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ORIGINAL ARTICLE

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Effects of endotoxin infusion on mean systemic filling pressure and flow resistance to venous return

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Abstract Mean systemic filling pressure (P_{sf}) is an indicator of the filling state of the systemic circulation. Cardiac output (Q') is related linearly to the difference between P_{sf} and central venous pressure (P_{cv}), according to: $Q' = (P_{sf} - P_{cv})/R_{sf}$, where R_{sf} is the flow resistance downstream from the sites where blood pressure is equal to P_{sf}. In 16 anaesthetized pigs we evaluated P_{sf}, R_{sf} and Q' during baseline conditions, continuous endotoxin infusion and after subsequent fluid loading. P_{sf} and R_{sf} were determined from simultaneous measurements of Q' and P_{cv} at seven levels of lung inflation. The following results were obtained. P_{sf} was 8.1 ± 1.8 mm Hg (mean ± SD) during baseline conditions, increased after endotoxin infusion to 9.9 ± 3.2 mm Hg ($P = 0.04$) and remained the same after infusion of 18 ml · kg^{-1} of Ringer's lactate. R_{sf} increased from 0.34 ± 0.07 to 0.80 ± 0.34 mm Hg · ml^{-1} · s by endotoxin and decreased after fluid infusion to 0.58 ± 0.14. Q' changed inversely proportional to R_{sf} ($P = 0.001$). R_{sf} changes were highly correlated with the changes in total systemic flow resistance (R_s) ($P < 0.001$). Endotoxin caused haemoconcentration and a decrease in plasma volume. The stability of P_{sf} during endotoxin infusion and after volume loading indicate that the stressed volume was well maintained and changes in blood volume are compensated by changes in non-stressed volume. The increase in R_{sf} can be attributed to arteriolar vasoconstriction, venous vasoconstriction and haemoconcentration.

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Introduction

Haemodynamic changes in sepsis are characterized by increases [1, 3] as well as decreases [4] in vascular tone in the pulmonary and systemic circulations depending on the species and the stage of disease. These changes can be related to the clinical pictures of severe infection with either high cardiac output (Q') and low systemic blood pressure or normal to low Q' and signs of severe peripheral vaso constriction. We supposed that during both clinical pictures the filling volume of the circulation is inadequate to maintain a normal pressure and Q'. The relationship of vascular tone to the stressed filling volume is best expressed by the mean systemic filling pressure (P_{sf}) [7, 8, 18, 21]. The P_{sf} is the pressure that exists in the whole systemic circulation when flow is zero. In the steady state Q' is related linearly to the difference between P_{sf} and the pressure in the central veins (P_{cv}), [9, 21] according to:

$$Q' = (P_{sf} - P_{cv})/R_{sf} \quad (1)$$

where R_{sf} is the flow resistance between the sites in the circulation where pressure is equal to P_{sf} and the right atrium. Changes in myocardial function will affect venous return through changes in P_{cv} due to a change in transmural P_{cv} if intrathoracic pressure is constant. The balance between venous return and cardiac function [9] has become general knowledge and can be found in many textbooks [20] and review papers.

The aim of this study was to determine P_{sf}, R_{sf}, P_{cv} and Q' in the intact, anaesthetized pig before and during continuous endotoxin infusion and subsequent volume restoration and to analyse the characteristic changes in the circulatory system.

Materials and methods

Surgical procedures

All experiments were performed in accordance with the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication No 85–23, Revised 1985) and under the regulations of the Animal Care Committee of the Erasmus University, Rotterdam, The Netherlands.

A total of 16 Yorkshire pigs [9.7 ± 1.2 kg body weight (BW), 8–10 weeks of age] were anaesthetized with 30 mg · kg^{-1} pentobarbitone sodium i.p. (Abbott) followed by a continuous infusion of 7.5 mg · kg^{-1} · h^{-1} i.v. The animals were placed supine on a thermo-controlled operating table. After tracheostomy the animals were ventilated at a rate of 10 breaths per min with use of a computer-controlled ventilator [15]. The inflation-to-expiration ratio was 2.4:3.6. The tidal volume was adjusted to maintain an arterial CO_2 partial pressure (P_{a,CO_2}) of 35–42 mm Hg. Positive end-expiratory pressure was maintained at 3 cm H_2O and the fractional O_2 concentration in inspired air (F_IO_2) was 0.4.

