with the method using 7 IPPs. Other columns: differences between P_{sf}-estimates and the reference values at each tidal volume. The X indicates a missing value. The lower rows respectively: mean, SD_c: the corrected standard deviation (see text for details), 95% CI: mean ± 95 % CI is the 95% confidence interval of the mean, repeatability: the standard deviation of the differences between the first and the second series, R: intra-class correlation coefficient, the ratio of variance between the animals to the total variance of the P_{sf} estimate, see text for further details.*

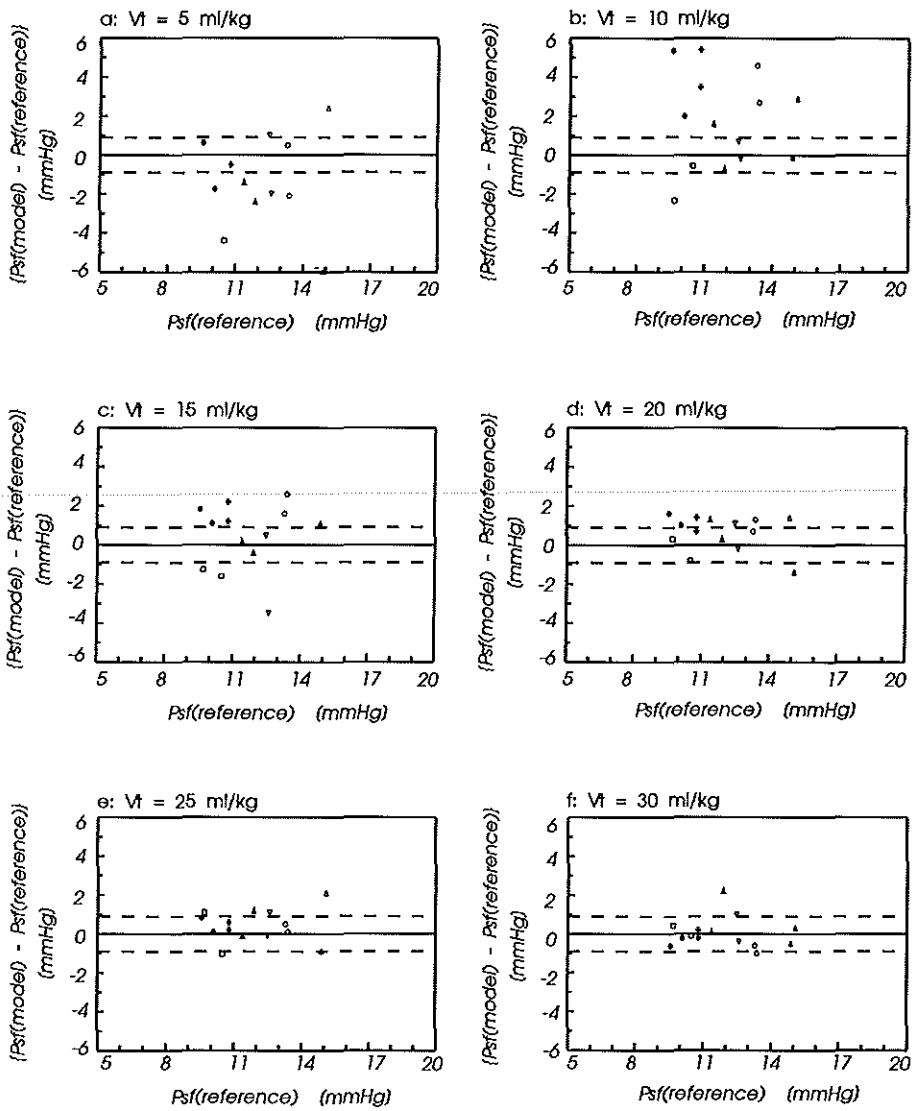

Fig.5a-f: *Scatterplot of the difference between the model estimates and the reference values of P_{sf} from IPPs at different tidal volumes: 5(A), 10(B), 15(C), 20(D), 25(E) and 30(F) ml/kg respectively. X-axes: reference value of P_{sf}, y-axes: difference between model estimates of P_{sf} and the reference values. Dashed lines: +1.0 and -1.0 mmHg, the previously reported repeatability of the reference method [6], presented to provide a comparison with the repeatability of the reference method.*

The individual values of the P_{sf} estimates of each IPP are shown in fig.5a-5f. We found no trend in the differences between the first and the second series, in the reference values, nor in the model estimates of the single IPPs, ($p > 0.3$ all series). Thus, the data of the first and second series were averaged. The differences between the mean values of the P_{sf} estimates at each tidal volume and the reference method are shown in Table 1. The Kolmogorov-Smirnoff test showed that the distributions of the differences between the model estimates of P_{sf} and the reference values were normal at all tidal volumes ($p \geq 0.13$). Therefore, the (corrected) standard deviations, 95% confidence interval and the repeatability were calculated, these values are presented in the lowest rows of Table 1.

At all tidal volumes the model estimates of P_{sf} were not significantly different from the reference values as the mean value was within the 95 % confidence intervals (Table 1). Both the corrected standard deviation and the repeatability showed the lowest values at the three largest tidal volumes. The repeatability of the reference method (0.29) was superior to the repeatability of the model estimates of P_{sf} (0.82 to 4.2). The intra-class correlation coefficient was high at the three largest tidal volumes ($R > 0.75$) and lower at the lowest tidal volumes ($R < 0.60$).

DISCUSSION

The results of this study showed that the model estimates of P_{sf} were not significantly different from the reference values of P_{sf}. The mean of the reference values of P_{sf} was in the range of values that were reported before [5,6,12]. At smaller tidal volumes, from 5 to 15 ml/kg the standard deviations of the model estimates were too large to obtain reliable results. The standard deviations and repeatabilities were smaller at the highest tidal volumes of 20, 25 and 30 ml/kg. The intra-class correlation coefficient (R), given in Table 1, was a measure of the reliability of a single measurement. If $R = 1$, all variance would be caused by the variance between the animals and the measurement would predict the actual value exact. We found high values of R ($R \geq 0.8$) at the three largest tidal volumes (20 to 30 ml/kg), R was lower at the lowest tidal volumes ($R \leq 0.6$). Therefore, we concluded that the model estimates from the IPPs at the three highest tidal volumes produced reliable estimates of P_{sf}. The estimates of P_{sf} from the IPPs at the lowest tidal volumes were not reliable.

Previously, methods have been developed to determine the P_{sf} with use of seven inspiratory pause procedures (IPPs) at different tidal volumes [5,12]. As these methods were time consuming (about 45 min.), we aimed to develop a faster method. In this study we obtained an estimate of P_{sf} using the recording of only one IPP, which lasted about 25 s. Such time span would make the determination of P_{sf} useful in clinical practice. However, to apply this new method in patients with intact thorax, a new method to determine right ventricular output beat-to-beat will be needed. The development of such methods for a beat-to-beat determination of right ventricular output has started recently [7].

In the present study the standard deviation of the differences was about 0.9 mmHg and the repeatability was about 1.3 mmHg. In the development of one of the methods mentioned above, we compared the determination of P_{sf}, based on the changes in aortic pressure, with the same reference method as we used here [5,6]. The standard deviation of the differences was then 1.16 mmHg [5], the repeatabilities were about 1.0 mmHg for the reference method [5,6] and 0.80 mmHg for the method based on the aortic pressure changes [5]. In the present study the standard deviation of the differences was about 0.9 mmHg and the repeatability was about 1.3 mmHg. These values were in the same range as in the previous study, indicating that P_{sf} could be estimated reliably with the present method, based on the model and a single IPP. The P_{sf} estimates of the procedures at the highest tidal volumes (20, 25 and 30 ml/kg) were equally reliable.

P_{sf} is determined by the ratio of total systemic stressed volume and total systemic compliance, therefore, it is constant if the control mechanisms of the circulation do not change [11]. Furthermore, it has been established that the resistances upstream (R_{su}) and downstream (R_{sd}) from P_{sf} do not change between the stationary levels of seven different IPPs [5,12]. Consequently, under stationary conditions, P_{sf} remains at the same site in the circulation with respect to the flow resistances [4]. This does not imply that it is also true for non-stationary conditions. But, the results with the present model, with constant compliance, flow resistance and P_{sf}, fitted the measured venous return closely during a whole IPP. We concluded that our assumption of constant P_{sf} and flow resistance was close to reality.

The sensitivity of the error function to deviations in P_{sf} from the optimal value, as presented in fig.4 was higher at higher tidal volumes. This probably contributes to a better

estimation of P_{sf}. The error function that was used here was based on the absolute differences between the simulated and measured flow. In fit procedures, very often an error function is used that is based on the squared differences between the simulation and the measurements (RMS-criterion). Such RMS-criterion gives more weight to outlying values in the measured signal. To reduce the effect of such outlying values, we preferred an error function based on absolute differences.

The sum of the resistances of the model ($R_{sd}(mod) = R_1+R_2$) should be equal to the values of R_{sd} that can be derived from the reference values of P_{sf} [12]. The $R_{sd}(mod)$ estimates have not been presented separately. The comparison of $R_{sd}(mod)$ with their reference values produced the same results as the estimations of P_{sf} (fig.5). The reason was that the estimates of P_{sf} and R_{sd} were correlated. Because the flow was fitted, simulated and measured flow were equal; if the optimization overestimates P_{sf} compared to its reference value, R_{sd} will also be overestimated to obtain an optimal fit of the simulated flow to the measured flow.

The compliance estimates, C, of the model did not represent the total venous compliance. As P_{sf} was located in the small veins or in the venules [11,12] the part of the compliance upstream from P_{sf} was not modelled. The compliance of the model could be estimated during transients of pressure and flow only, when the dynamic properties of the system were challenged. As P_{sf} was constant in this model, the compliance that was localized in that region was not estimated. Furthermore, the compliance of the central veins was not estimated because the central venous pressure was used as an input signal. The model described only the venous circulation downstream from P_{sf} and upstream from P_{cv}. The C estimates represented an effective compliance that was needed to obtain a fit of the model to the measured data during dynamic changes of the venous return.

In these experiments an IPP was performed to fit the simulated to the measured flow. This manoeuvre was chosen because a reference value of P_{sf} could be derived from a series of IPPs. The use of IPPs to fit the model to the data was not required. If the measurements are accurate enough, other special ventilatory procedures may be used. Such procedures should cause changes of similar magnitude in central venous pressure and venous return.

In conclusion, P_{sf} could be estimated by fitting the simulated venous return of the model to the measured venous return. The estimates of P_{sf} at the highest tidal volumes (20 to 30

ml/kg) produced results that were not significantly different from the reference values. Thus, a new method is provided to determine the P_{sf} with a single ventilation procedure in the intact circulation. This method is much faster than the old method which generally takes about 45 min, whereas the new method takes about 30 s.

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DOES P_{sf} REMAIN CONSTANT AND AT THE SAME SITE IN THE CIRCULATION DURING DYNAMIC CHANGES, INDUCED BY MECHANICAL VENTILATION ?

INTRODUCTION

Mean systemic filling pressure (P_{sf}) is defined as the equilibrium pressure in the systemic circulation if the heart has stopped beating and flow is zero. A linear relationship between central venous pressure (P_{cv}) and venous return ($\dot{Q}_v$) has been found by Guyton [1], and confirmed by others [2-6], at different steady states of P_{cv} and $\dot{Q}_v$, assuming P_{sf} to be constant. This relationship was written as:

$$(1) \qquad \dot{Q}_v = \frac{(P_{sf} - P_{cv})}{R_{sd}} = \frac{(P_{ao} - P_{sf})}{R_{su}}$$

In this relationship P_{ao} denotes the aortic pressure. The linearity of eq.(1) implied that the resistances upstream (R_{su}) and downstream (R_{sd}) from P_{sf} were constant, which was confirmed in the intact circulation during steady states [2-4,6]. A logical consequence of these constant resistances was the existence of a location in the circulation at which the pressure was constant and equal to P_{sf}. We emphasize that such a constant pressure, which we denote as P_{Psf}, was only shown for steady states [2]. It was unknown whether P_{Psf} was such a characteristic driving pressure during dynamic changes of central venous pressure and venous return as occur during mechanical ventilation.

We aimed to investigate whether P_{Psf} was also a characteristic driving pressure during dynamic changes, implying that the downstream resistance, R_{sd}, was constant. Therefore, we analyzed the dynamic changes in venous pressures, at the sites in the circulation where the flow resistance is equal to R_{sd}. Previously, we simulated the changes in venous return, caused by mechanical ventilation, and estimated P_{Psf} with use of a model and a single procedure with the ventilator [7]. The model was based on the existence of a constant resistance downstream from P_{Psf} and a constant value of P_{Psf} during dynamic changes of $\dot{Q}_v$ and P_{cv}. We extended our previous model to a five element model, to simulate two upstream venous pressures (fig.1). We hypothesized that the fluctuations of these venous pressures became smaller towards P_{Psf}. The model approach was chosen because we were not able to measure pressures of the magnitude of P_{Psf} accurately in the intact circulation, as these pressures are situated in the small veins or the venules [4,6]. Pressure measurements in the venules are possible [8,9], but as far as we know such measurements have not been performed in animals in vivo during mechanical ventilation.

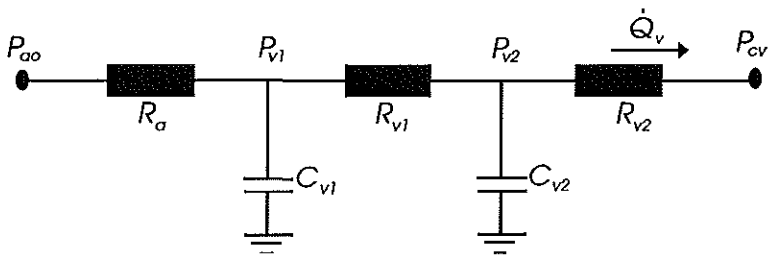

Fig.1: *The model of the circulation to compute the venous return as described in the text. P_{ao} and P_{cv} are input signals for the model. The model parameters are R_a, R_{v1}, R_{v2}, C_{v1} and C_{v2}, the model is computed by solving the differential equations for P_{v1} and P_{v2} as a function of the input signals and the model parameters. The model output is the venous return ($\dot{Q}_v$), (see text for details). The model output is fitted to the measured venous return by optimization of the model parameters. The meaning of the symbols is explained in the text.*

METHODS

MODEL

Because it has been reported that the largest part of the venous compliance is located in the small veins or the venules [6,10,11], we extended our previous model [7] with an upstream compliance and resistance (fig.1). Estimates of the resistances and compliances of the model were obtained from the fit of the model to measurements of venous return. The model was a lumped representation of the systemic circulation. It consisted of three resistances (R_a, R_{v1} and R_{v2}) and two compliances (C_{v1} and C_{v2}). The pressures over the compliances C_{v1} and C_{v2} were named P_{v1} and P_{v2} respectively. The model was computed by solving the coupled differential equations 2 and 3:

$$(2) \quad \frac{dP_{v1}(t)}{dt} = -P_{v1}(t)\cdot\left(\frac{1}{R_a\cdot C_{v1}} + \frac{1}{R_{v1}\cdot C_{v1}}\right) + \frac{P_{ao}(t)}{R_a\cdot C_{v1}} + \frac{P_{v2}(t)}{R_{v1}\cdot C_{v1}}$$

$$(3) \quad \frac{dP_{v2}(t)}{dt} = -P_{v2}(t)\cdot\left(\frac{1}{R_{v1}\cdot C_{v2}} + \frac{1}{R_{v2}\cdot C_{v2}}\right) + \frac{P_{v1}(t)}{R_{v1}\cdot C_{v2}} + \frac{P_{cv}(t)}{R_{v2}\cdot C_{v2}}$$

In these equations the addition of "(t)" indicates the time dependence of the variables. The resistances and the compliances were constants. The equations were linear and the

pressures P_{v1} and P_{v2} could be calculated if the input signals (aortic pressure, P_{ao}, and central venous pressure, P_{cv}) were known. At this point two extra parameters, $P_{v1,0}$ and $P_{v2,0}$, representing the values of P_{v1} and P_{v2} at the start of the simulation, had to be set as initial conditions of the differential equations. The output of the model was the venous return which was computed as a function of time from equation 4:

$$(4) \qquad \dot{Q}_v(t) = \frac{P_{v2}(t) - P_{cv}(t)}{R_{v2}}$$

The venous return was computed for a given set of values of the parameters (R_a, R_{v1}, R_{v2}, C_{v1}, C_{v2}, $P_{v1,0}$ and $P_{v2,0}$), with $P_{ao}(t)$ and $P_{cv}(t)$ as the model inputs. Subsequently the computed venous return was compared to the measured venous return. The model estimate of the total resistance was $R_{s,sim} = R_a + R_{v1} + R_{v2}$.

