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# Systemic filling pressure in the intact circulation determined with a slow inflation procedure

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**Abstract** In eight mechanically ventilated, anaesthetized pigs weighing 10.3 ± 0.8 kg (mean ± 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 underestimated $P_{sf}$ compared with 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 neurohumoral control mechanisms are suppressed as during intensive care and anaesthesia.

**Key words** Venous return · Central venous pressure · Inspiratory pause procedures · Venous capacity · Venous resistance · Mechanical ventilation

## Introduction

During stationary conditions venous return ($\dot{Q}_v$) varies linearly with central venous pressure ($P_{cv}$) according to

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

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where a and b are constants [3, 4]. According to Hagen-Poiseuille's law, this can also be written as

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

where $R_{sd}$ is the flow resistance between the sites in the circulation where the blood pressure is equal to the systemic filling pressure ($P_{sf}$) on the one hand, and the entrance of the central veins into the right atrium ($P_{cv}$) on the other [2–5, 9]. Equations 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 $P_{sf}$, 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 $P_{cv}$ the lung was inflated to seven different tidal volumes ($V_T$). 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 $\dot{Q}_v$ to mechanical ventilation and IPPs in pigs [8]. During inflation, $\dot{Q}_v$ decreases and, in the first 2 s of an inspiratory pause, flow increases again towards a new stationary level, lower than the level at end-expiration. In Fig. 1, an analogue model of this is presented, in which $\dot{Q}_v$ is determined by:

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

where

$\dot{Q}_{in} = (P_{sf} - P_v)/R_1$, $\dot{Q}_v = (P_v - P_{cv})/R_2$, and

$\dot{Q}_c = C_v\ dP_v/dt$

where $\dot{Q}_{in}$ is the inflow into the venous system $\dot{Q}_c$ the inflow into the venous capacitance $C_v$, $P_v$ the venous pressure and $R_1$ and $R_2$ segmental flow resistances. During stationary conditions the pressures, averaged

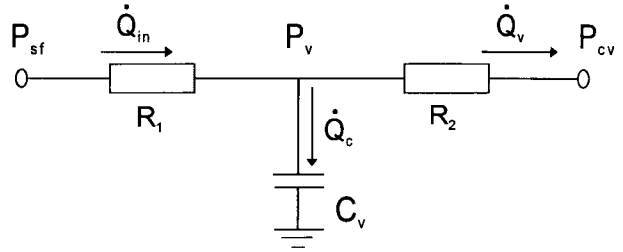


**Fig. 1** Venous circulation model with two resistances and one capacitor. The sum of the resistances ($R_1$ and $R_2$) is equal to $R_{vd}$ as defined in Eq. 2. The capacitor is the total capacity ($C_v$) downstream from the site in the circulation where the pressure is equal to the mean systemic filling pressure ($P_{sf}$). $\dot{Q}_{in}$ is the inflow into this segment of the venous system, $P_v$ is the venous pressure, $\dot{Q}_c$ the inflow into $C_v$, $\dot{Q}_v$ the venous return to the heart and $P_{cv}$ the central venous pressure

over a heart cycle, are constant, $\dot{Q}_c$ is zero and $\dot{Q}_v = \dot{Q}_{in}$, fulfilling Guyton's equation 2 [3, 4]. During mechanical inflation of the lungs, $P_{cv}$ 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 for 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, after which 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 to be equal to $\dot{Q}_v$. The $P_{sf}$ was determined off-line from the extrapolation of the linear regression of $\dot{Q}_v$ on $P_{cv}$ during the inflation to $\dot{Q}_v = 0$. As $\dot{Q}_v$ is lower during inflation than predicted by Eq. 2 because of the loading of the venous capacity ($\dot{Q}_c$), using a SIP will underestimate $P_{sf}$, compared with the value obtained during stationary conditions using IPPs. However, this underestimation should decrease when longer inflation times are used.

## Materials and methods

### Surgery

The experimental set-up has been described in detail in previous papers [9, 10]. The following thus summarizes 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 pentobarbitone sodium i.p., followed by a continuous infusion of 9.0 mg · $kg^{-1}$ · $h^{-1}$. 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 $V_T$ adjusted to maintain arterial $PCO_2$ of about 40 mm Hg, while a positive end-expiratory pressure of 2 cm $H_2O$ was applied to minimize atelectasis. $PCO_2$, airway pressure and air flow were measured in the tracheal cannula. The animals were placed in a supine position on a thermocontrolled operating 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: a Swan-Ganz catheter into the pulmonary artery to measure pulmonary artery pressure and sample mixed venous blood and a quadruple-lumen catheter into the superior vena cava to measure $P_{cv}$ and infuse anaesthetic and pancuronium bromide (Pavulon, Organon Teknika Boxtel, the Netherlands). The catheters for blood pressure measurements were kept patent by an infusion of saline (3 ml/h).