A polyethylene catheter was inserted via the carotid artery to monitor aortic pressure (P_{ao}) and to sample arterial blood. Three catheters were inserted via the right external jugular vein: (1) a 5Fr Swan-Ganz thermodilution catheter into the pulmonary artery to monitor blood temperature, pulmonary artery pressure and to sample mixed venous blood, (2) a double-walled catheter into the right atrium for injection of cold saline and (3) a modified 7Fr four lumen catheter near the entrance of the right atrium for the measurement of P_{cv} and for infusions. Blood loss during the operation was minimal. Blood loss due to sampling was 5 ml · h^{-1} and was replaced by saline. Surgery was completed in 55–100 min. The average total fluid administration for all infusions and thermodilution measurements was 40 ml · h^{-1}. After surgery, muscle relaxation was induced with 0.1 mg · kg^{-1} D-tubocurarine intravenously and maintained with a continuous infusion of 0.2 mg · kg^{-1} · h^{-1}.

Measurements and estimations

The electrocardiogram (ECG), P_{ao}, pulmonary artery pressure (P_{pa}), P_{cv} and the blood temperature were continuously recorded on a chart recorder (Hewlett Packard, type HP7758A) and at specific times sampled by a computer (250 Hz). The heart rate was calculated from R-R intervals of the ECG. Blood pressures were calculated beat-to-beat. These mean values were averaged over a ventilatory cycle as well as during parts of an inspiratory pause beginning 1.5 s after peak inflation. The zero level of the pressures was set at the level of the ventral side of the trachea near the manubrium. Q' was estimated using two methods: the thermodilution method (Q'_{td}) and the direct Fick method for oxygen (Q'_F) [13]. The latter was used to check the computation constant for Q'_{td} during each experimental condition. Q'_{td} was estimated as the mean of four thermodilution measurements at phases 0 (start of inflation), 25, 50 and 75% of the ventilatory cycle [13]. At intervals of 1 min, 2.5 ml saline at room temperature was automatically injected into the right atrium after a trigger signal from the ventilator. The computation of Q'_{td} was based on the Stewart-Hamilton equation. To estimate Q'_F, O_2 consumption was obtained from ventilatory rate and volume as given by the ventilator and the difference between FIO_2 and the expired O_2 concentration (FIO_2). A correction for the difference between inspired and expired volume was made by assuming no volume change of N_2. The ventilator was calibrated with a spirometer. Respiratory gases were analysed with a mass spectrometer (Perkin-Elmer, Model MGA 1100, Pomona, California). Arterial and mixed venous blood samples were analysed in a blood gas analyzer (Radiometer, type ABL3, Copenhagen). O_2 saturation and haemoglobin (Hb) were measured in a haemoximeter (Radiometer, type OSM2, Copenhagen, Denmark).

P_{sf} determination

Mean P_{sf} was estimated from a series of inspiratory pause procedures (IPP) [24]. An IPP consisted of 2.4 s inflation, 7.2 s inspiratory pause (IP) and 3.6 s expiration. The series of IPPs consisted in all experiments of seven tidal volumes which were applied at 5-min intervals in the order of 10, 30, 0, 5, 25, 15 and 20 ml · kg^{-1}. Then, 1 s after peak inflation, saline was injected and a thermodilution curve recorded. During an IPP the tail of the thermodilution curve often was beyond the end of the inspiratory pause whereby the sudden increase in blood flow during the subsequent expiration caused a decline in the tail of the thermodilution curve. For that reason a model of a log-normal distribution was fitted to the undisturbed part of a dilution curve and extrapolated to obtain an undisturbed tail of the curve [14].

The seven Q'_{td} versus P_{cv} values yielded a linear relationship with a negative slope. The value of P_{sf} was determined from this relationship as that P_{cv} corresponding to the extrapolated value of $Q'_{td} = 0$. An example is shown in Fig. 1. The validity of this extrapolation is based on previous experiments [24], in which venous return was assumed to be equal to right ventricular Q' during an IPP, because P_{cv} and right ventricular Q' were constant. The R_{sf} was estimated from the inverse of the slope of the regression line. The total systemic vascular resistance (R_s) was calculated from

$$R_s = (P_{ao} - P_{cv}) / Q'_{td} \quad (2)$$

The duration of the IP (7.2 s) was short enough to avoid effects of circulatory counterregulation during the procedure [24], thus, for example, the heart rate remained constant.