P_{v1} and P_{v2} depended on the input signals P_{ao} and P_{cv} and the model parameters. From the simulated values of P_{v1} and P_{v2}, we analyzed whether our previous model with constant P_{Psf} and constant resistance downstream from P_{Psf}, also held during dynamic changes in central pressure and venous return.

OPTIMIZATIONS

For each set of parameter values, the model was computed with a mixed 2^{nd}-3^{rd} order Runga-Kutta method provided by the software package MATLAB (The MathWorks, USA), at intervals of 0.1 s, starting at t=0. The simulated venous return was then known at 251 time points. To obtain values of the measured central venous pressure and the venous return at the same instants, we interpolated the beat-to-beat signals by a cubic spline. MATLAB performed the interpolation automatically during the simulation. At each computation instant the absolute difference between the simulated flow and the interpolated measured flow was calculated. The error D_q was defined as the mean of the absolute differences. The Simplex method, provided by MATLAB, was used to find the optimal parameter set, defined as the set having minimal error, $\min(D_q)$.

SURGERY & MEASUREMENTS

Observations were made in five pigs, having body weights of 10.6 ± 0.5 kg (mean ± SD). Surgery, anaesthesia, maintenance of stability, measurements and the application of inspiratory pause procedures (IPPs) have been described previously [2]. Briefly, the animals

were anaesthetized with 9.0 $mg \cdot kg^{-1} \cdot h^{-1}$ pentobarbital sodium. After surgery they were paralysed with an infusion of 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ pancuronium bromide (Pavulon, Organon, the Netherlands), after a loading dose of 0.1 mg/kg^{-1} in 3 min. Mechanical ventilation was set at 10 breaths per minute with tidal volume adjusted to an arterial P_{CO_2} of 38 to 42 mmHg. These conditions were kept constant throughout the experiments.

Two catheters were inserted via the right external jugular vein: a Swan-Ganz catheter was placed into the pulmonary artery for pressure measurements and sampling of mixed venous blood; secondly, a four lumen catheter was inserted, into the superior vena cava, to measure central venous pressure (P_{cv}) near the right atrium and to infuse pentobarbital sodium and Pavulon. Aortic pressure (P_{ao}) was measured with a catheter, inserted into the aortic arch, via the right common carotid artery, this catheter was also used to sample arterial blood.

Cardiac output was estimated with use of the direct Fick method for oxygen. Right ventricular output was measured with an electromagnetic flow probe and calibrated against the cardiac output of the Fick method. The probe was placed around the pulmonary artery after a left intercostal thoracotomy in the second intercostal space. Right ventricular output averaged over a heart beat was taken as mean venous return of the previous heart cycle. We used the mean values of pressure and flow per heart beat in the model simulations.

INTERVENTIONS

Recordings of central venous pressure (P_{cv}) and venous return ($\dot{Q}_v$) during an Inspiratory Pause Procedure (IPP) and a preceding period of normal ventilation (total 25 s) were used in the simulations. An IPP consisted of an inflation of 2.4 s, an inspiratory pause of 12 s and an expiration of 3.6 s (total 18 s). One series of observations consisted of seven different IPPs at tidal volumes of 0 to 30 ml/kg in steps of 5 ml/kg, randomly applied at intervals of at least 5 min. In each animal two series of IPPs were performed.

The total resistance of the systemic circulation ($R_{s,meas}$) was determined as the ratio of the mean pressure gradient (P_{ao}-P_{cv}) and the mean flow during the last 5 s of the pause period of each IPP. The values of $R_{s,meas}$ were compared to the model estimates of the total resistance ($R_{s,sim} = R_a + R_{v1} + R_{v2}$). Thus, each model estimate $R_{s,sim}$ had a corresponding reference value $R_{s,meas}$ for each IPP.

The reference value of P_{Psf} was obtained from the method that used the different steady states of central venous pressure and venous return during the seven IPPs [2,3]. P_{Psf} was determined from the extrapolation of the linear regression between central venous pressure and venous return to zero flow. R_{sd}, the resistance downstream from the sites in the circulation where P_{Psf} existed, was the inverse of the slope of the linear regression.

STATISTICS

With a two-way ANOVA we tested whether significant differences between resistances ($R_{s,meas}$) of the different IPPs were present. Subsequently, the model estimates of the resistance ($R_{s,sim}$) were compared with their corresponding values of $R_{s,meas}$. Before the differences were analyzed we first tested with the Kolmogorov-Smirnoff test (K-S test) whether the differences between the model estimates and the reference values had a normal distribution. If the distributions were normal, then mean values and standard errors were calculated and a paired t-test was used to test for significant differences. The significance level was set at $p=0.05$. To compare the compliance estimates between experiments, the range was calculated in percentage of the median value.

RESULTS

To fit the model output to the measured venous return, we only used the IPPs at tidal volumes of 20, 25 and 30 ml/kg. Previously [7], we showed that the changes in pressures and flow during smaller IPPs were insufficient for reliable parameter estimations. An example of a fit of the model to the data at a tidal volume of 20 ml/kg is shown in fig.2. In the lower panel the course of P_{v1} and P_{v2} in time are shown. The variations in P_{v1} were small compared to the variation in P_{v2} and P_{cv}. During the IPP, both P_{v1} and P_{v2} showed qualitatively the same characteristics as the central venous pressure (P_{cv}), a rise in pressure due to the inflation followed by a steady state during the last part of the pause. No overshoot was observed in P_{v2} or P_{v1}. At the largest tidal volume (30 ml/kg) the rise in P_{v1} was on average 0.9 mmHg (SD = 0.4 mmHg), whereas the rise in central venous pressure was 4.4 mmHg (SD = 0.4 mmHg).

ESTIMATES OF MODEL PARAMETERS

On average there was no difference ($p>0.1$) between results of the first and second series of mean systemic filling pressure (P_{sf}), total resistance ($R_{s,meas}$) and resistance downstream

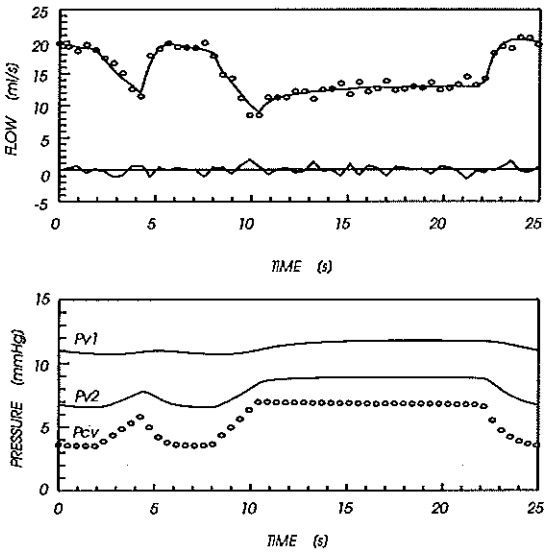

Fig.2: *An example of an optimal fit of the model to the measured venous return. Upper panel: the circles represent the, experimentally measured, mean flow per heart beat; solid lines: the optimal fit through the measured values and, below, the residual (difference) between the data and the fit. Lower panel: the measured values of central venous pressure (P_{cv}, circles) and the simulated pressures P_{v1} at the top and P_{v2} in the middle (solid lines).*

from P_{sf} (R_{sd}). The two-way ANOVA showed that there were also no differences between the total resistances during the IPPs at different tidal volumes and between the model estimates ($R_{s,sim}$) and their reference values ($R_{s,meas}$) ($p>0.30$). These differences were normally distributed ($p>0.20$).

Furthermore, the sum of the model estimates of the venous resistances ($R_{v1}+R_{v2}$) was compared to the corresponding reference value of R_{sd}. All differences were distributed normally ($p>0.20$). At all tidal volumes (20 to 30 ml/kg) the values of $R_{v1}+R_{v2}$ (0.44 mmHg·s·ml^{-1}) were significantly lower than those of R_{sd} (0.54 mmHg·s·ml^{-1}), with p-values of 0.02, 0.009 and 0.001 respectively (paired t-test).

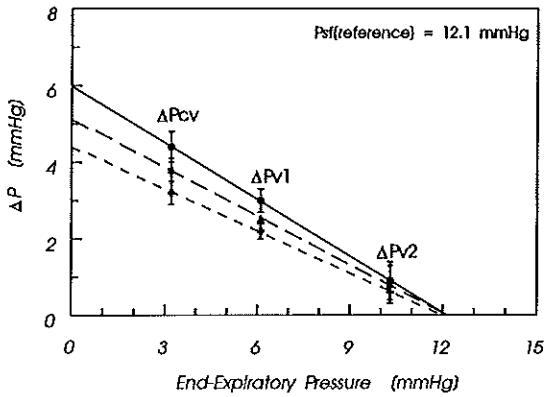

Fig.3: *Average change venous pressures as measured (P_{cv}) and simulated (P_{v1}, P_{v2}). The values are the means of 10 series of IPPs from five animals. X-axis: end-expiratory levels of P_{cv}, P_{v1} and P_{v2}. Y-axis: pressure changes from the end-expiratory level to the levels during the pause of the IPPs, for all three tidal volumes respectively. Solid line: IPP at 30 ml/kg, long dashed line: IPP at 25 ml/kg and short dashed line IPP at 20 ml/kg. P_{sf}(reference) is the value of P_{sf} obtained from the reference method, based on seven IPPs.*

Because the changes in the most upstream pressure P_{v1} were small, the estimates of the model compliances became unreliable. The model estimates of compliance ranged from 1.6 to 9.6 ml·mmHg^{-1}·kg^{-1} and tended towards infinity in some procedures.

ANALYSIS OF VENOUS PRESSURE TRANSIENTS

We analyzed the changes in P_{cv}, P_{v2} and P_{v1} during the IPPs at all three tidal volumes (20, 25 and 30 ml/kg). The mean changes of all series of IPPs in the five experiments (n = 10) are presented in fig.3. The changes in venous pressures decreased in the more upstream parts of the circulation (P_{v1}). A linear regression was computed through the pressure changes. Extrapolation of this linear regression to the intersection with the x-axis, produced an estimate of a pressure in the circulation that remained constant during the IPPs. These values should be equal to P_{sf}. In these experiments the reference value of P_{sf} was 12.1 mmHg. The intersections with the x-axis in fig.3 produced P_{sf}(est) = 12.2 mmHg from the IPPs with tidal volumes of 25 and 30 ml/kg and P_{sf}(est) = 12.0 mmHg from the IPP of 20 ml/kg.

In all individual experiments P_{sf} could also be estimated from the simulated change in P_{v1}. The extrapolation performed in fig.3 can be computed numerically by:

$$(5) \qquad P_{sf} = P_{cv_0} + \frac{P_{v1_0} - P_{cv_0}}{1 - \frac{\Delta P_{v1}}{\Delta P_{cv}}}$$

In which P_{cv_0} and P_{v1_0} denoted the end-expiratory values of P_{cv} and P_{v1}. The term $\Delta P_{v1}/\Delta P_{cv}$ was the relative increase of P_{v1} to P_{cv} and was calculated by taking the differences between both pressure at the end-expiratory levels and the steady states during the pause of the IPP. The extrapolated estimates of P_{sf}, according to eq.(5), during IPPs at tidal volumes of 20 to 30 ml/kg in all experiments are presented in fig.4. At all three tidal volumes there was no significant difference between these model estimates of P_{sf} and the reference values of P_{sf}, obtained from the method based on seven IPPs ($p>0.1$).

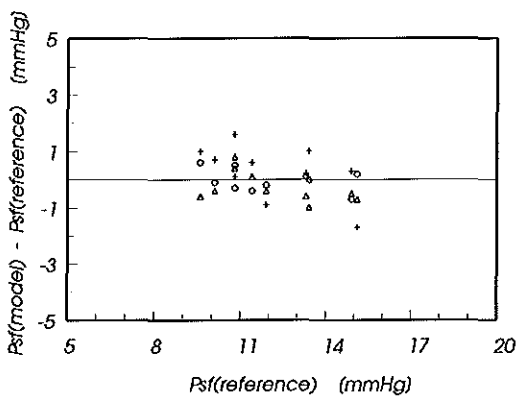

Fig.4: *P_{sf} estimates with use of the five-element model presented in this paper (fig.1). The estimates are derived from the changes in P_{v1} and measured changes in central venous pressure (P_{cv}). From these changes we extrapolated to the pressure in the circulation that remained constant. This pressure was assumed to be an estimate of P_{sf} and was compared to the reference value of P_{sf} obtained from all seven IPPs (see text for further details). The model estimates P_{sf}(model) were not significantly different from the reference values, P_{sf}(reference) at all tidal volumes: 20 ml/kg (crosses): $p=0.30$, 25 ml/kg (circles): $p=0.82$, 30 ml/kg (triangles): $p=0.13$.*

DISCUSSION

In this study we aimed to analyze whether P_{Psf} remained at a constant site in the circulation during dynamic changes of central venous pressure and venous return. Therefore, we analyzed the venous pressure changes, between P_{Psf} and P_{CV}, during mechanical ventilation. We chose to use a five-element-model to simulate the more upstream parts of the venous system, towards P_{Psf} and optimized the model parameters to fit the simulated to the measured venous return. Although this model had no assumptions on the distribution of the resistances and compliances beforehand, the best fits were always obtained with a large value of R_a compared to R_{v1} and R_{v2}. At the largest tidal volumes (20 to 30 ml/kg), the sum of the resistances ($R_{v1}+R_{v2}$) was slightly smaller than the value of R_{sd} that was determined independently, and $R_{v1}+R_{v2}$ was found to be constant between the three IPPs that were analyzed. As a consequence, the pressure P_{v1} (fig.1) was slightly smaller than P_{Psf}, which was the blood pressure in the circulation that was equal to P_{sf} during steady states.