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 then sutured. The thorax was closed airtight. The evacuation of air and fluid was accomplished by applying a negative pressure of 10 cm $H_2O$ to the suction catheters for 1–2 min. After surgery, the animals were paralysed with an i.v. infusion of Pavulon (0.3 mg · $h^{-1}$ · $kg^{-1}$), after a loading dose of 0.1 mg/kg in 3 min.

### Measurements

The electrocardiogram (ECG), aortic pressure, pulmonary artery 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 in real time for 30-s periods at 250 Hz. Areas of the flow curves were analysed 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 $O_2$ 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 $P_{sf}$, two different procedures for changing $P_{cv}$ were used. First we used the IPP method to obtain a reference value of $P_{sf}$ [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. $V_T$ was changed from 0 to 30 ml/kg in seven steps of 5 ml/kg. The IPPs were randomly applied with intervals of at least 5 min to maintain haemodynamic stability. The second method was based on a 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. The durations of the inspiratory pauses were thus 12.0, 9.6, 7.2, 4.8 and 2.4 s respectively. Each SIP was performed at a $V_T$ of 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 undertaken 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 $P_{sf}$ using IPPs. The $P_{sf}$ was obtained as the extrapolated value of $P_{cv}$ at zero flow from the linear regression of the heart-beat values of $\dot{Q}_{rv}$ on 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 analysed and tested with a two-tailed, paired $t$-test. $P < 0.05$ was regarded as significant.

## Results

In Fig. 2 the $P_{sf,IPP}$ of the series before the SIPs (A) is compared with $P_{sf,IPP}$ of the series after the SIPs (B). The illustration shows the difference between the two as a function of the mean of both. 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 $-0.22 \pm 1.16$ mm Hg (mean ± SD). There was one outlier in these observations (experiment no. 3, in which the difference was $-2.9$ mm Hg). Without this outlier the mean difference of both series was $0.17 \pm 0.46$ mm Hg.

Two individual examples of the determination of $P_{sf}$ with two SIPs, with inflation times of 4.8 and 12 s and a $V_T$ of 30 ml/kg, are presented in Fig. 3, together with the data of one of the series of IPPs. In accordance with the theory, $P_{sf}$ was underestimated less during a SIP at larger $T_i$ compared with $P_{sf,IPP}$. Similar results were observed in all animals (Table 1). There was no significant difference between the values of $P_{sf,SIP}$ obtained at both $V_T$ values for $T_i = 7.2$, 9.6 and 12.0 s ($P = 0.33$, 0.40 and 0.76 respectively). The $P_{sf,SIP}$ values from a series with a $V_T$ of 30 ml/kg and a $T_i$ of 2.4 or 4.8 s were significantly lower than those from the series with a tidal volume of 15 ml/kg ($P = 0.004$ and 0.01 respectively).

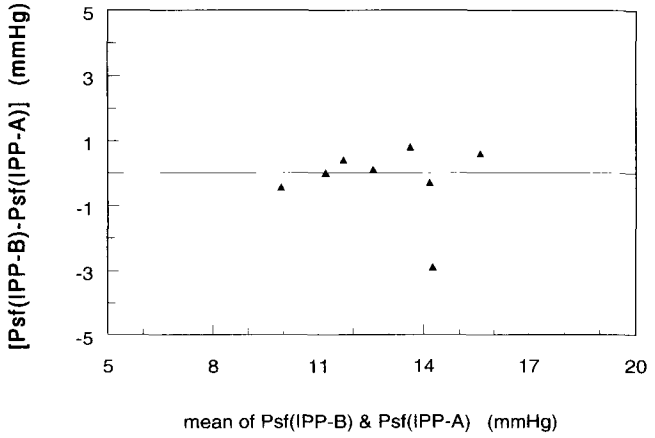


**Fig. 2** Scattergram of $P_{sf}$ values from both experimental series (A,B) employing inspiratory pause procedures (IPP) to measure $P_{sf}$. On the $x$-axis is the mean value of $P_{sf,IPP,A}$ and $P_{sf,IPP,B}$ determined in the IPP series before and after all slow inflation procedures (SIPs) respectively. The $y$-axis represents the differences between the values of both $P_{sf,IPP}$ series