Experimental Protocol

After surgery the animals were allowed to stabilize over 45–60 min. The 16 animals were divided into two groups. A control group ($n = 3$) was used to determine whether the preparation was adequately stable. These animals received a saline infusion for 6 h

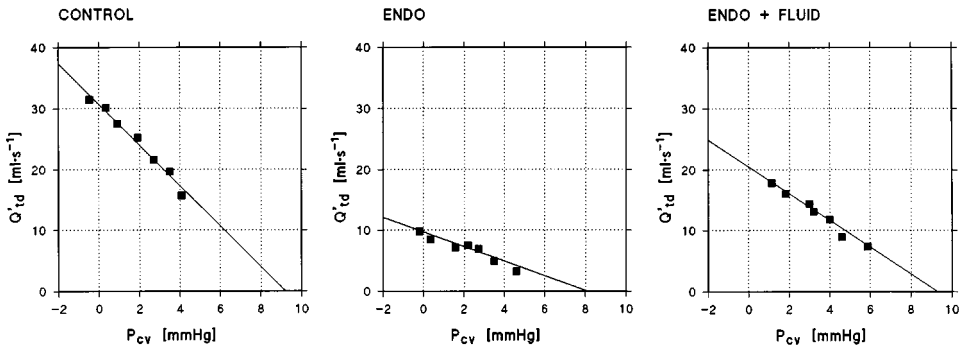


Fig. 1 Plots of cardiac output (Q'_{td}) vs central venous pressure (P_{cv}) from experiment 7 during control (*CONTROL*), after 4 h endotoxin (*ENDO*) and after fluid infusion (*ENDO+FLUID*). $P_{sf} = P_{cv}$ at $Q'_{td} = 0$

instead of endotoxin. P_{sf} was determined during the periods corresponding to those in the endotoxin group. An experimental group ($n = 13$) received i.v. endotoxin (*E. coli* O55:B5, Mallinkrodt, St. Louis, Mo., USA) at 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for the 1st hour and 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 6 h after a baseline period of 1 h. This administration of endotoxin produced severe haemodynamic and respiratory impairment with an acceptable mortality compared with higher doses or bolus injections [16]. Three animals died at different stages of the endotoxin infusion before two IPP series could be completed and were withdrawn from further analysis. After 5 h of endotoxin infusion Ringer's lactate solution was infused to restore blood volume to control values. The volume to be infused was determined by assuming that the [Hb] serves as an intravascular marker, and that the amount of Hb in the vascular system during the experiment changes only due blood sampling [10]. The amount of infused fluid was 18 ± 4.5 ml/kg (mean ± SD). Three series of IPP's were carried out: during the baseline period after 4 h of endotoxin infusion and 15 min after subsequent volume infusion, while the endotoxin infusion was continued. Haemodynamic variables, blood gases and oxygen consumption were determined before and after each series of IPPs and averaged.

Statistics

Data are presented as mean ± SD. The three series of IPPs were analysed. Linear regressions were fitted using the least-squares method. The changes between the three experimental conditions were tested by repeated measures ANOVA (Systat, V. 5.0, MGLH 1992) and by a paired *t*-test to compare, first, baseline with endotoxin infusion and, second, endotoxin with endotoxin plus fluid replacement. We considered $P < 0.05$ to indicate a significant difference.

Results

Although a group of three animals is small, the results in the time control group were adequate to conclude that none of the measured and calculated variables changed significantly during the 7–8 h of the experiment (Table 1). The baseline values of the endotoxin group were similar to those of the control group (Table 2).

Table 1 Measured and estimated haemodynamic variables in the control group. Data are mean ± SD (*HR* heart rate, P_{ao} aortic pressure, P_{pa} pulmonary artery pressure, P_{cv} central venous pressure, Q'_{td} cardiac output measured by thermodilution, P_{sf} systemic filling pressure, R_{sf} resistance between P_{sf} and P_{cv}, R_s resistance of the systemic circulation, *Hb* haemoglobin)