Versprille et al. [2,5] showed that P_{Psf} was at a fixed site in the circulation, with respect to the up- and downstream flow resistances (R_{su} and R_{sd}), if the different steady states during the pause of the IPPs were compared (fig.5). Because the pressure gradient decreased, this implied that the pressures turned around the value of P_{Psf}, to lower values upstream and higher values downstream from the sites where P_{Psf} was present. With the present model we obtained the best fits of the model output to the measured venous return with a pressure P_{v1} that was situated downstream from P_{Psf}. Because P_{v1} is situated downstream from P_{Psf}, it should rise towards P_{Psf} during an IPP, but its value should not increase above P_{Psf}. Indeed, this behavior of P_{v1} was observed during the simulated IPPs (fig.2). We found no transient periods where P_{v1} was larger than P_{Psf}. The shape of the P_{v1} curve was always congruent with the shape of the P_{CV} curve, but the pressure changes of P_{v1} were small (fig.3). The resistances ($R_{v1}+R_{v2}$) remained constant between the different IPPs. Because the parts of the venous circulation upstream from P_{v1}, towards P_{Psf}, are also compliant and resistant, the pressure changes in these parts will probably be smaller than those of P_{v1}. Therefore, we suppose that the linear extrapolation to a pressure that remains constant, as shown in fig.3, is correct. Thus, there will be sites in the circulation where the pressure remained constant during dynamic changes, induced by mechanical ventilation.

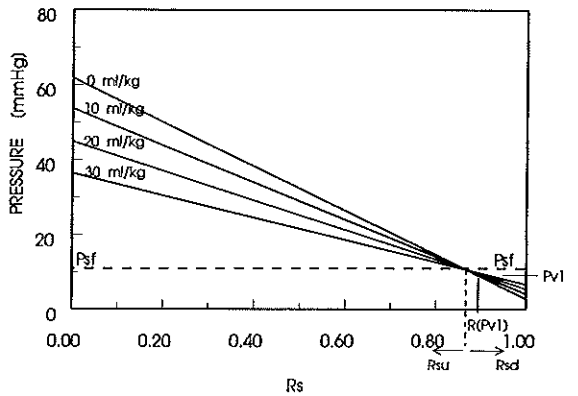

Fig.5: *P_{Psf} as turning point in the circulation during different inspiratory pause procedures (IPPs). X-axis: Total resistance (R_s) as fraction of its real value. Left y-axis: aortic pressure (P_{ao}), right y-axis: central venous pressure (P_{cv}). The circles indicate the values of P_{ao} and P_{cv} during the steady state of the pause of the IPP, the tidal volumes are indicated in the figure. The data of P_{cv} and P_{ao} are taken from an actual experiment. The lines between the corresponding circles intersect at one point, at this site in the circulation the blood pressure is equal to the mean systemic filling pressure and called P_{Psf}, the dashed line indicates the value of P_{sf} and, thus, P_{Psf}. R_{su} and R_{sd} are the resistances upstream and downstream from P_{Psf} respectively. $R(P_{v1})$ denotes the **site** in the circulation at which the model estimates of C_{v1} and P_{v1} are situated, the corresponding (changing) value of P_{v1} is indicated on the right y-axis.*

With the use of this model and eq.(5), estimates of P_{sf} were obtained from the steady states. But, because the end-expiratory value of P_{v1} could not be determined easily, this method to estimate P_{sf} was supposed to be less reliable. The good agreement between these estimates of P_{sf} and the reference value of P_{sf} (fig.4) provides an extra indication that P_{Psf} was constant and at a constant site in the circulation during dynamic changes of pressures and flow caused by mechanical ventilation.

CONCLUSION

From this study we conclude that it is very likely that the flow resistance upstream and downstream from the sites in the circulation where the blood pressure is equal to P_{sf} (P_{Psf}) are constant during dynamic changes, caused by mechanical ventilation. The consequence is that the venous return is determined by the central venous pressure, P_{Psf}, the constant

venous flow resistance downstream from P_{Psf} and the compliance of the larger veins during dynamic conditions. A three-element model with two venous resistances, a compliance and P_{Psf} as driving pressure for the venous return, as introduced before (Chapter 4), is a good approximation of the behavior of the venous system during mechanical ventilation.

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NEW METHODS TO DETERMINE TOTAL SYSTEMIC COMPLIANCE IN THE INTACT CIRCULATION IN PIGS.

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INTRODUCTION

Total systemic vascular compliance is generally defined as the ratio of a change in blood volume (dQ) to the corresponding increase in P_{sf}: $C_T = dQ/dP_{sf}$ [1-10]. Two main methods have been described to estimate the total systemic vascular compliance. The first method is based on the change in mean systemic filling pressure (P_{sf}) after a change in blood volume [1-6]. Because P_{sf} is defined as the equilibrium pressure in the circulation after the heart has stopped beating, this method requires a total stop of the circulation. The second method is based on a right heart bypass with reservoir and a pump, to keep the flow into the pulmonary circulation constant. The compliance is determined from the change in reservoir volume for a step change in central venous pressure [9-13]. In both methods the circulation is not intact. As far as we know the total systemic vascular compliance has not been determined in the intact circulation. We aimed to estimate the (total systemic vascular) compliance in the intact circulation and used simulation procedures based on two different models.

Method A. With use of a model (fig.1A) we have shown previously [14] that P_{sf} can be estimated during an inspiratory pause procedure (IPP), consisting of an inflation of the lung, a pause of 12 s and an expiration. In our present study we additionally performed an IPP, characterized by a blood infusion into the arterial system during the pause period of the IPP. The increase in P_{sf} during the infusion was simulated and the compliance was determined by the ratio of infused blood volume and the estimated change in P_{sf}.

Method B. This method was based on a lumped model of the total systemic circulation (fig.1B [15]). Previously, we failed to estimate the compliances (C_X, C_V) of this model reliably during a normal IPP, because of the small changes in the pressure (P_X) over the upstream compliance (C_X). Therefore, an infusion of blood was applied during the IPP, which should load the venous system, causing a change in P_X , which allowed us to estimate the model compliances. The sum of the model compliances ($C_X + C_V$) represented the total venous compliance and was considered as an estimate of the total systemic vascular compliance. The model estimates of the compliance were obtained directly from the fit of the simulated to the measured venous return during the IPP with infusion.

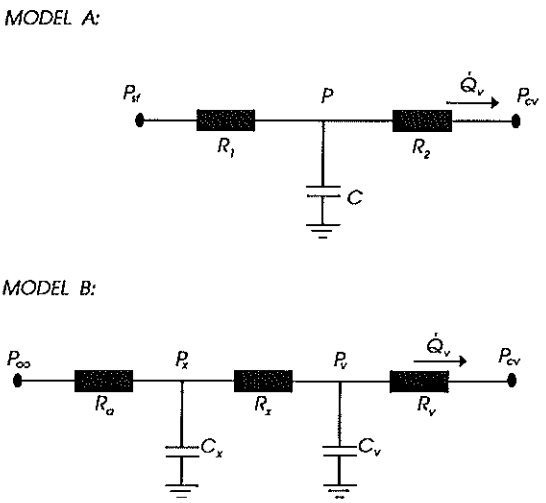

Fig.1: *Models of the systemic circulation to compute the venous return.* ***Model A*** *consists of two resistances (R_1, R_2) a compliance (C) and a constant pressure as driving pressure, this pressure is the mean systemic filling pressure (P_{sf}). The central venous pressure (P_{cv}) is the input of the model, the venous return ($\dot{Q}_v$) the output of the model.* ***Model B*** *is a lumped model of the total systemic circulation, with an arterial resistance (R_a), two venous resistances (R_x and R_v) and two venous compliances (C_x and C_v). In this model the aortic pressure (P_{ao}) and central venous pressure (P_{cv}) are input signals and the venous return is computed.*
The parameters of model A and B are different and cannot be compared.

Method A and B were both used to estimate the compliance from the data obtained during a rapid fluid infusion. Furthermore, the compliance was estimated during hypovolemia to investigate whether it remained unchanged as has been described in the literature [7,10].

METHODS

Eight pigs with a mean body weight of 10.8 ± 0.6 kg (mean ± SD) were used. The anaesthesia, maintenance of body temperature (38 °C) and stability, most part of the surgery, data analysis and the application of inspiratory pause procedures (IPPs) has been described previously [23], as well as the simulations with model A and B [14,15]. The

animals were anaesthetized with 9.0 $mg \cdot kg^{-1} \cdot h^{-1}$ pentobarbital sodium and paralysed after surgery with 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ pancuronium bromide (Pavulon, Organon, the Netherlands) after a loading dose of 0.1 mg/kg. Mechanical ventilation was set at 10 breaths per minute and tidal volume adjusted to an arterial P_{CO_2} of 35 to 45 mmHg.

SURGERY

Via the right carotid artery, a catheter was inserted to measure aortic pressure (P_{ao}) and to sample arterial blood. Two catheters were inserted via the external jugular vein, a Swan-Ganz catheter to measure pulmonary artery pressure and sample mixed venous blood and a 4-lumen catheter to measure central venous pressure (P_{cv}) near the right atrium and infuse pentobarbital sodium and pancuronium bromide. Right ventricular output was measured with an electro-magnetic flow probe around the pulmonary artery after a left intercostal thoracotomy in the second intercostal space. Two suction catheters, one dorsal and one ventral, were placed in the left pleural space. A pressure catheter was positioned in the pericardium, which was sutured. Thereafter, the thorax was closed airtight. The evacuation of air and fluid was accomplished by applying a negative pressure of 10 cmH_2O to the suction catheters for one or two minutes, in combination with a positive end-expiratory pressure of 10 cmH_2O. After closure of the thorax a mercury-cord was fixed around the thorax to monitor changes in thoracic volume.

Right ventricular output, averaged per heart beat, was considered to be equal to the mean venous return of the previous heart cycle. The calibration factor for the electro-magnetic flow signal was determined from a 48 s recording during normal mechanical ventilation, using the mean of two cardiac output estimates with the direct Fick method for oxygen as the reference.

After surgery the animal blood was anti-coagulated by a constant infusion of 0.5 ml/h heparin (5000 IE/ml). Next, the arterial pressure catheter was removed from the right carotid artery and replaced by a loop of polyethylene tubing to recover the flow in the right carotid artery (fig.2). The tubing had an outer diameter of 4.0 mm and an inner diameter of 3.0 mm. A side branch served to infuse blood and to bleed rapidly. The side branch was closed with a clamp until it was used for the infusions of blood. Next, the arterial catheter was

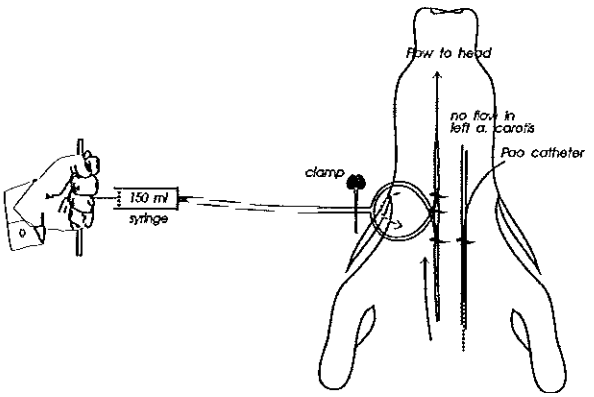

Fig.2: Schematic drawing of the arterial canula. The canula is placed with a loop in the right a. carotis. The side port of the canula is connected to a syringe of 150 ml that can be moved manually, the clamp is closed during normal ventilation and during normal IPPs. Arrows indicate the direction of blood flow during normal ventilation.

inserted in the left carotid artery to measure aortic pressure again. This order of events served to maintain the circulation to the brain.

INTERVENTIONS

After surgery, we infused 150 ml rheomacrodex (dextran 40 with 5% glucose) and bled the animal 5 min later with 150 ml arterial blood to recover normovolemia. This blood was kept, airtight at 38 °C, and used for infusions during the procedures.

All following interventions were based on inspiratory pause procedures (IPPs) applied with a computer controlled ventilator [25]. Such an IPP consisted of an inflation of 2.4 s, an inspiratory pause of 12 s and an expiration of 3.6 s. The data, used in the analysis consisted of an IPP preceded and followed by normal ventilatory cycles, in total 45 s. All IPPs were performed at a tidal volume of 30 ml/kg, as that tidal volume produced reliable results in the parameter estimations [14].

Besides the normal IPPs, we performed IPPs while infusing blood into the arterial system via the polyethylene loop, during the pause of the IPP. We aimed to maintain arterial pressure at its end-expiratory level. The manually guided infusion lasted from the start until

the end of the pause of the IPP. When the data sampling (45 s) had terminated, the animal was bled with the same volume as was infused, the infused volume being not longer in the circulation than 60 s. We performed three pairs of IPPs, each pair consisting of a normal IPP, followed by an IPP with infusion. The interval between both IPPs was at least 5 min.

After these series, in 4 animals hypovolemia was induced by withdrawing 15 ml/kg blood. After a stabilisation period of at least 15 min another series of 3 pairs of a normal IPP and an IPP with infusion was performed. In two other experiments we started with the hypovolemic state, established by an additional bleeding of 15 ml/kg. After the protocol was performed, as mentioned above, the normovolemic condition was recovered, a stabilisation period of at least 15 min inserted and the protocol of IPPs repeated.

MODELS

In previous chapters we described two models to simulate venous return [14,15]. In both models (fig.1) all parameters were assumed to be constant and the models were described by first order linear differential equations. Each model was used in a different method to estimate the total systemic vascular compliance, model A was used in method A and model B in method B.

Model A. The parameters of this model were a constant pressure (P_{sf}) as the driving pressure for venous return, two resistances (R_1, R_2) and a compliance (C). The pressure P was computed in time, dependent on the model parameters and as a function of the input signal, the central venous pressure (P_{cv}). This required an extra parameter P_0, which was the initial pressure at P. The venous return was computed as the output of the model from: $\dot{Q}_v(sim) = (P - P_{cv})/R_2$. The simulated venous return was fitted to the measured values in pigs, by optimization of the model parameters [14].

Model B. The model parameters were the resistances: R_a (arterial), R_x and R_v (venous resistances) and the venous compliances: C_v and C_x [15]. The input signals were the central venous pressure (P_{cv}) and the aortic pressure (P_{ao}). The pressures P_x and P_v were computed in time as a function of the input signals. This required two extra parameters $P_{x,0}$ and $P_{v,0}$ that represented the initial values of P_x and P_v respectively. The venous return was computed from: $\dot{Q}_v(sim) = (P_v - P_{cv})/R_v$. Analogous to model A we fitted the simulated venous return to its measured values by an optimization procedure.