By fitting an exponential function to the data of each experiment, we determined the value of $T_i$ necessary to obtain a reliable estimate of $P_{sf}$. This exponential function fitted the data best. The inflation time ($\theta_{SIP}$) at which the difference between the exponential function and the $P_{sf,IPP}$ was less than 0.75 mm Hg, was calculated from the fit. The value of 0.75 mm Hg was based on the reproducibility of the determinations of the $P_{sf,IPP}$ in this experiment. Excluding the outlier, the standard deviation of the differences in $P_{sf,IPP}$ of series A and B was 0.46 mm Hg (Fig. 2). The 95 % coefficient of repeatability (one-tailed) was calculated as 1.64· SD

**Table 1** Individual results of all experiments employing slow inflation procedures (SIPs) to measure systemic filling pressure ($P_{sf,SIP}$). SIPs were carried out in eight 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 inspiratory pause procedures ($P_{sf,IPP}$)

| Experiment No. | $V_T$ | $T_i$ (s) | | | | $P_{sf,IPP}$ |
|---|---|---|---|---|---|---|
| | (ml/kg) | 2.4 | 4.8 | 7.2 | 9.6 | 12.0 | (mm Hg) |
| 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 | |

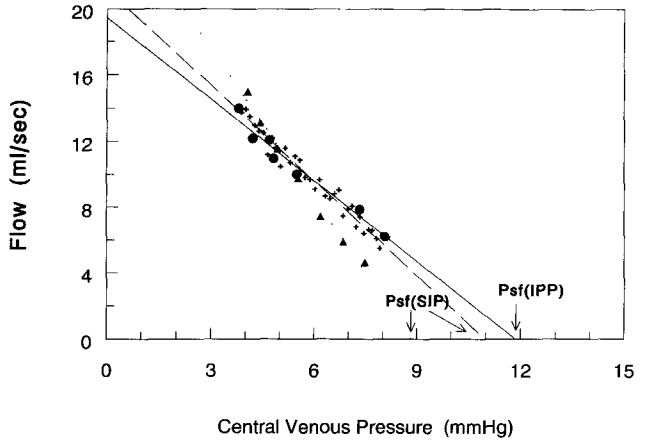


**Fig. 3** An example of two SIPs compared with series of IPP. The *filled circles* are the means of venous return ($\dot{Q}_v$) and central venous pressure ($P_{cv}$) determined in the stationary part of the IPP. The *crosses* are the beat-to-beat values of $\dot{Q}_v$ and mean $P_{cv}$ during a SIP with an inflation time of 12 s. The *triangles* represent the beat-to-beat values of $\dot{Q}_v$ and $P_{cv}$ during a SIP with an inflation time of 4.8 s

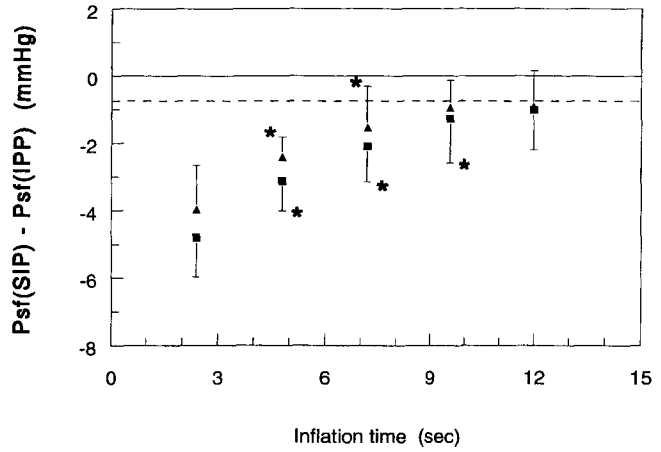


**Fig. 4** Underestimation of $P_{sf}$. The mean differences ($P_{sf,SIP}$–$P_{sf,IPP}$) from all eight experiments are shown as a function of inflation time at two tidal volumes ($V_T$). The *vertical bars* show the SD. The *squares* represent the values at $V_T$ = 30 ml/kg, the *triangles* represent the values at $V_T$ = 15 ml/kg. The *dotted line* at −0.75 mm Hg is the estimate of the inflation time required to produce 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 $V_T$