time (min)	−60 to 0	240 to 300	340 to 400
n	3	3	3
HR (beats/min)	187 ± 28	179 ± 38	167 ± 77
P_{ao} (mm Hg)	111 ± 3	106 ± 9	111 ± 5
P_{pa} (mm Hg)	13.0 ± 1.8	13.2 ± 3.9	15.2 ± 0.2
P_{cv} (mm Hg)	0.33 ± 0.39	0.68 ± 0.27	0.57 ± 0.26
Q'_{td} ($ml \cdot s^{-1} \cdot kg^{-1}$)	2.57 ± 0.20	2.39 ± 0.15	2.35 ± 0.11
P_{sf} (mm Hg)	7.6 ± 1.0	9.1 ± 1.7	8.1 ± 1.6
R_{sf} (mm Hg $\cdot$ $ml^{-1} \cdot s$)	0.27 ± 0.07	0.31 ± 0.09	0.28 ± 0.10
R_s (mm Hg $\cdot$ $ml^{-1} \cdot s$)	4.2 ± 0.4	4.3 ± 0.6	4.6 ± 0.7
Hb (g/dl)	9.43 ± 1.05	9.71 ± 1.52	9.63 ± 1.57

Endotoxin

The reaction to continuous endotoxin infusion was biphasic (Fig. 2). During the first 15–30 min after the beginning of endotoxin infusion, mean P_{pa} for all animals increased from 9.3 ± 0.9 to 32 ± 8 mm Hg ($P < 0.0001$) and P_{cv} from −0.1 ± 0.8 to 2.2 ± 2.4 mm Hg ($P = 0.002$). These values were higher than those after 4 h of endotoxin infusion (Table 2). Concomitantly with the increases in P_{pa} and P_{cv}, Q'_{td} decreased by 20% but, 45–60 min after the beginning of endotoxin infusion Q'_{td} had increased, almost returning to the baseline level. Thereafter Q'_{td} decreased continuously until 180 min after the beginning of endotoxin infusion, after which heart rate, P_{ao}, P_{pa}, P_{cv} and Q'_{td} were stable for a further 2 h. During this stable period the effect of endotoxin on P_{sf} and R_{sf} was evaluated with a series of IPPs after 240 min of endotoxin infusion. After 240 min endotoxin infusion (Table 2) heart rate was 40% increased, P_{pa} and P_{cv} were significantly higher and Q' was 50% lower whereas P_{ao} did not change. Hb and the haematocrit (Hct) were increased by 30% whilst P_{sf} was higher in seven out of ten animals ($P = 0.046$). Total systemic pressure gradient ($P_{ao} - P_{cv}$) and venous pressure gradient ($P_{sf} - P_{cv}$) were unchanged. R_{sf} and R_s were more than doubled and correlated highly ($r = 0.96$, $P < 0.001$).

Endotoxin plus fluid

The most striking haemodynamic changes 30 min after the rapid administration of 18 ± 4.5 $ml \cdot kg^{-1}$ Ringer's lactate (Table 2) were a significant fall in heart rate of

Fig. 2 Haemodynamic profile during the whole observation period of all experiments, together with the protocol for infusion of endotoxin (*hatched*) and blood volume expansion by fluid infusion (*filled box*) at the bottom. *Vertical bars* are SD

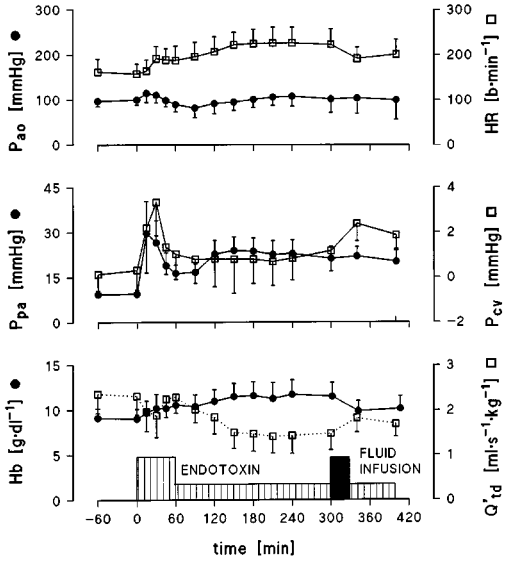


Table 2 Measured and estimated haemodynamic variables in the endotoxin group. Data presented as mean ± SD