OPTIMIZATIONS

The optimization of the simulated venous return to the measured venous return was based on the search for the minimum value of an error function, which was performed by a simplex method. The error function was defined as the mean of the absolute differences between the simulated venous return and the measured venous return [14]. We computed the simulated flow at time intervals of 0.1 s. To obtain values of the measured flow at these instants, we interpolated the measured venous return by a cubic spline. The simulation started at the start of the computer recording of the data and lasted until the end of the pause of the IPP. The models were programmed in MATLAB, which provided the Simplex procedure, the cubic spline and the procedures to solve the differential equations.

DATA ANALYSIS

Method A. If all parameters of model A were known, we could compute the pressure variations (due to the infusion) at the site in the circulation where the pressure was equal to P_{sf} (P_{Psf}), based on the assumption that the sum of all flows to P must be zero. Thus we obtained: $\dot{Q}_{in} = \dot{Q}_c + \dot{Q}_v$. In which $\dot{Q}_{in}$ was the flow into the venous system, $\dot{Q}_c$ was the loading of the venous compliance and $\dot{Q}_v$ was the venous return:

(1) $\dot{Q}_{in} = (P_{sf} - P)/R_1$

(2) $\dot{Q}_c = C \cdot dP/dt$

(3) $\dot{Q}_v = (P - P_{cv})/R_2$

From these equations it followed that:

(4) $P_{Psf} = P_{cv} + \dot{Q}_v \cdot (R_1 + R_2) + C \cdot R_1 \cdot dP_{cv}/dt + C \cdot R_1 \cdot R_2 \cdot d\dot{Q}_v/dt.$

The pressure at the site in the circulation where it was equal to P_{sf} (P_{Psf}) could be computed if P_{cv} and $\dot{Q}_v$ were measured and the model parameters R_1, R_2 and C were known and remained constant. The pressure was called P_{Psf} to discriminate it from P_{sf} which is by definition a virtual parameter, characteristic for a given hemodynamic condition. With use of an IPP with infusion, the total systemic vascular compliance was estimated from the ratio of the infused blood volume (ΔQ_{inf}) and the rise in P_{Psf}:

(5) $C_{t,A} = \Delta Q_{inf}/\Delta P_{Psf}$

First, the values of the parameters of model A were estimated during a normal IPP. Then, we performed a second IPP with infusion of blood during the pause period. The parameter

values of the first IPP, plus the measurement of P_{cv} and $\dot{Q}_v$ during the second IPP were used to compute P_{Psf} with eq.(4). The (total systemic vascular) compliance was then calculated by eq.(5). ΔP_{Psf} was determined as the difference between the value of P_{Psf} before and at the end of the infusion. This method was based on the assumption that a stationary hemodynamic condition was obtained immediately after the infusion.

Method B. The second method was based on optimizations of model B (fig.1) on only the IPPs with infusion. In this model the pressure, P_x, at the upstream compliance C_x was approximately equal to P_{sf} under stationary hemodynamic conditions, but in contrast with model A this pressure was not assumed to be constant [15]. During the IPPs with infusion the pressure in this region increased due to the filling of the venous system, necessary to increase the venous return. This challenge of the circulation was necessary to estimate the model parameters C_x and C_v reliably. The sum C_x+C_v was assumed to be equal to the total venous compliance, which was an estimate of the total systemic vascular compliance, $C_{t,B}$. Thus, the estimate of the total systemic vascular compliance ($C_{t,B}$) was directly obtained from the estimates of the model parameters C_x and C_v.

Methods A & B. The simulations were terminated at the time point where the heart rate changed, near the end of the pause in the normal IPPs. These changes in heart rate coincided with changes in central venous pressure, aortic pressure and venous return and indicated changes in the activity of the circulatory controls. The optimizations of model B to IPPs with infusion were terminated at the same instant as the normal IPPs.

STATISTICS

Because we obtained estimates of the compliance from two different methods and at two volemic states, we had to perform multiple comparisons. The distributions of the differences between groups were analyzed with a Kolmogorov-Smirnoff test. Because distributions of the differences between both methods were normal ($p>0.20$), we used a paired t-test to test the differences between the two methods. The significance level was set at $p = 0.05$. The results of the compliance estimates during normo- and hypovolemia were compared for both methods separately with an ANOVA for 6 animals, 2 volemic states and 3 repeated measurements.

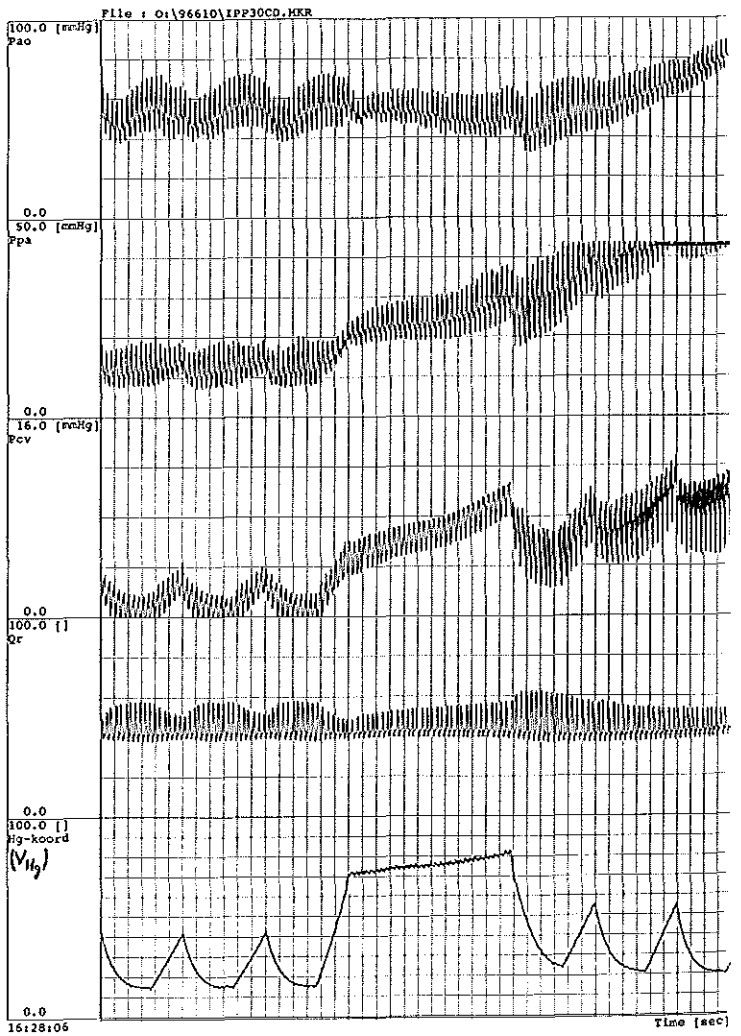

Fig.3: *An original recording of an inspiratory pause procedures (IPP) with a rapid infusion of blood during the pause, indicated by the arrows at the top. From the upper to the lower panel the aortic pressure (P_{ao}), the pulmonary artery pressure (P_{pa}), the central venous pressure (P_{cv}) the right ventricular output ($\dot{Q}_r$) and the thorax volume (V_{hg}) are presented. The pressures were measured in mmHg the flow was measured in arbitrary units and calibrated off-line. During the infusion P_{pa}, P_{cv}, $\dot{Q}_r$ and V_{hg} increased and P_{ao} was approximately constant. The events after the pause, leading to a period of heart failure, are discussed in the text* ***(discussion)***.

RESULTS

The hemodilution with 150 ml rheomacrodex resulted on average (SD) in a decrease of the hemoglobin from 10.6 (0.6) to 7.9 (0.4) g/dl. The P_{CO_2} of the infused blood was determined just after it was withdrawn from the animal and just before the infusion was performed. In 32 of the 42 procedures with infusion, the P_{CO_2} of the blood was within the range of 35 to 45 mmHg. In 10 cases the P_{CO_2} was between 45 and 50 mmHg. The transient decrease in core temperature of the circulation, measured in the pulmonary artery, due to the infusion of blood was 0.1 to 0.3 °C.

A recording during an IPP with infusion is shown in fig.3. During the infusion (in the pause period of the IPP), P_{cv}, $\dot{Q}_v$, pulmonary artery pressure (P_{pa}) and thorax volume (V_{Hg}) increased, whereas they were constant during a normal IPP [14-18].

Method A. The use of method A is depicted in fig.4A and 4B. The result of a parameter estimation procedure of model A to a normal IPP is shown in fig.4A. The optimal values of the parameters were subsequently used to compute the course of P_{Psf} during the IPP with infusion (fig.4B) using eq.(4). The total change in P_{Psf} (ΔP_{Psf}) was determined at the end of the infusion (t=27 s). After the infusion P_{Psf} was relatively stable again. In some experiments ΔP_{Psf} decreased slightly after the infusion and then reached a steady state.

Method B. The use of method B is depicted in fig.4C, in this figure the fit of model B to the IPP with infusion is presented for the same data as fig.4A & 4B. The simulation was terminated at the end of the infusion.

To compare both methods all estimates of the compliance, during normo- and hypovolemia, were pooled. There was a significant difference between the compliance estimates of method A and B of 0.16 (SD: 0.38) $ml \cdot mmHg^{-1} \cdot kg^{-1}$, $p=0.007$. In the normovolemic state only, the mean value (and SD) with method A in all animals was $C_{t,A}$ = 1.56 (0.22) $ml \cdot mmHg^{-1} \cdot kg^{-1}$. The mean value with method B was $C_{t,B}$ = 1.44 (0.30) $ml \cdot mmHg^{-1} \cdot kg^{-1}$.

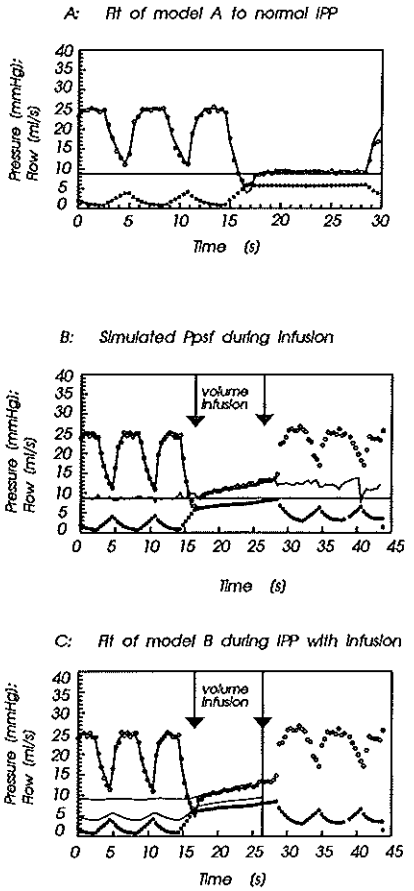

Fig.4: *In fig.4A an example of a fit of model A to a measurement of the venous return during a normal IPP is presented. The circles represent the beat-to-beat values of venous return, the dots represent the values of central venous pressure. The solid line through the circles is the fit of the model output to the measured data, the dotted line indicates the mean systemic filling pressure (P_{sf}) estimate. In fig.4B the dashed line represents the P_{sf}-estimate from the first IPP. The bold, solid line is the simulated in P_{Psf} the blood pressure in the circulation equal to P_{sf}, that is computed from the model parameters obtained from fig.4A and the venous return and central venous pressure as input signals. The arrows indicate the period of infusion. The total change in P_{Psf} is determined at the end of infusion. In fig.4C the fit of model B to the IPP with infusion is presented for the same data. The simulation is terminated at the end of the infusion (vertical line). The dotted lines are the simulated pressures P_x and P_v of model B respectively.*

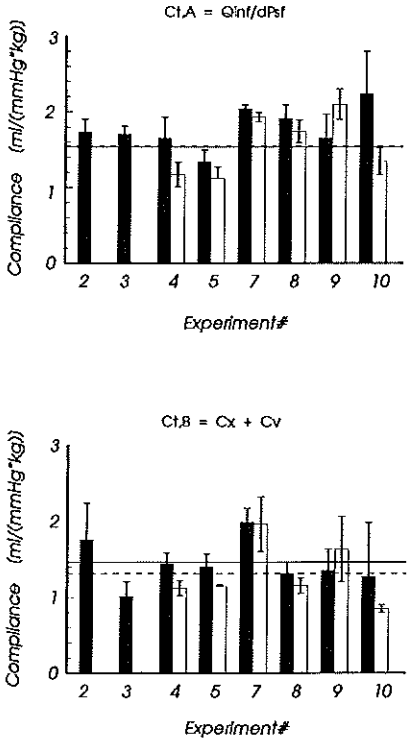

Fig.5: *Comparison of compliance estimates in normo- and hypovolemia for both methods. In fig.5A the results of method A are shown. The solid bars are the results during normovolemia, the open bars during hypovolemia. The mean values during normo- and hypovolemia of experiments 4 to 10 are indicated by the solid and the dashed line respectively. In fig.5B the results of method B are shown with the same legends as in fig.5A.*

In 6 of 8 animals a hypovolemic state was induced. The optimizations of the normal IPPs (model A only) during hypovolemia, produced lower values of P_{sf} in all cases, the mean difference (SD) in P_{sf} between both volemic states was 3.1 (1.0) mmHg, $p<0.001$.

The results of the compliance estimates in normo- and hypovolemia are presented in fig.5A and 5B, for both methods separately. With both methods there was no significant difference in the compliance estimates between normo- and hypovolemia. With method A

during hypovolemia the mean compliance was $C_{t,A}$ = 1.54 (0.41) ml·mmHg^{-1}·kg^{-1}. With method B the mean values of compliance during hypovolemia state was $C_{t,B}$ = 1.31 (0.41) ml·mmHg^{-1}·kg^{-1}.

DISCUSSION

We aimed to determine the total systemic vascular compliance while the circulation was intact. Two methods have been used to estimate the compliance from an inspiratory pause procedure (IPP) with an infusion of blood into the arterial system during the pause of the IPP.

METHODOLOGY

We placed a loop in the right carotid artery at the end of surgery. This order of events was deliberately chosen, to avoid anti-coagulation during surgery. After the loop had been placed, the arterial pressure catheter was inserted into the left carotid artery to measure arterial pressure. We avoided pressure measurements in the loop because of the infusions into it.

To perform the IPPs with infusion we used diluted homologuous blood. From the data of the arterial P_{CO_2} and the temperature changes we concluded that the condition of the infused blood was sufficiently maintained to minimize its influence on the circulation.

STABILITY OF THE ANIMAL

Previously, we used IPPs with a pause of 7.2 [23] or 12 s [14-17]. In none of these studies an influence of control mechanisms was observed. In the present study, with a pause of 12s, we used the same anaesthetic as before. But, now we observed a number of IPPs in which changes in control mechanisms were present, indicated by an increase in heart rate, central venous pressure, right ventricular output, pulmonary artery pressure and aortic pressure. Also during the IPPs with infusion we observed changes in heart rate. As the sample frequency was 250 Hz the minimum detectable change in heart interval was 4 ms. To avoid the effects of control mechanisms, the fit procedures of the models were performed in those parts of the data in which the heart interval changed less than 12 ms. In 10 of the 42 IPPs we found an increase in heart interval larger than 12 ms near the end of the infusion, mostly from the 7th second to the end of the pause. The maximum increase in

heart interval, observed during an IPP, was 24 ms, from the 5th s of the pause towards the end, corresponding with an decrease in heart rate from 162 to 152 beats/min.