**Table 2** Individual results fitting the experimental data to an exponential relationship of the form $P_{sf,SIP} = (P_{sf,\ IPP} - \beta) \cdot (1 + e)^{-T_i/\alpha} + \beta$ where $\alpha$ and $\beta$ are fitting parameters and $\theta_{SIP}$ is the calculated $T_i$ at which the difference between $P_{sf,\ IPP}$ and the exponential fit is less than 0.75 mmHg: $\theta_{SIP} = -\alpha \ln[0.75/(P_{sf} - \beta)]$. The range of $\theta_{SIP}$ values was [6–16 s] at $V_T$ = 15 ml/kg and [8–18 s] at $V_T$ 30 ml/kg

| Experiment No. | $V_T$ (ml/kg) | $\alpha$ (s) | $\beta$ (mm Hg) | $\theta_{SIP}$ (s) | $P_{sf,\ IPP}$ (mm Hg) |
|---|---|---|---|---|---|
| 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 (excluding outlier) | | 5.47 ± 2.00 | 5.55 ± 2.25 | 11.8 ± 3.9 | |

and was 0.75 mm Hg [1]. The individual values of $\theta_{SIP}$ are presented in Table 2. Excluding the outlier reduced the mean ± SD $\theta_{SIP}$ from 13.3 ± 7.0 to 11.8 ± 3.9 mm Hg and we calculated the 90 % limits of agreement [1] as [11.8 ± 1.64·SD] = [5.4; 18.2] mm Hg. The mean values of ($P_{sf,SIP} - P_{sf,IPP}$) for all animals are shown as a function of $T_i$ for the two tidal volumes (15 and 30 ml/kg) in Fig. 4. At a $T_i$ of 12 s, $P_{sf,SIP}$ is still significantly different from $P_{sf,IPP}$ ($P$ = 0.023, one-tailed, paired $t$-test).

## 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 experiment in which a large increase in heart rate from 2.5 to 3.5 beats/s occurred. In all other animals ($n$ = 8) 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).

Our aim was to estimate $P_{sf}$ with one SIP. A $T_i$ of 12 s was too short to obtain equality between $P_{sf,SIP}$ and $P_{sf,IPP}$. The exponential function fitted through the differences between $P_{sf,SIP}$ and $P_{sf,IPP}$ for each experiment predicted (excluding the outlier) a mean satisfactory $T_i$ of 11.8 s. The 90% limits of agreement ranged from 5–18 s. Accordingly, a $T_i$ of 18 s should be satisfactory for 95% of all animals. An advantage of a long $T_i$ is that more data points are available for the linear regression. On the other hand, however, the activity of the circulatory control mechanisms during a long $T_i$ 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.

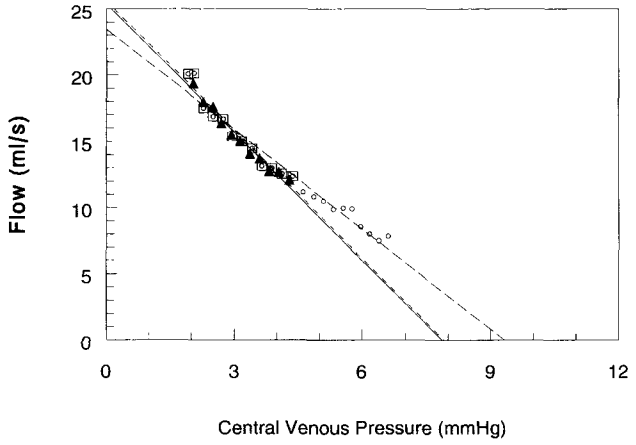


**Fig. 5** The relationship between $\dot{Q}_v$ and $P_{cv}$ at two inflation volumes with equal inflation velocities. The *triangles* show data from a SIP at $V_T$ = 15 ml/kg with an $T_i$ of 4.8 s, the corresponding regression line is the *solid line*. The small circles represent the data during a SIP with $T_i$ = 9.6 s and $V_T$ = 30 ml/kg (*long-dashed line*). The first half of this procedure is also analysed separately. (The *circles within squares*, *short-dashed line*) thus yielding three values of $P_{sf}$. The $P_{sf}$ values at $V_T$ = 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

In these experiments we used SIPs at a $V_T$ of 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 $P_{sf,SIP}$ for these procedures differ significantly (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, $P_{cv}$ is increased, whereas the rise in $P_v$ is delayed due to $C_v$. 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 $\dot{Q}_v$ to fall more rapidly than in the linear part immediately thereafter. As a consequence, a linear regression of 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 with the shorter SIP at low $V_T$ the procedures are, on average, not different (group I $P = 0.38$, group II $P = 0.34$). $P_{sf}$ 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 beforehand.

A disadvantage of the SIP is the necessity of a beat-to-beat determination of $\dot{Q}_{rv}$, or at least obtaining a signal that is proportional to this variable. Such technique is not (yet) available in practice, but will become possible if an adequate pulse contour method can be developed for the pulmonary circulation. The advantage of a SIP for the estimation of $P_{sf}$ is that only one special procedure of less than a min is needed, whereas the IPP method takes about 45 min. Because over 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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