time (min)	Baseline −60 to 0	Endotoxin 240 to 300	endotoxin plus fluid 340 to 400
n	10	10	6
HR (beats/min)	164 ± 26	229 ± 29	199 ± 35**#
P_{ao} (mm Hg)	96 ± 10	99 ± 24	94 ± 40
P_{pa} (mm Hg)	9.3 ± 0.9	22.7 ± 3.3	20.7 ± 3.0**
P_{cv} (mm Hg)	−0.1 ± 0.8	1.1 ± 0.9	2.3 ± 1.0*#
Q'_{td} (ml · s^{-1} · kg^{-1})	2.56 ± 0.39	1.27 ± 0.26	1.53 ± 0.24**#
P_{sf} (mm Hg)	8.1 ± 1.9	9.9 ± 3.2	10.1 ± 2.1*
R_{sf} (mm Hg · ml^{-1} · s)	0.34 ± 0.07	0.80 ± 0.34	0.58 ± 0.14*
R_s(mm Hg.ml^{-1}.s)	3.6 ± 0.7	7.5 ± 2.6	5.3 ± 5.3*#
Hb (g/dl)	8.9 ± 1.2	11.6 ± 1.5	9.7 ± 1.5**##

* $P < 0.05$, ** $P < 0.001$ (paired *t*-test) for comparison between baseline and endotoxin
# $P < 0.05$, ## $P < 0.001$ (paired *t*-test) for comparison between endotoxin and endotoxin plus fluid

19 ± 11 beats per min and an increase in P_{cv} of 1.0 ± 0.7 mm Hg. P_{ao} and P_{pa} were unchanged. The Q' increased in all animals 5–70% ($P = 0.03$). Hb fell significantly but remained above control values. We also measured Hct routinely. Because Hct changed in the same way as Hb concentration the data are not shown. There was no change in the Hb concentration during the series of IPPs ($P = 0.43$). Despite the fluid administration P_{sf} did not change. The venous pressure gradient decreased after fluid loading in all animals ($P = 0.05$) and the total systemic pressure gradient was unchanged. R_{sf} and R_s fell by 25%, but only R_s fell significantly ($P = 0.004$). The changes in R_{sf} and R_s were highly correlated ($r = 0.97$, $P < 0.001$).

Discussion

Relation to clinical sepsis

Clinical septic shock is clearly different from the effect of endotoxin in many species. The applied dose of endotoxin was at the upper limit [16] with an acceptable mortality of 3 out of 13. There were two potential reasons for the lack of a hyperdynamic state with vascular failure in our pigs, namely, too high a dose of endotoxin and the short time course of our experimental condition compared with the much longer periods of clinical sepsis. With respect to the first possibility, preliminary experiments with lower infusion rates of endotoxin infusion (1.0, 0.1 and 0.01 μm $kg^{-1}h^{-1}$ also failed to elicit a hyperdynamic state. Considering the second reason, it is possible that the return of Q'_{td} close to baseline after the phase of pulmonary hypertension (45–60 min of endotoxin infusion) is analogous to clinical sepsis. However, this situation lasts for only 30–45 min whereafter Q'_{td} decreases again, in contrast to clinical sepsis in which the vasoplegic state often lasts for several days. It is more likely that our experiments represent an early stage of endotoxaemia that is also well known in patients at the beginning of a severe infection.

Mean systemic filling pressure and "venous" flow resistance

Mean systemic filling pressure is a measure expressing the relation between the volume of the vessels and the volume of blood distending the vessels. The blood volume has been separated conceptually into an unstressed (Q_0) and a stressed (Q_s) volume [21] where Q_0 is the maximal volume of the vessel without stretching the vessel wall, i.e., without tension in the wall or pressure on the blood. It accounts for about 75% of the total blood volume [20]. Q_s represents the remaining 25%, necessary to generate a positive pressure within the blood vessels. P_{sf} would be the pressure existing in the whole systemic circulation if blood flow were zero and is the filling pressure of the systemic circulation. P_{sf} is thus a measure for the stressed blood volume. Adaptations to changes in blood volume involve mainly changes in the unstressed volume [18]. Since P_{sf}, P_{cv} and R_{sf} are essential factors in the control of cardiac output (Q') [9], we evaluated these parameters during the early phase of endotoxaemia.