DISCUSSION OF METHODS

Method A. With this method the total systemic vascular compliance was calculated as the ratio of infused blood volume and simulated increase in P_{Psf}, the pressure in the circulation equal to P_{sf}. P_{Psf} was estimated by a model which also incorporated two resistances and a compliance. This compliance was a model parameter, used to fit the model output to the measurements, and had no physiological significance. With method A there were two major sources of errors.

Firstly, when the blood was infused during the pause, the venous return and, as a consequence, the right ventricular output increased. This increase in flow caused an increase in pulmonary arterial pressure (fig.3), indicating an increase in pulmonary arterial and probably total pulmonary blood volume. This was also indicated by the increase in thorax volume measured by the mercury-cord (fig.3). This increase in pulmonary blood volume was supplied by the infused blood volume. The increase in P_{Psf} was thus caused by a smaller amount of blood than the infused volume and the compliance was overestimated. We were not able to quantify the increase in pulmonary blood volume during the IPPs with infusion, to make a correction.

Secondly, method A was based on the simulation of the increase in P_{Psf} and the calculation of eq.(4). This equation is only valid for stationary conditions. It was assumed that the infused blood was immediately distributed over the venous compliances. This assumption seemed reasonable because the arterial pressure was kept constant or slightly decreased and the simulated P_{Psf}, with eq.(4), was relatively constant after the infusion. In some IPPs the simulated P_{Psf} slightly decreased after the infusion, or showed more fluctuations than before the IPP. Probably, the hemodynamic condition was not stable just after the infusion, or the resistances (R_1 and R_2) were not constant, both as a result of elicited changes in the activity of the circulatory control mechanisms.

Method B. This method was based on the direct estimation of the parameters of model B by fitting the simulated to the measured venous return during an IPP with infusion. In the model only venous compliances and no arterial compliances were incorporated. Therefore,

the total systemic vascular compliance was theoretically underestimated with use of this model. If we assume a venous to arterial compliance ratio of about 30 [6,8], the compliance will have been underestimated by about 3%. Furthermore, model B did not incoporate the compliance of the most downstream (central) veins. It is not known how large this part of the venous compliance is, but it has been reported that largest part of the venous compliance is located in the small veins and the venules [11,12], which was confirmed by the simulations with this model [15]. With the use of method B the exact amount of infused blood was irrelevant. The infusion of blood served to induce changes in P_x (fig.1B). These changes were necessary to obtain reliable estimates of the model

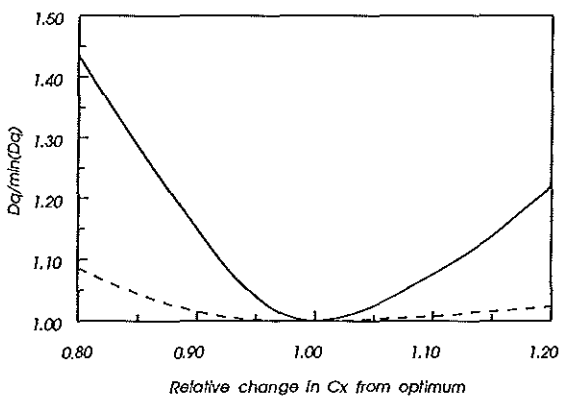

Fig.6: *Sensitivity plot of the parameter C_x of model B during a normal inspiratory pause procedure (IPP) and an IPP with blood infusion. On the x-axis the relative change in the parameter C_x from the optimal values is plotted, the other model parameters remain at their optimal values. The optimal values are obtained from the fit of the simulated to the measured venous return. On the y-axis is the relative change in the error (Dq). The dashed line shows the relative change in Dq for changes in C_x during a normal IPP, the solid line shows the same for an IPP with infusion. During an IPP with infusion Dq is more sensitive to changes in C_x, suggesting that C_x is estimated more reliably.*

compliances. Furthermore, method B did neither involve an estimation of P_{Psf} nor the achievement of a stationary condition. A requirement was that no changes in the activity of the circulatory control mechanisms occurred.

The influence of the infusion on the parameter estimation is indicated in fig.6. The relative change of the error, was put against the relative change in the parameter C_x (sensitivity plot), whereas all other parameters were kept constant at their optimal values. The error was more sensitive to changes in C_x in an IPP with infusion than in a normal IPP, implying that the estimates of C_x were more reliable from an IPP with infusion of blood. The sensitivity plots of C_v showed similar characteristics.

EFFECTS OF INFUSIONS TO THE RIGHT HEART

In the IPPs with infusion, the circulatory conditions after the pause were unstable for some time (5 to 15 min). The extra volume loading of the venous compliance caused an increase in venous return during the pause as we expected. In spite of the immediate bleeding after the pause procedure, the right ventricle needed for some time an increased filling pressure to pump the venous return into the pulmonary circulation. This was undoubtedly due to the large increase in pulmonary arterial pressure. The increase in filling pressure was indicated by an increase in transmural P_{cv}, reflected by an increase in P_{cv} that was much larger than that of the intrathoracic pressure (the latter probably due to the increase in lung blood volume). In five of the eight animals such effects were prominently present, leading to short periods of heart failure (about 5 min), reflected by a very low cardiac output, a very low aortic pressure (about 20 to 30 mmHg), a fall in heart rate (from about 3 Hz to 1 Hz) and a high value of P_{cv} (14 to 18 mmHg). In the case of fig.3 mean aortic pressure decreased about 5 to 10 s after the end of the recording to a level of about 25 mmHg. Such critical situations could be diminished by infusing less volume during the pause, refraining from the condition that the aortic pressure should remain approximately constant during the infusion period. After all, especially with method B, the condition of constant aortic pressure had not necessarily to be fullfilled to obtain values of the compliance. The critical periods occurred mostly when volume infusion of more than 10 ml/kg were given. Volume infusions of 5 to 7 ml/kg, used in the IPPs after such critical situations, were satisfactory to obtain a change in P_{sf} and an estimate of the total systemic vascular compliance, without the occurrence of periods of heart failure. There was no correlation between infused volume and the compliance estimates.

REVIEW OF OTHER METHODS

Estimates of the total systemic vascular compliance in humans have been obtained by measuring the increase in right atrial pressure after a volume loading of the intact circulation [24]. It is doubtful that the change in right atrial pressure will have been equal to the change in mean systemic filling pressure, because the right atrial pressure was also affected by changes in the heart function due to the volume loading [7,8,24]. Therefore, the value of compliance thus obtained is sometimes called the effective compliance of the systemic circulation [8].

In the past, mainly two methods have been used to determine the total systemic vascular compliance in animal experiments. In the first method (stop flow method) the determination of compliance was combined with the determination of mean systemic filling pressure (P_{sf}). The condition of zero flow, to obtain P_{sf}, was usually obtained by fibrillation of the heart [1-5] or inflation of a right atrial or pulmonary arterial balloon [6]. Total vascular compliance was determined by measuring the change in mean systemic filling pressure after volume loading of the circulation. This determination of the total vascular compliance incorporated the compliance of the pulmonary circulation, which is about 20% to 30% of the total [7,8].

In the second method (venous reservoir method) to determine total systemic vascular compliance a right heart bypass was used. The inferior and superior vena cava were cannulated and connected, via a reservoir, to a pump. The output of the pump was drained into the right atrium or the pulmonary artery. The flow could be kept constant when a change in pressure just before the reservoir, as a substitute of right atrial pressure, was applied [9-13,26]. Total systemic vascular compliance was then obtained by applying a step change in "right atrial" pressure and measuring the volume change in the reservoir.

Most determinations, with the two methods mentioned above, have been performed in dogs and rats. In rats the values of total systemic compliance ranged from 1.5 to 2.4 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ [6,18,19]. Values of the compliance determined in dogs are presented in Table 1. Studies that involved a splenectomy [1,4,9,20] have been omitted from the table because after splenectomy the compliance was considerably lower [1,3]. In the studies in which the total vascular compliance was estimated, marked with an asterix, values in the table are 75% of the values reported in the original article to correct for the pulmonary

Authors	Year	Method	$C_{t,sys}$ $ml \cdot mmHg^{-1} \cdot kg^{-1}$
Shoukas & Sagawa [26]	1973	Venous reservoir method.	2.0 (0.2)
Caldini et al. [11]	1974	Venous reservoir method.	1.70 (0.13)
Holtz et al. [21]	1981	Conscious dogs; volume loading 2 and 4 ml/kg; bleeding 2 and 4 ml/kg; $C_{tot,vasc}$ is slope of ΔVolume to ΔP_{ra} curve, flow not constant.	2.2 * (0.3)
Greene & Shoukas [10]	1986	Venous reservoir method.	1.59 (0.47)
Ogilvie & Zborowska-Sluis [12]	1987	Venous reservoir method.	2.6 (0.3)
Lee et al. [3]	1987	Stop flow method.	1.65 * (0.08)
Hirakawa et al. [2]	1992	Stop flow method, including an arterial-venous shunt.	1.35 * (0.08)
Rose, Shoukas [22]	1993	Two-port analysis of systemic circulation. Cardiopulmonary bypass; venous and arterial impedances fitted from response to flow oscillations.	0.79 (0.15)
Shigemi et al. [13]	1994	Cardiopulmonary bypass, venous reservoir method.	1.4 (0.4)
present study	1996	Calculated increase in P_{sf}, estimated by model A, during infusion in IPP.	1.56 (0.22)
present study	1996	Parameter estimation of model B during IPP with infusion.	1.44 (0.30)

Table 1: *A table of the results of determinations of the total systemic vascular compliance in dogs. The used methods are in the table, the stop flow method and the venous reservoir method are described in the* ***discussion****. The values of compliance have been normalized to body weight. In the experiments indicated with an asterix the total vascular compliance was determined, the values in this table are 75% of the values reported by the original paper to account for the pulmonary vascular compliance.*

vascular compliance [7,8]. The values of methods A and B of the present study: 1.56 and 1.44 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ respectively, were in the range of values in dogs of 0.79 to 2.6 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ that have been reported .

With our methods A and B, there was no significant difference in the compliance between normo- and hypovolemia, probably because changes in control mechanisms would change the unstressed vascular volume and not the compliance [7,10].

CONCLUSION

By performing infusions during the pause of an IPP it was possible to estimate total systemic vascular compliance, while the circulation was intact, with use of a parameter estimation technique and two different models of the circulation. Both models provided data corresponding to literature values obtained from other methods. Method A, should be corrected for the shift of volume into the pulmonary circulation to avoid an overestimation. With method B the arterial compliance and the compliance of the central veins were not estimated, but their contribution to the total systemic vascular compliance was probably small. Therefore, method B seemed to provide a more reliable estimate of the total systemic vascular compliance. Both methods may be applied in the intact circulation in animal experiments, but the infusions should be performed with care to avoid hemodynamic problems.

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FINAL CONSIDERATIONS

The main objectives of this study were: 1) to develop a faster method to determine the mean systemic filling pressure (P_{sf}), applicable in patients in the intensive care or during surgery; 2) to evaluate whether the resistances upstream and downstream from the sites in the circulation where the pressure is equal to the mean systemic filling pressure (P_{Psf}), are constant during dynamic changes induced by mechanical ventilation.

The conclusion in Chapter 2 was that the resistances upstream and downstream from P_{Psf} remain constant for different levels of central venous pressure and venous return for a given circulatory condition, i.e. P_{Psf} remained at the same site in the circulation with respect to the resistances. The application of a three element model, used in Chapters 3 and 4, was based on the assumption that the resistances upstream and downstream from P_{Psf} would also be constant during dynamic changes in the circulation. The estimate of P_{sf}, based on this model, provided a fast method to determine P_{sf} in the intact circulation in vivo (Chapter 4). The results of the study described in Chapter 5, based on a five-element model, indicated that the assumption of constant resistances upstream and downstream from P_{Psf} seemed reasonable during dynamic changes in the circulation, caused by mechanical ventilation. Both the three-element model and the five-element model were used in Chapter 6 to estimate the total systemic vascular compliance with two different methods. In Chapters 2, 4, 5 and 6 the determination of P_{sf} was based on the use of inspiratory pause procedure (IPP). In the next part of this chapter the results of some simulations are reported, to test whether other ventilatory procedures could be used as well. Thereafter, a few major assumptions are discussed that have been made in the course of the studies, described in this thesis.

THE IPP AND OTHER VENTILATORY PROCEDURES TO DETERMINE P_{sf}

In this thesis Inspiratory Pause Procedures have been applied, with a computer controlled ventilator, to determine P_{sf}. Theoretically, IPPs are not required to estimate P_{sf} with the method of Chapter 4; the estimation is based on the simulation of venous return, with the three-element model, during dynamic changes of central venous pressure. Furthermore, the computer controlled ventilator may provide opportunities to use other ventilatory procedures [1]. With use of the three-element model we tested whether other types of

central venous pressure changes, i.e. patterns of mechanical ventilation, could also be used. In fig.1 five simulated patterns of central venous pressure changes are shown. With these patterns of central venous pressure and a given set of parameter values, venous return ($\dot{Q}_V$) was simulated by the model. The flow was computed at time steps of 0.4 s, corresponding to a heart rate of 2.5 Hz. Then, noise, with a standard deviation of 0 (undisturbed), 0.3, 0.6, 0.9 and 1.2 ml/s, was added to this venous return, to obtain a simulated disturbed flow ($\dot{Q}^*_V$). The same noise was added to the simulated flow of the different input patterns. This data set of simulated P_{cv} and corresponding $\dot{Q}^*_V$ was regarded as a "measurement". For each input pattern the parameters were re-estimated at all noise levels by fitting the model output to the disturbed flow, $\dot{Q}^*_V$. The whole procedure of adding noise at different levels and then re-estimating the parameters was repeated five times. Thus, for each pattern, at each noise level five (slightly) different simulated flow curves were constructed. The parameters were re-estimated for each curve, so standard deviations of the parameter estimates could be calculated. On average the values of the parameters were retrieved in all procedures. But, as indicated in fig.2, the standard deviations of the estimates differed

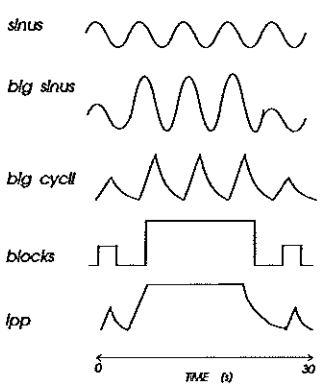

Fig.1: *Different simulated patterns of central venous pressure, representing different ventilation patterns. From top to bottom: five cycles normal sinus (sinus), sinus with three cycles at larger tidal volume (big sinus), standard ventilation pattern with three cycles at large tidal volume (big cycli), block pattern with one "pause procedure" at large tidal volume (blocks), normal IPP as used in this thesis (IPP).*

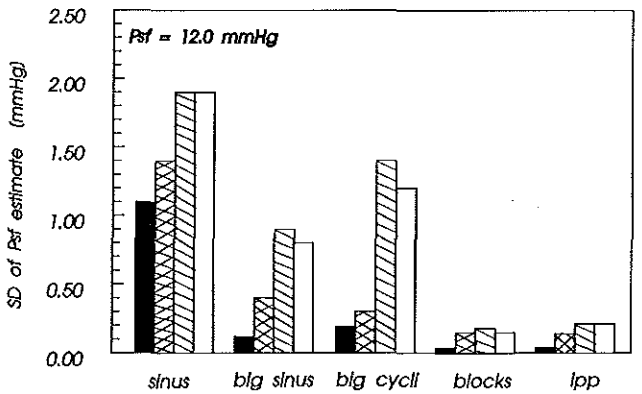

Fig.2: *Results of simulations with different input patterns of central venous pressure. X-axis: patterns as described in Fig.1 at four different levels of noise (SD-noise) for the "measured flow" ($\dot{Q}^*_v$), see text for details. Closed bars: SD-noise = 0.3 mmHg; double hatched bars: SD-noise = 0.6 mmHg; hatched bars: SD-noise = 0.9 mmHg; open bars: SD-noise = 1.2 mmHg.*
Y-axis: standard deviation (SD) of five P_{sf}-estimates. The actual value of P_{sf} was 12.0 mmHg.

considerably. The smallest standard deviations of the estimates of P_{sf} was found with the IPP and the block as input signals. The explanation for this phenomena was probably that those procedures had two distinct levels ("end-expiratory" and the "pause" of the IPP or block) making an estimate of P_{sf} and the resistance downstream from P_{sf} (R_{sd}) more accurate because the flow was fitted. The conclusion was that the IPP provided the most suitable procedure to estimate the P_{sf} reliably.

VENOUS RETURN VS. RIGHT VENTRICULAR OUTPUT

In all experiments we used right ventricular output as a substitute of venous return. Averaged over a heart cycle, venous return and right ventricular output were assumed to be equal. This assumption may be wrong during mechanical ventilation because changes in intrathoracic and central venous pressure will occur, causing not only changes in venous return, but also in right ventricular end diastolic volume. Direct determination of the venous return requires the measurement of three flows: in the inferior and the superior vena cava

and the coronary sinus. These flows should be summed. Besides the problems of such measurements, the sum of these measurements will undoubtedly produce larger errors than the differences between venous return and right ventricular output due to right ventricular volume changes. Furthermore, the flows will be equal during the steady state periods of the pauses of the IPPs, which we used to estimate the reference values of P_{sf}. The development of a method to determine the right ventricular output beat-to-beat has been revitalized recently in our laboratory, after a new method to estimate cross sectional area of vessels became available for animal experiments [2,3].

CONSTANT P_{sf} DURING IPPS

A main assumption of the methods described in this thesis was a constant P_{sf} during all manoeuvers during mechanical ventilation. Although this assumption seems to be confirmed by the results of the experiments, there is one aspect of the influence of mechanical ventilation to the circulation to which less attention has been paid in this thesis. As stated in the Introduction (Chapter 1), an amount of blood is redistributed from the pulmonary into the systemic circulation during the inflation of the lung. In experiments with a similar design as those described in this thesis, Versprille & Jansen estimated the shift of blood by determination of the beat-to-beat differences in left and right ventricular stroke volume. They reported a shift of blood to the systemic circulation of about 1.2 ml per kg body weight, for the IPPs at the highest tidal volume (30 ml/kg) [4]. The authors stated that this would produce an overestimation of P_{sf} of about 1 mmHg and no further attention was paid to this point [5]. Recently, it has been shown, in experiments with a different experimental design, that during an IPP of 25 ml/kg as much as 2.3 ml blood per kg body weight shifted from the pulmonary into the systemic circulation [6]. These data were obtained with use of a double indicator dilution method.

Assuming that the shift of blood volume from the pulmonary into the systemic circulation is linearly related to the tidal volume of the IPP, it will also be linearly related to the increase in central venous pressure. Because the increase in P_{sf} is linearly related to the increase in blood volume (ΔQ_p) if the compliance is constant, the increase in P_{sf} is probably linearly related to the increase in P_{cv} ($dP_{sf} = \xi \cdot dP_{cv}$). The consequence is that the

relationship between venous return ($\dot{Q}_v$) and central venous pressure is disturbed and becomes: $\dot{Q}_v = a - b \cdot P_{cv} + \xi \cdot b \cdot (P_{cv} - P_{cv,ee})$ in which ξ is the slope of the relation between P_{sf} and P_{cv}. $P_{cv,ee}$ is the end-expiratory level of P_{cv}, this term is added because the shift of blood is supposed to be zero at end expiration. The disturbed equation is also linear, but is less steep than Guyton's venous return curve. The estimate of P_{sf} ($P_{sf}\{exp\}$) obtained in the experiments is found from this disturbed linear relationship between venous return and P_{cv}, leading to an overestimation of P_{sf}. The undisturbed P_{sf} would be the value of P_{sf} determined at end-expiration ($P_{sf,ee}$), when no blood has been shifted. $P_{sf}\{exp\}$ is related to the undisturbed P_{sf} ($P_{sf,ee}$) as follows:

$$(1) \qquad P_{sf}\{exp\} = \frac{P_{sf,ee}}{1-\xi} - \frac{\xi}{1-\xi} P_{cv,ee}$$

In our experiments the total vascular compliance was about 16 ml/mmHg. From the data reported by Versprille & Jansen the shift of blood was about 12 ml. Thus, we obtain dP_{sf} = 0.75 mmHg for an average increase in P_{cv} of 6 mmHg at a tidal volume of 30 ml/kg, the end-expiratory value of P_{cv} was about 1.5 mmHg. These data would result in: $\xi = 0.75/6 = 0.125$ and $P_{sf}\{est\} = 1.14 \cdot P_{sf} - 0.14 \cdot P_{cv,ee}$. This leads to an overestimation of P_{sf} of about 1.2 mmHg, for an undisturbed P_{sf} of 10 mmHg. If the shift of blood from the pulmonary to the systemic circulation would have been in the range of values reported by Te Nijenhuis [6], ξ would be about 0.23 and the overestimation of P_{sf} would be about 2.5 mmHg for an undisturbed P_{sf} of 10 mmHg.

The results of this analysis probably provide an estimate of the maximal overestimation of P_{sf} due to this shift of blood, because there may be some effects to diminish it. The undisturbed P_{sf} ($P_{sf,ee}$) would be obtained at end-expiration, but it might be more useful to determine the average P_{sf} during normal mechanical ventilation. This would produce a slightly higher P_{sf} than the value obtained at end-expiration. Furthermore, the shift of blood might reach a maximum at higher inflation volumes of the IPPs, decreasing the value of ξ and, thus, the overestimation of P_{sf}.

The only way to avoid this error is to determine not only the right and left ventricular output beat-to-beat, but also the total systemic compliance.

VENOUS COMPLIANCE

Mean systemic filling pressure is closely related to the distribution of arterial and venous compliance. Studies in which total systemic compliance has been estimated, report values of the venous to arterial compliance ratio of 30 to 75 [7-10]. In some physiological textbooks [11,12] a venous to arterial compliance ratio of about 15 to 20 is reported. The estimates reported in these textbooks are based on the fact that an increase in venous volume should be supplied by a decrease in arterial volume:

$$(2) \qquad -C_a \cdot dP_a = C_v \cdot dP_v$$

Although the analysis described in the textbooks, based on eq.(2), is theoretically correct, the disturbing factor is found in the difference between theory and reality. When a model of the circulation is constructed, a continuum of resistances and compliances is lumped into one compartment. Thus, in reality the venous compliances are not loaded equally and simultaneously, whereas in a model all compliances act the same, since they are lumped into one compliance. The increase in pressure in the central veins is larger than in the more upstream parts of the venous system, whereas the largest part of the venous compliance is situated in the more upstream veins [7-9,13-15]. Thus, the venous compliance will be subjected to an increase in pressure that is smaller than the increase in the central veins. Consequently, the increase in central venous pressure is not a good representative of the mean venous pressure increase, where the mean venous pressure is weighed by the distribution of the venous compliance. If models of the systemic circulation are constructed, a flow resistance should be placed downstream from the venous compliance.

On the arterial side, $C_a \cdot dP_a$ may be replaced by $C_a \cdot dP_{ao}$ without making a large error, because the largest part of arterial compliance is situated in the large arteries [12,13] and an error in arterial pressure of about 5 mmHg has much less influence on the results, due to its high pressure. The results of model simulations and optimizations described in Chapters 5 and 6, confirmed that the largest part of the venous compliance was not in the central veins, but in the smaller veins. The mean change in venous pressure (dP_v) was smaller than the change in central venous pressure, indicating that the ratio C_v/C_a was much larger than dP_{ao}/dP_{cv}.

ESTIMATING P_{sf} IN PATIENTS

An estimate of P_{sf} in patients could become possible with the method that has been developed in Chapter 2. The advantage of this method is that no measurement of flow is required to obtain an estimate of P_{sf}. Only measurements of central venous pressure and aortic pressure are required. These pressure measurements are more accurate and less complicated in intensive care or during surgery than flow measurements. With this method only the ratio of resistances upstream and downstream (R_{su}/R_{sd}) from the blood pressure in the circulation that is equal to P_{sf} is obtained and not the absolute values. Because it may also be relevant to monitor changes in the systemic resistances (vasoconstriction or vasodilation), it will be useful to determine the absolute values of R_{sd} and R_{su} additional to P_{sf}. These estimates of resistance can be obtained from an additional determination of the total systemic flow resistance, for example by determining cardiac output with the thermodilution method. From the total resistance and the ratio R_{su}/R_{sd}, both R_{sd} and R_{su} can be calculated.

The SIP-method, presented in Chapter 3, is based on only one ventilatory procedure with a slow inflation. Furthermore, no calibrated flow measurement is required. If a beat-to-beat signal is obtained, proportional to the right ventricular output, P_{sf} could be determined from the linear regression between the central venous pressure and the proportional signal, but then, R_{sd} cannot be calculated. If an accurate calibrated beat-to-beat determination of right ventricular output would be available in patient care, the method described in Chapter 4 would be preferable to the SIP-method. The method of Chapter 4 requires a single IPP to estimate P_{sf}, whereas the SIP method requires long inflation times. In pigs an inflation time of 18 s was predicted satisfactory in 95 % of the experiments. During such long inflations, changes in neuro-humoral control mechanisms may affect the circulation and no quasi-stationary state will be obtained. Furthermore, it should be investigated first what inflation times will be required in humans before the method can be used in patients. The method described in Chapter 4, based on a three-element model, provides a direct estimate of P_{sf} and R_{sd}. A method to determine right ventricular output could be obtained from a combination of a pulse contour method [16] or a model flow method [17] with the determination of pulmonary arterial compliance and impedance [2].

CLINICAL RELEVANCE OF P_{sf}

In this thesis a method to determine P_{sf} with use of a single ventilation procedure has been developed. In the Introduction (Chapter 1) it was stated that P_{sf} is a measure of the effective filling state of the circulation and it is an important determinant of venous return [7,8,11]. In Chapter 6, experiments with a hypovolemic period were performed. It was found that all values of P_{sf} during hypovolemia were lower than the values during normovolemia in the same animal, as was expected. These findings confirmed that changes in the filling state could be followed by monitoring changes in P_{sf}.

In 1996 Hiesmayr et al. described hemodynamic changes in pigs caused by endotoxin infusion and the changes after fluid administration [18]. After the administration of 18 ml/kg fluid the aortic to venous pressure difference and P_{sf} did not change, while the cardiac output increased considerably. The decrease in flow resistance and unaltered P_{sf} after the fluid infusion were explained by a vasodilation, which increased the unstressed volume and not the compliance and shifted P_{sf} downstream by decreasing R_{sd}. In the literature there is a number of studies where changes in unstressed volume, with constant compliance, have been described under various circumstances [7,19-22]. Hiesmayr et al. clearly showed that not only P_{sf}, but also R_{sd} and R_{su} are important parameters to evaluate changes in the systemic circulation. The determination of compliance, e.g. with the method described in Chapter 6, would further improve this evaluation.

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ABSTRACTS

CHAPTER 1

Because the bloodvessels are distensible, the vessel volume increases (dQ) if the transmural pressure increases (dP). De derivative (dQ/dP) of the pressure-volume relationship is denoted as the compliance of the vessel. Mean systemic filling pressure (P_{sf}) is the mean pressure of the systemic circulation, weighed by the compliances of the blood vessels. Theoretically, P_{sf} can be found as the equilibrium pressure of the circulation if the heart beat has been stopped and the flow is zero everywhere. P_{sf} is an indication of the filling state of the systemic circulation.

According to Guyton's theory, P_{sf} is the driving pressure for venous return during steady states. Furthermore is the flow resistance, downstream from the sites in the circulation where blood pressure is equal to P_{sf}, (R_{sd}) constant for different steady states. Therefore, the relationship between venous return ($\dot{Q}_v$) and central venous pressure (P_{cv}) is linear: $\dot{Q}_v = (P_{sf}-P_{cv})/R_{sd}$. As a consequence P_{sf} is a determinant of cardiac output, because the heart can only pump out the blood volume that is returned to it.

In the next part of chapter 1, a review of methods, used by various authors, to determine P_{sf} was given. The most important of these methods for this thesis, was the method of Versprille & Jansen, because it was used as the reference method. This method was based on the application of inspiratory pause procedures (IPP) during normal mechanical ventilation. An IPP consists of an inflation of the lungs, a pause (12 s in this thesis) and an expiration. During the inflation central venous pressure (P_{cv}) increases, which causes a decrease in venous return ($\dot{Q}_v$). Then, during the pause of the IPP P_{cv} and $\dot{Q}_v$ reach a new steady state, in which $\dot{Q}_v$ is lower and P_{cv} is higher than before the inflation, following Guyton's theory. In a series of seven different IPPs, at inflation volumes of 0 to 30 ml/kg, seven different steady states were obtained. P_{sf} was obtained from the extrapolation of the linear regression, between $\dot{Q}_v$ and P_{cv}, to the intersection with the P_{cv}-axis. At this point the flow is zero and all pressures should be equal to P_{sf}.

The aim of this study was to find a faster method to determine P_{sf} and to investigate whether the resistance, downstream from the sites in the circulation where the blood

pressure is equal to P_{sf}, was also constant during dynamic changes of pressure and flow, caused by mechanical ventilation.