Our method for extrapolating P_{sf} from seven pairs of P_{cv} and Q'_{td} values obtained from seven different levels of sustained inflation [24] has several advantages. This method allows the construction of Guyton-type venous return curves with the circulation intact, thus obviating the need for a right-heart bypass pump, an arteriovenous fistula or stopping the heart. In the present experiments we determined blood flow using the thermodilution method during the stationary phase of an IPP [14] so as to avoid an electromagnetic flow measurement and, therefore, thoracotomy. These venous return curves were straight lines with a mean correlation coefficient of 0.97 ± 0.02. The linearity of the fits was affected neither by the changes in the haemodynamic condition during endotoxin nor during endotoxin after fluid infusion. Our P_{sf} values during the baseline conditions were in the range (7.6–10.7 mm Hg) found for the intact circulation during normovolaemic conditions [2, 5, 11, 12, 17, 23–25]. P_{sf} increased by 1.7 ± 2.3 mm Hg after endotoxin and did not further

change after volume expansion. The fact that Hb was significantly lower after fluid infusion and remained constant during the following hour required for a series of IPPs indicates that the infusion of Ringer's lactate resulted in an effective blood volume expansion, which was surprising because one would expect a gradual increase in Hb concentration again [18]. It might be possible that this phenomenon was similar to the observation of a constant cardiac output for many hours after volume loading to recover cardiac output which had been decreased by application of positive end-expiratory pressure during mechanical ventilation [19]. The recovered cardiac output remained below its baseline value. Perhaps therefore no counteracting control mechanisms were activated.

The changes in [Hb] indicate that changes in blood volume occurred. [Hb] increased during the 4 h of endotoxin infusion. No blood was given during the experiments. The total amount of Hb in the animals decreased only slightly due to blood sampling. Two reasons for the increase in [Hb] can be considered, namely, haemoconcentration by loss of intravascular fluid and release of blood cells from body stores. The loss of intravascular fluid cannot be estimated accurately. If; however, the total amount of Hb remained approximately constant and the increase in [Hb] were due to a loss of intravascular fluid, the effective circulating blood volume must have decreased on average by about 23%, a value consistent with that found in other experiments in which endotoxin was given and blood volume measured [22]. We used this estimate, together with the assumption of a piglet blood volume of 80 ml/kg, to estimate the fluid requirement after 5 h of endotoxin infusion. The mean volume of fluid was 18 ml/kg with a broad range (11–26 ml/kg) according to the individual haemoglobin changes. No significant changes in [Hb] occurred during the series of IPPs after the volume expansion. We thus assumed that blood volume remained constant for the period of the IPPs.

Model analyses

In the non-controlled circulation an increase in blood volume will be reflected by an increase in P_{sf} [7, 18]. In our experiments, in which control mechanisms were not specifically eliminated, we found no change in P_{sf} after volume expansion during endotoxin infusion.

We will consider first the slight, but significant, increase in P_{sf} despite reduced blood volume during endotoxin compared with baseline. Despite this slight increase in P_{sf}, Q'_{td} was decreased to 50% of the baseline values. The rise in P_{cv} was about the same as the rise in P_{sf}, implying no change in the venous pressure gradient. The increase in R_{sf} was thus inversely proportional to the fall in cardiac output (eqn.1) and proportional to the rise in R_s. An increase in R_{sf} may be caused by (1) an increased length of the vascular bed between the sites in the circulation where pressure is equal to P_{sf} and the right atrium, (2) a decreased cross-section of this vascular bed, (3) increased blood viscosity the blood or (4) a combination of these reasons.

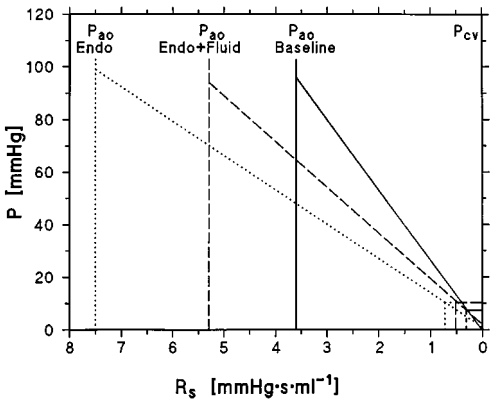
The changes in P_{ao} and P_{cv}, Q' and R_s are illustrated schematically in Fig. 3, in which vascular flow resistance is projected linearly onto the x-axis. We have used this graphical model previously to analyse differences between stationary conditions in the circulation [24]. The three conditions are illustrated as follows:

1. Baseline between the perpendicular, P_{ao}-baseline and the right perpendicular, where P_{cv} is plotted, during baseline conditions,
2. Endotoxin between the perpendicular, P_{ao}-endo, and the P_{cv} axis at the right, after 4 h endotoxin infusion, and
3. Endotoxin plus volume expansion between the perpendicular P_{ao}-endo + fluid, and the P_{cv} axis, 15 min after fluid loading.