CHAPTER 2

In the intact circulation, mean systemic filling pressure (P_{sf}) is determined by applying seven IPPs and using Guyton's equation of venous return: $\dot{Q}_v = (P_{sf} - P_{cv})/R_{sd}$, as described in Chapter 1. During an IPP, a steady state is observed. Therefore, we can also formulate for flow: $\dot{Q}_s = (P_{ao} - P_{sf})/R_{su}$, where R_{su} is the systemic flow resistance upstream to P_{sf}. Because both flows ($\dot{Q}_s$ and $\dot{Q}_v$) are equal, it follows that:

$$P_{ao} = P_{sf}\cdot(1 + R_{su}/R_{sd}) - R_{su}/R_{sd}\cdot P_{cv}.$$

This equation implies a method to determine mean systemic filling pressure on the basis of aortic pressure measurements instead of flow determinations. Using 22 IPP procedures in 10 piglets, we determined the mean systemic filling pressure, and we compared the values obtained from the flow curves with those obtained from the aortic pressure curves. The mean difference between the two methods was 0.03 $\pm$ 1.16 (s_{diff}) mmHg. Using aortic pressure measurements, the mean systemic filling pressure can be estimated as accurately as in using flow determinations. The advantage of the new method is that estimation of cardiac output is not required.

CHAPTER 3

During inflation of the lung the venous compliance is filled due to the rise in venous pressure. Therefore, during inflation venous return is depressed more than is described by Guyton's equation of venous return. Consequently, P_{sf} is underestimated if it is derived from the relationship between venous return and central venous pressure during inflation. Based on a simple model we hypothesized that P_{sf} may be estimated during inflation, if the inflation time is sufficiently long. In 8 mechanically ventilated, anaesthetized pigs of 10.3 $\pm$ 0.8 kg (mean $\pm$ SD) we studied the effect of the inflation time of the lung on the estimation of the mean systemic filling pressure (P_{sf}) from the changes in venous return and central

venous pressure during inflation of the lung. For this purpose we applied slow inflation procedures (SIP) to the lung with inflation times of 2.4, 4.8, 7.2, 9.6 and 12 s at tidal volumes (V_T) of 15 and 30 ml/kg. The data were compared with the values of P_{sf} obtained from inspiratory pause procedures (IPPs). A linear regression between venous return and central venous pressure applied during a SIP produced an underestimation of P_{sf} compared to the value obtained with IPPs. An exponential fit through the values of P_{sf} obtained from the different SIPs predicted an inflation time of about 15 s for an estimation of P_{sf} that is not different from the P_{sf}(IPP). The advantage of the SIP-method is that the P_{sf} can be determined much faster than with the method based on IPPs. However, due to the rather long inflation time needed, the method may be only applicable under circumstances where neuro-humoral control mechanisms are suppressed as during intensive care and anaesthesia.

CHAPTER 4

We have demonstrated that P_{sf} can be derived in the intact circulation from measurements of central venous pressure and venous return by applying seven graded inspiratory pause procedures (IPP). The IPPs were performed at intervals of 5 to 10 min. Thus, this method, although reliable, might be too time consuming for clinical application. In this study we aimed to evaluate a new method of P_{sf} determination with a single IPP. During series of 7 graded IPPs we measured central venous pressure and venous return in 7 pigs and fed these data to a model. The model consisted of two venous flow resistances and a venous compliance. For each IPP P_{sf} was model-estimated as the constant driving pressure for venous return. The reference value of P_{sf} was provided by our earlier method of the seven IPPs. The reference P_{sf} in the 7 pigs ranged from 9.9 to 15.0 mmHg, with a mean of 11.9 (SD 1.9) mmHg. Single IPP estimates at the three highest tidal volumes of 20, 25 and 30 ml/kg differed on average 0.6, 0.4 and 0.1 mmHg from the reference respectively, with a SD of 0.9 mmHg. With use of the model and a single IPP P_{sf} can be estimated reliably in the intact circulation.

CHAPTER 5

Mean systemic filling pressure (P_{sf}) is the equilibrium pressure in the systemic circulation if the heart has stopped and the flow is zero. The pressure in the circulation that is equal to P_{sf}, during steady states, was denoted P_{Psf}. P_{Psf} and the resistance downstream from P_{Psf} (R_{sd}), are constant between different steady states of central venous pressure (P_{cv}) and venous return ($\dot{Q}_v$) for a given activity of the circulatory control mechanisms. We investigated whether P_{Psf} and R_{sd} were also constant during dynamic changes of central venous pressure and venous return as occur during mechanical ventilation. A model of the systemic circulation was used to simulate two upstream venous pressures. The model consisted of two venous compliances (C_{v1} and C_{v2}) and three resistances, R_a, R_{v1} and R_{v2}. Venous return was computed as the model output and fitted to measurements of the venous return. With this method, estimates of the resistances and compliances were obtained from an IPP and transients in venous pressure could be analyzed. Reference values of P_{sf} and R_{sd} were obtained with the method based on seven inspiratory pause procedures (IPP). In total ten series of seven IPPs were performed in five pigs. Only the IPPs at the three highest tidal volumes were used in the analysis. The estimates of the sum of the venous resistances ($R_{v1}+R_{v2}$) was slightly smaller than R_{sd}: 0.44 mmHg·s·ml^{-1} vs. 0.54 mmHg·s·ml^{-1}, $p \leq 0.02$. Therefore, the pressure, P_{v1}, over the upstream compliance of the model was slightly smaller than P_{Psf}. Because the increase in P_{v1} was smaller than the increase in P_{cv} (0.9 mmHg vs. 4.4 mmHg), we extrapolated to a pressure that did not change during the IPP. The pressures thus obtained turned out to be equal to P_{sf}. We concluded from these simulations that the pressure variations at P_{Psf} were probably zero during the IPPs. Therefore, a model, as we previously presented, with two constant resistances, a compliance and P_{Psf} as driving pressure appeared satisfactory to simulate the changes in venous return during mechanical ventilation.

CHAPTER 6

Systemic vascular compliance has not yet been determined under normal circulatory conditions in the intact circulation. Determination of the systemic compliance involves a

total stop of the circulation or a right heart bypass with a pump. In this paper we presented two new methods to estimate the systemic vascular compliance in the intact circulation during normo- and hypovolemia, with use of models.

METHOD A. In model A the venous system, downstream from the pressure in the circulation equal to P_{sf} (P_{Psf}) is simulated. With this model P_{Psf} and the other model parameters could be estimated from the hemodynamic changes during a inspiratory pause procedure (IPP) during mechanical ventilation. An IPP consisted of an inflation, a pause (12 s) and an expiration. To estimate the total systemic compliance two IPPs were performed: 1) a normal IPP to estimate the model parameters; 2) an IPP with infusion of blood to determine the increase in P_{Psf}. The total systemic vascular compliance was estimated from the ratio between infused blood volume and increase in P_{Psf}.

METHOD B. Model B represented the total systemic circulation, consisting of three resistance and two venous compliances. The model parameters were estimated during an IPP with infusion. The sum of the estimated model compliances provided total venous compliance.

We performed experiments in eight piglets of 10.8 (SD 0.6) kg, in which both methods were used. With method A the total systemic vascular compliance was estimated at 1.53 (0.23) $ml \cdot mmHg^{-1} \cdot kg^{-1}$ (mean value (SD)). With method B significantly lower values were obtained: 1.46 (0.27) $ml \cdot mmHg^{-1} \cdot kg^{-1}$, $p=0.007$. In six of eight pigs a hypovolemic state was induced by bleeding of 15 ml/kg. During hypovolemia the estimated compliance was not significantly different from normovolemia with both methods, Method A: 1.54 (0.41) $ml \cdot mmHg^{-1} \cdot kg^{-1}$ and method B: 1.31 (0.41) $ml \cdot mmHg^{-1} \cdot kg^{-1}$. All values were in the range of literature data: 0.79 to 2.6 $ml \cdot mmHg^{-1} \cdot kg^{-1}$.

With both models and a rapid infusion of blood during the pause of an IPP the systemic vascular compliance in the intact circulation could be estimated.

CHAPTER 7

Theoretically it is not necessary to apply an IPP to estimate P_{sf}, if the method described in chapter 4 is used. Other ventilatory manoeuvres may also be used to induce changes in

central venous pressure and venous return. From model simulations we concluded that the IPP was one of the preferable procedures to estimate P_{sf}.

In the studies described in this thesis, there were two sources of errors to which not much attention has been paid. Firstly, we substituted the measurement of venous return with the determination of right ventricular output. During steady states both are equal. During dynamic changes of central venous pressure small differences in right ventricular volume may occur, causing a difference between right ventricular output and venous return. But, it is not possible to determine the venous return directly.

A second source of error may be due to the shift of blood from the pulmonary into the systemic circulation. This shift of blood, due to the mechanical ventilation, may cause an error in the estimation of P_{sf} of about 1 to 3 mmHg.

Finally, the clinical relevance of P_{sf} was discussed. It was demonstrated that a determination of only P_{sf} was not satisfactory to describe hemodynamic changes in the circulation of an animal or a patient. Not only P_{sf} but also the resistances (R_{sd} and R_{su}) and the compliance are important to describe changes in the circulation.

NEDERLANDSE SAMENVATTING

HOOFDSTUK 1

Doordat de bloedvaten rekbaar zijn, wordt het vaatvolume groter (dQ) bij een toenemende drukverschil over de vaatwand (dP). De afgeleide (dQ/dP) van de druk-volume-relatie wordt de compliantie van het vat genoemd. De gemiddelde systemische vullingsdruk (P_{sf}) is de gemiddelde druk in de systeemcirculatie, gewogen met de complianties van de bloedvaten. Theoretisch kan de P_{sf} worden gevonden als de evenwichtsdruk die in de circulatie heerst, wanneer de hartslag gestopt is en de stroomsterkte overal nul is. De P_{sf} is een maat voor de vullingstoestand van de systeemcirculatie.

Onder stationaire omstandigheden is, volgens de theorie van Guyton, P_{sf} de drijvende druk voor de veneuze stroomsterkte naar het rechter atrium (veneuze toevoer). Bovendien is de stromingsweerstand, stroomafwaarts van de plaatsen in de circulatie waar de bloeddruk gelijk is aan P_{sf} (R_{sd}), constant. Daardoor is de relatie tussen de veneuze toevoer ($\dot{Q}_v$) en de centraal veneuze druk (P_{cv}) lineair:

$$(Vgl.1) \qquad \dot{Q}_v = \frac{(P_{sf} - P_{cv})}{R_{sd}}$$

Aangezien P_{sf} de drijvende druk voor de veneuze toevoer is, is deze tevens een parameter die het hartminuutvolume bepaalt, omdat het hart alleen het toegevoerde bloed kan wegpompen.

Vervolgens werden een paar methoden beschreven die door verschillende auteurs zijn gebruikt om de P_{sf} te bepalen. De belangrijkste daarvan, voor dit proefschrift, was de methode van Versprille en Jansen, die steeds als referentiemethode gebruikt is. Deze methode is gebaseerd op het gebruik van inspiratoire pauze-procedures (IPP) tijdens de gewone beademing. Een IPP bestaat uit een insufflatie van de longen, gevolgd door een pauze (in dit proefschrift 12 s) en een expiratie. Tijdens de insufflatie stijgt de centraal veneuze druk, waardoor de veneuze toevoer wordt verminderd. In de pauze van de IPP bereiken de veneuze toevoer en de centraal veneuze druk een nieuw stationair niveau, waarop de gemiddelde waarde over de hartcyclus constant is. Op dit nieuwe stationaire niveau is de veneuze toevoer lager dan voor de insufflatie, als gevolg van de verhoogde

centraal veneuze druk. Dit komt overeen met de theorie van Guyton (Vgl.1). In een serie van zeven IPPs, op insufflatievolumes van 0 tot 30 ml/kg in stappen van 5 ml/kg, werden zeven verschillende stationaire niveaus van de centraal veneuze druk en de veneuze toevoer verkregen. Vervolgens werden de centraal veneuze druk en de veneuze toevoer tegen elkaar uitgezet en werd een lineaire regressie door deze zeven meetpunten berekend. P_{sf} werd bepaald door het snijpunt van de lineaire regressie met de centraal veneuze druk-as te berekenen. Op dit punt is de veneuze toevoer nul en zijn volgens de bovengenoemde theorie alle drukken gelijk aan P_{sf}.

Het doel van dit onderzoek was om een snellere methode te vinden om P_{sf} te bepalen. Bovendien werd onderzocht of de stromingsweerstand R_{sd}, stroomafwaarts van de plaatsen in de circulatie waar de bloeddruk gelijk is aan P_{sf}, ook constant is tijdens dynamische veranderingen, die ontstaan als gevolg van de beademing.

HOOFDSTUK 2

Tijdens de pauze van een IPP, zoals beschreven in Hoofdstuk 1, bereiken niet alleen de centraal veneuze druk en de veneuze toevoer een nieuw stationair niveau, maar ook het hartminuutvolume en de aortadruk. De centraal veneuze druk (P_{cv}) is verhoogd en de veneuze toevoer ($\dot{Q}_v$), het hartminuutvolume ($\dot{Q}_s$) en de aortadruk (P_{ao}) zijn verlaagd. Het doel van dit onderzoek was om de gemiddelde systemische vullingsdruk (P_{sf}) te schatten uit de afname in de aortadruk (P_{ao}) bij toenemende centraal veneuze druk, in een serie van zeven IPPs.

Voor de veneuze toevoer geldt de relatie van Guyton: $\dot{Q}_v = (P_{sf} - P_{cv})/R_{sd}$ (Vgl.1), waarin R_{sd} de weerstand is, zoals gedefinieerd in Hoofdstuk 1. Voor de instroom in de systeemcirculatie kunnen we schrijven: $\dot{Q}_s = (P_{ao} - P_{sf})/R_{su}$, waarin R_{su} de stromings-weerstand is, stroomopwaarts van de plaatsen in de circulatie waar de bloeddruk gelijk is aan P_{sf}. De instroom ($\dot{Q}_s$) en de uitstroom ($\dot{Q}_v$) van de systeemcirculatie zijn gelijk voor een stationaire toestand, zoals tijdens de pauze van een IPP. Hierdoor kunnen we een relatie tussen de aortadruk en de centraal veneuze druk afleiden:

$$(Vgl.2) \qquad P_{ao} = P_{sf} \cdot (1 + \frac{R_{su}}{R_{sd}}) - \frac{R_{su}}{R_{sd}} \cdot P_{cv}$$

Volgens deze relatie neemt P_{ao} inderdaad af met een toenemende P_{cv}. Deze relatie is lineair indien R_{su}/R_{sd}, de verhouding van de weerstanden, constant is. P_{sf} kan dan bepaald worden uit een lineaire regressie tussen de aortadruk en de centraal veneuze druk.

In een serie van zeven IPPs op insufflatievolumes van 0 tot 30 ml/kg, zoals beschreven in Hoofdstuk 1, werden de veneuze toevoer, de aortadruk en de centraal veneuze druk bepaald tijdens het stationaire deel van de pauze van de IPPs. De waarden van P_{sf} verkregen uit de lineaire regressie tussen de aortadruk en de centraal veneuze druk, zijn in dit onderzoek vergeleken met de waarden van de referentiemethode (Hoofdstuk 1). In tien biggen van gemiddeld 10 kg was in 22 series IPPs het gemiddelde verschil in P_{sf} waarden 0.03 mmHg met een standaarddeviatie (SD) van 1.16 mmHg. Onze conclusie was dat de P_{sf} even nauwkeurig bepaald kan worden uit de relatie tussen aortadruk en centraal veneuze druk (Vgl.2) als uit die van de veneuze toevoer en de centraal veneuze druk (Vgl.1). Het voordeel van deze nieuwe methode is dat er geen slag-op-slag bepaling van de veneuze toevoer nodig is.

HOOFDSTUK 3

De lineaire relatie van Guyton tussen de veneuze toevoer en de centraal veneuze druk (Vgl.1) geldt alleen voor stationaire toestanden. Tijdens dynamische veranderingen van de centraal veneuze druk, zoals gedurende de insufflatie van de longen bij beademing, is de veneuze toevoer lager dan tijdens een stationaire toestand, voor eenzelfde niveau van de centraal veneuze druk. Dit wordt veroorzaakt door de opvulling van het veneuze vaatbed, als gevolg van de stijgende veneuze bloeddruk. Hierdoor wordt P_{sf} onderschat wanneer deze bepaald wordt met behulp van een lineaire regressie tussen de veneuze toevoer en de centraal veneuze druk tijdens de insufflatie van de longen. De extra vermindering van de veneuze toevoer door de opvulling van het veneuze systeem wordt relatief minder naarmate de insufflatie langzamer wordt gedaan. We stelden de hypothese dat, indien de

insufflatietijd lang genoeg is, het mogelijk is P_{sf} te schatten uit de relatie tussen de veneuze toevoer en de centraal veneuze druk tijdens een enkele insufflatie.

We bestudeerden de invloed van de insufflatietijd op de schatting van P_{sf} uit de relatie tussen de veneuze toevoer en de centraal veneuze druk tijdens de insufflatie van de longen. In acht beademde biggen van 10.3 (0.8) kg (gemiddelde en SD) hebben we gebruik gemaakt van ventilatieprocedures met een langzame insufflatie (Slow Inflation Procedure → SIP), opgelegd door onze computergestuurde ventilator. De insufflatietijden waren 2.4, 4.8, 7.2, 9.6 en 12.0 s op insufflatievolumes van 15 en 30 ml/kg. De waarden van P_{sf} die uit de SIP werden verkregen (P_{sf}{SIP}), werden vergeleken met het gemiddelde van twee waarden bepaald met de referentiemethode (P_{sf}{IPP}). De lineaire regressie tijdens de insufflatie leverde bij alle insufflatietijden een onderschatting op van P_{sf}{SIP} ten opzichte van P_{sf}{IPP}. Het verschil tussen de waarden van P_{sf}{SIP} en de referentiewaarden P_{sf}{IPP} werd kleiner naarmate de insufflatietijd toenam. Een exponentiële functie, met de insufflatietijd als variabele, werd gepast door de verschillen tussen de waarden van P_{sf}{SIP} en P_{sf}{IPP}. Uit deze functie werd afgeleid dat een insufflatietijd van ongeveer 18 s in 95 % van de biggen voldoende is om waarden van P_{sf}{SIP} te verkrijgen die minder dan 0.75 mmHg verschillen van de referentiewaarden. Het voordeel van de SIP-methode boven de referentiemethode is dat de P_{sf}{SIP} bepaald kan worden met behulp van een enkele ventilatieprocedure. Maar, door de tamelijk lange insufflatietijd, noodzakelijk voor een betrouwbare schatting, is de methode mogelijk alleen geschikt wanneer de neuro-humorale regelmechanismen onderdrukt zijn, zoals onder omstandigheden van intensive care en tijdens operaties.

HOOFDSTUK 4

Een nadeel van de methoden om P_{sf} te schatten op basis van zeven IPPs (referentiemethode en de methode uit Hoofdstuk 2) is dat de totale tijd voor een P_{sf}-bepaling ongeveer 45 min bedraagt. Zo'n periode zou te lang kunnen zijn voor toepassing in patiënten, doordat de bepaling over de gehele meetperiode een stabiele haemodynamische toestand vereist. De methode op basis van een langzame insufflatie (Hoofdstuk 3) heeft als nadeel dat de

benodigde insufflatietijd lang is, ongeveer 18 s. Om deze redenen zochten we naar een nieuwe methode om P_{sf} te schatten uit een enkele IPP. In zeven beademde biggen werd de centraal veneuze druk gemeten en de veneuze toevoer bepaald. Deze gegevens werden vervolgens ingevoerd in een model van het veneuze systeem. Het model bestond uit twee stromingsweerstanden, een compliantie en P_{sf} als constante drijvende druk voor de veneuze toevoer. Met dit model werd de veneuze toevoer als functie van de gemeten centraal veneuze druk gesimuleerd. Door de parameters aan te passen kon het verschil tussen de gesimuleerde veneuze toevoer en de in het experiment bepaalde waarden ("gemeten" veneuze toevoer) geminimaliseerd worden. De waarde van P_{sf} bij het minimale verschil tussen gesimuleerde en gemeten veneuze toevoer leverde een modelschatting van P_{sf} op. De referentiewaarde van P_{sf} werd bepaald uit de referentiemethode, gebaseerd op de zeven IPPs.

In zeven biggen zijn steeds twee series van zeven IPPs uitgevoerd, zodat in totaal 14 referentiewaarden van P_{sf} werden verkregen. Een modelschatting van P_{sf} werd uit ieder van deze IPPs afzonderlijk verkregen. De referentiewaarden van P_{sf} varieerden van 9.9 tot 15.0 mmHg, met een gemiddelde van 11.9 (SD:1.9) mmHg. De modelschattingen van P_{sf} uit de afzonderlijke IPPs van de drie hoogste insufflatievolumes, 20, 25 en 30 ml/kg, verschilden respectievelijk 0.6, 0.4 en 0.1 mmHg van de referentiewaarden, met SD = 0.9 mmHg. Deze verschillen waren niet significant. Bij de lagere insufflatievolumes waren de verschillen gemiddeld eveneens niet significant, maar de standaarddeviaties waren 2.5 mmHg of meer, zodat deze P_{sf} schattingen onbetrouwbaar werden geacht. Met deze methode kan P_{sf} betrouwbaar worden geschat met behulp van een computermodel en een enkele IPP met een insufflatievolume van 20 ml/kg of meer.

HOOFDSTUK 5

De druk in de circulatie die tijdens stationaire toestanden gelijk is aan P_{sf} noemen we P_{Psf}. Voor een gegeven haemodynamische toestand hebben we in Hoofdstuk 2 aangetoond dat de stromingsweerstanden stroomopwaarts en -afwaarts van P_{Psf} (R_{su} en R_{sd}) constant zijn voor verschillende stationaire niveaus van veneuze toevoer en centraal veneuze druk. Het

is evenwel niet bekend of P_{Psf}, R_{su} en R_{sd} ook constant zijn gedurende dynamische veranderingen van druk en stroomsterkte, zoals tijdens de beademing. We hebben onderzocht in welke mate de veneuze drukken veranderen tijdens dynamische veranderingen van de centraal veneuze druk. Omdat de druk die gelijk is aan P_{Psf} heerst in de kleine venen of de venulen, is het niet mogelijk deze druk te meten. Daarom hebben we een model gebruikt, bestaande uit drie stromingsweerstanden (R_a, R_x, R_v) en twee veneuze complianties (C_x, C_v). De veneuze toevoer werd door het model gesimuleerd en vergeleken met de gemeten waarden tijdens een IPP. De geschatte waarden van de parameters (R_a, R_x, R_v, C_x, C_v) waren die waarden waarbij het verschil tussen de simulatie en de meting minimaal was. Referentiewaarden voor P_{sf} en R_{sd} werden bepaald met de gebruikelijke referentiemethode, gebaseerd op de zeven IPPs.

In vijf biggen werden steeds twee series van zeven IPPs uitgevoerd. De simulaties werden alleen gedaan met de IPPs met een insufflatievolume van 20 tot 30 ml/kg. De geschatte waarden van de veneuze weerstanden ($R_{v1}+R_{v2}$) was significant kleiner dan R_{sd}: 0.44 mmHg·s·ml^{-1} versus 0.54 mmHg·s·ml^{-1}, $p \leq 0.02$. Daardoor was de druk P_{v1} over de meest stroomopwaartse compliantie iets kleiner dan P_{Psf}. Omdat de toename in P_{v1} tijdens de IPPs kleiner was dan de toename van P_{cv} (0.9 versus 4.4 mmHg), extrapoleerden we naar een druk in de circulatie die constant bleef. De druk die op deze manier verkregen werd bleek gelijk te zijn aan de referentiewaarde van P_{sf}. In voorgaande hoofdstukken (3 en 4) hebben we een model gebruikt met twee constante weerstanden, een compliantie en P_{sf} als constante, drijvende druk voor de veneuze toevoer. Dit model lijkt te voldoen om veranderingen in de veneuze toevoer, als gevolg van de beademing, te simuleren.

HOOFDSTUK 6

De compliantie van de systeemcirculatie is, voor zover wij weten, tot nu toe niet bepaald in de intacte circulatie. Bepalingen van de compliantie werden gedaan door de circulatie volledig stil te leggen, of door een omleiding met een pomp langs de rechter harthelft aan te leggen. In dit hoofdstuk werden twee methoden onderzocht om de compliantie te

schatten in de intacte circulatie met behulp van twee modellen en een infusie van bloed tijdens de pauze van een IPP.

Methode A. Met het eerste model werd het veneuze deel van de circulatie, stroomafwaarts van P_{Psf} gesimuleerd (Hoofdstuk 4). Met dit model kon P_{sf} worden geschat tijdens een normale IPP. In deze experimenten hebben we naast een gewone IPP, met een insufflatievolume van 30 ml/kg, ook eenzelfde IPP uitgevoerd waarin we tijdens de pauze bloed infundeerden via een canule in de rechter arteria carotis. Deze infusie werd zodanig uitgevoerd dat de arteriële bloeddruk ongeveer constant bleef. Tijdens deze IPP met infusie werd het drukverloop van P_{Psf} gesimuleerd. Uit de gesimuleerde toename van P_{Psf} en de hoeveelheid geïnfundeerd bloed werd de compliantie geschat.

Methode B. Het tweede model representeerde de gehele systeemcirculatie en bestond uit drie weerstanden en twee veneuze complianties, zoals het model in Hoofdstuk 5. In dat hoofdstuk bleek dat de complianties van dit model niet geschat kunnen worden tijdens een normale IPP, doordat de variaties in de meer stroomopwaartse veneuze drukken te klein waren. De infusie van bloed tijdens de pauze van de IPP diende om veranderingen in die veneuze drukken teweeg te brengen, zodat de complianties wel geschat konden worden. Met dit tweede model volgde de schatting van de veneuze compliantie direct uit de aanpassing van de gesimuleerde veneuze toevoer aan de gemeten waarden tijdens de IPP met infusie. Deze schatting van de veneuze compliantie werd tevens gezien als schatting van de compliantie van de gehele systeemcirculatie.

De experimenten werden uitgevoerd in acht biggen van gemiddeld 10.8 (0.6) kg. Beide methoden werden gebruikt in alle experimenten en vergeleken. Het protocol werd in enkele biggen herhaald tijdens hypovolaemie. De compliantie zoals bepaald met methode A, was gemiddeld (SD): 1.53 (0.23) $ml \cdot mmHg^{-1} \cdot kg^{-1}$. Tijdens hypovolaemie was deze waarde niet significant verschillend: 1.54 (0.41) $ml \cdot mmHg^{-1} \cdot kg^{-1}$. De compliantie geschat met methode B, leverde significant lagere waarden op. Voor alle bepalingen samen, onder normo- en hypovolaemische condities, was het verschil gemiddeld 0.16 $ml \cdot mmHg^{-1} \cdot kg^{-1}$ ($p=0.01$). Voor normo- en hypovolaemie apart waren de waarden met methode B respectievelijk: 1.46 (0.27) $ml \cdot mmHg^{-1} \cdot kg^{-1}$ en 1.31 (0.41) $ml \cdot mmHg^{-1} \cdot kg^{-1}$. De gevonden

waarden kwamen overeen met de literatuur. De conclusie was dat de compliantie van de systeemcirculatie geschat kan worden in de intacte circulatie, met behulp van de twee modellen en een infusie van bloed tijdens een IPP.

HOOFDSTUK 7

Theoretisch is het niet noodzakelijk om een IPP te gebruiken om de P_{sf} te schatten voor de methode beschreven in Hoofdstuk 4. Ook andere ademmanoeuvres komen in aanmerking om veranderingen in de centraal veneuze druk en de veneuze toevoer te genereren. Uit modelsimulaties bleek dat de IPP één van de best bruikbare manoeuvres is om de P_{sf} te schatten.

Gedurende dit onderzoek zijn een paar foutenbronnen onderbelicht. Voor de veneuze toevoer hebben we steeds als substituut de uitstroom van het rechter ventrikel genomen. Onder stationaire condities zijn deze gelijk. Tijdens dynamische veranderingen van de centraal veneuze druk kan er mogelijk een klein verschil optreden door volume-veranderingen van het rechter ventrikel. Hierdoor kan er een verschil ontstaan tussen de uitstroom van het rechter ventrikel en de veneuze toevoer. Het is echter niet mogelijk de veneuze toevoer direct te bepalen. Een tweede foutenbron kan de invloed van de verplaatsing van bloed uit de longcirculatie naar de systeemcirculatie zijn. Deze verplaatsing van bloed, als gevolg van de beademing, kan een fout in de P_{sf} schatting veroorzaken van 1 tot 3 mmHg.

Tot slot werd aangegeven dat een bepaling van alleen de P_{sf} niet voldoende is om veranderingen in de haemodynamische conditie van een patiënt of een proefdier te beschrijven. Naast een bepaling van P_{sf} zijn ook bepalingen van de weerstanden R_{su} en R_{sd} en de compliantie nodig om veranderingen in de bloedcirculatie te beschrijven.

List of abbreviations

BW	Body weight
C	Compliance
C_a	Arterial compliance
C_T	Total vascular compliance
C_v	Venous compliance
cmH_2O	Centimeters water, unit of pressure
D_q	Error between simulated and measured variable
ECG	Electro cardiogram
h	hour, unit of time
IPP	Inspiratory pause procedure
kg	Kilograms, unit of mass
mg	Milligrams, unit of mass
ml	Milliliters, unit of volume
mmHg	Millimeters mercury, unit of pressure
P	Pressure
P_{ao}	Aortic pressure
P_{CO_2}	Partial pressure of carbon dioxide
P_{cv}	Central venous pressure
P_{pa}	Pulmonary artery pressure
P_{sf}	Mean systemic filling pressure
P_{Psf}	The pressure in the circulation that is equal to the mean systemic filling pressure
P_{tm}	Transmural pressure
PEEP	Positive end-expiratory pressure
Q	Blood volume
Q_0	Unstressed blood volume
$\dot{Q}$	Flow
$\dot{Q}_v$	Venous return
R	Hemodynamic flow resistance
R_s	Total systemic flow resistance
R_{sd}	Resistance downstream from P_{Psf}
R_{su}	Resistance upstream from P_{Psf}
s	Seconds, unit of time
SD	Standard deviation
SIP	Slow inflation procedure
t	Time
T_i	Inflation time
V_T	Tidal volume

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