The numeric data for mean P_{ao} and P_{cv} are taken from Table 2 to plot the pressure values on the vertical lines. The values of flow resistances were found from the differences between mean P_{ao} and mean P_{cv} pressure divided by mean Q'. These resistance values are hardly different from the values of R_s calculated from the mean of the individual data. The lines connecting P_{ao} and P_{cv} represent the pressure gradient (ΔP) over R_s, so that the slopes of these lines represent Q' ($Q'_{td} = \Delta P/R$).

Starting at baseline we observed a large increase in R_s after 4 h endotoxin infusion, causing an enlargement of the x-axis and a decrease in flow (slope of the pressure gradient). During baseline P_{sf} was 8 mm Hg and during endotoxin 10 mm Hg. If the P_{sf}

Fig. 3 Conceptual model of the systemic circulation. The x-axis represents the linear projection of vascular flow resistance (R_s) between aortic valves and right atrium [15]. In this projection the arterioles represent about 55% of this axis, whereas the aorta takes 2% and the remaining arterial system about 15% of the axis. On the y-axis at the right central venous pressure (P_{cv}) is plotted and on the remaining y-axis aortic pressure (P_{ao}). Further explanation is given in the text



value is indicated on the pressure gradient line the flow resistance (R_{sf}) between the sites where pressure is equal to P_{sf} and the right atrium (P_{cv}) is found. During endotoxin infusion the P_{ao}-P_{cv} pressure difference was approximately constant and Q' decreased substantially. These data show that R_s increased compared with control. The increase in R_s caused an upstream shift of the blood pressure equal to P_{sf} on the flow resistance axis. If such a shift were to be caused solely by an increase in arteriolar flow resistance, then the shift of the pressure equal to P_{sf} would also be an anatomical upstream shift. Guyton et al. [7] have indicated already an increase in flow resistance downstream from the sites were pressure is equal to P_{sf} due to an increase in R_s. However, we cannot exclude some constriction of the venous downstream vessels which would increase R_{sf}. This possibility is supported by the fact that endotoxin caused a rise in P_{sf} while the blood volume was decreased, which we attribute to a decreased non-stressed volume of the systemic circulation including undoubtedly the venous system. Such vasoconstriction will increase venous flow resistance also. Furthermore, the observed haemoconcentration also will cause an increase in blood viscosity and, therefore, flow resistance. We have estimated this increase to be less than 8% [6]. So, we concluded that the three reasons for a changes in R_{sf} by endotoxin infusion mentioned above will have been involved.

After fluid loading Q' increased again, while the P_{ao}-P_{cv} pressure difference was the same and P_{cv} increased. Therefore, the rise in Q' was attributed to a decrease in R_s causing an increased venous return and higher cardiac filling pressure. Thus although the slope of the pressure gradient was steeper than that after endotoxin, fluid loading did not return Q' fully to its control value and P_{sf} remained at about 10 mm Hg. We therefore conclude that vasodilation of the capacitance vessels leads to an increase in the non-stressed volume of the vascular system. The steeper slope compared with that during endotoxin infusion, means that the same P_{sf} is found on the pressure gradient at a smaller R_{sf}. This decrease can be explained again with all three mechanisms mentioned above. A decrease in arteriolar flow resistance would cause a decrease of the flow resistance downstream of the blood pressure equal to P_{sf}, which explains the fall in R_{sf}. Again we suppose that the decrease in blood viscosity by haemodilution contributes slightly to the decrease in R_{sf} proportional to the fall in R_s.

In summary, the stability of the P_{sf} during endotoxin infusion and after volume loading lead us to conclude that the stressed volume is maintained and that changes in blood volume are compensated by changes in the non-stressed volume of the circulatory system. Q' was reduced to 50% of baseline value due to an increased total vascular resistance, which coincided with a proportional increase in flow resistance, R_{sf}, between the sites at which blood pressure is equal to P_{sf} and the right atrium. This rise in flow resistance can be accounted for by (1) an upstream shift of the blood pressure equal to P_{sf} due to arteriolar vasoconstriction, (2) venous vasoconstriction and (3) a slight increase in blood viscosity. These changes are reversed partially by volume loading, attributable to the opposite behaviour of the same mechanisms.

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