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Chapter 4

Evaluation of mean systemic filling pressure from pulse contour cardiac output and central venous pressure

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Abstract
The volemic status of a patient can be determined by measuring mean systemic filling pressure (Pmsf). Pmsf is obtained from the venous return curve, i.e. the relationship between central venous pressure (Pcv) and blood flow. We evaluated the feasibility and precision of Pmsf measurement. In ten piglets we constructed venous return curves using seven 12-second inspiratory holds transiently increasing Pcv to seven different steady-state levels and monitored the resultant blood flow, by pulse contour (COpc) and by flow probes around the pulmonary artery (COr) and aorta (COI). Pmsf was obtained by extrapolation of the venous return curve to zero flow. Measurements were repeated to evaluate the precision of Pmsf.
During the inspiratory holds, 133 paired data points were obtained for COr, COI, COpc and Pcv. Bland-Altman analysis showed no difference between COr and COI, but a small significant difference was present between COI and COpc. All Pcv versus flow (COI or COpc) relationships were linear. Mean Pmsf was 10.78 with COI and 10.37 mmHg with COpc. Bland-Altman analysis for Pmsf with COI and with COpc, showed a bias of 0.40 ± 0.48 mmHg. The averaged coefficient of variation for repeated measurement of Pmsf with COI was 6.2% and with COpc 6.1%. In conclusion, during an inspiratory hold pulmonary flow and aortic flow equilibrate. Cardiac output estimates by arterial pulse contour and by a flow probe around the aorta are interchangeable. Therefore, the venous return curve and Pmsf can be estimated accurately by pulse contour methods.
Introduction

Usually, a pulmonary artery catheter (PAC) is placed for the assessment of cardiac output (CO) and of intravascular volume status, by measuring central venous pressure (Pcv) and pulmonary capillary wedge pressure (Pcwp). However, the values of Pcv and Pcwp are often considered to be misleading in estimating volume status and the effect of volume loading.¹,² In patients on mechanical ventilation, inflation increases pleural pressure and central venous pressure, which in turn may respectively decrease systemic venous return, right ventricular (RV) filling, and transiently impair RV ejection.³ Therefore, RV stroke volume decreases during the inflation and recovers during expiration (figure 4.1). The larger the cyclic changes in RV output induced by mechanical ventilation and hence in left ventricular (LV) preload are, the larger the cyclic changes in LV stroke volume (SVV) and arterial pulse pressure (PPV). These cyclic changes in LV output induced by mechanical ventilation are thought to be larger when the heart operates on the steeper rather than on the flat portion of the Frank-Starling curve.⁴,⁵ Therefore, SVV and PPV have been proposed as an indicator of fluid responsiveness, i.e. predictors of an increase in cardiac output with fluid loading.⁵-⁸ However, SVV and PPV have never shown to be an effective measure of filling status (also called stressed volume) of a patient. As a consequence, SVV and PPV do not give basis for protection against a too high filling status, which can result in pulmonary edema, myocardial ischemia and difficulties in weaning of mechanical ventilation; increasing hospital stay and even mortality.⁹ Therefore, the search for a measure of volume status and a predictor of fluid loading on cardiac output continues.

Given the clinical relevance of a measure of effective filling status, we investigated how this fits with Guyton’s theory on venous return.¹⁰,¹¹ A theory that follows the fundamental physical law, of Newton, that a force is needed to accelerate a mass, or that flow can only be the result of a pressure gradient. According to Guyton’s concept the difference between mean systemic filling pressure (Pmsf) and right atrial pressure (Pra) or Pcv is the driving force for venous return. Where Pmsf is the equilibrium pressure in the systemic circulation under condition of no flow and Pcv is the back pressure to venous return. Recently, we validated a bedside technique to estimate mean systemic filling pressure.¹² In this and previous animal research papers³,¹³-¹⁵ we made several assumptions for the determination of mean systemic filling pressure. Firstly, we assumed that venous return to the heart equals left ventricular output during the end of an inspiratory hold (figure 4.1). Secondly, we expected arterial pulse contour cardiac output to be equal to left ventricular output measured by a flow probe. And thirdly in our clinical study we reasoned that three or four inspiratory holds were enough to describe reliable a venous return curve.

The aim of this study was to test the validity of these assumptions and to determine the precision of the estimated value of mean systemic filling pressure.
Materials and methods

All experiments were performed in accordance with the “Guide for Care and Use of Laboratory Animals” published by the US National Institute of Health and the protocol was approved by the local Animal Care Committee.

![Graphs showing effects of inspiratory hold on Pao, Pcv, Pt, CO, COt, COl, COpc over time.](image)

**Figure 4.1 Example of an inspiratory hold procedure**

Effects of an inspiratory hold on aortic pressure (Pao), central venous pressure (Pcv), airway pressure (Pt) and beat-to-beat cardiac output (CO) with a probe around the pulmonary artery (COt), around the aorta (COl) and by pulse contour analysis (COpc). Preceding the hold the effects of a normal ventilation cycle are plotted. Note the difference in beat-to-beat changes of COt and COl or COpc.

Surgery

Ten piglets (8-10 wk, mean weight 11.0 ± 0.9 kg) were studied. Anesthesia was induced with 30 mg·kg⁻¹ sodium pentobarbital intra-peritoneally, 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 and with a tidal volume adjusted to maintain arterial pCO₂ of approximately 5.33 kPa (40 mmHg), while a positive end-expiratory pressure of 2
cmH\textsubscript{2}O was applied. pCO\textsubscript{2}, airway pressure (Pt) and airflow were measured in the tracheal cannula. The animals were placed in supine position on a thermo-controlled operating table (38°C). A catheter was inserted through the right common carotid artery into the aortic arch to measure arterial pressure (Pao) and to sample arterial blood. Two other catheters were inserted through the right external jugular vein. A pulmonary artery catheter was inserted to measure pulmonary artery pressure, to measure thermodilution cardiac output (COtd) and to sample mixed venous blood. A quadruple-lumen catheter was inserted into the superior vena cava to measure Pcv and to infuse sodium pentobarbital and pancuronium bromide (Organon N.V., Boxtel, the Netherlands). The catheters for vascular pressure measurements were kept patent by an infusion of saline with 2.5 IE Heparin ml\textsuperscript{-1} at 3 ml\textsuperscript{•}h\textsuperscript{-1}. The bladder was cannulated trans-abdominally to check urine loss in order to maintain fluid balance. After an intercostal thoracotomy in the second left intercostal space, two electromagnetic flow probes (type transfow 601, model 400, Skalar, Delft, the Netherlands) were placed within the pericardium with one probe around the pulmonary artery and another around the ascendant part of the aortic arch to measure pulmonary artery flow (COr) and aortic flow (COl). Two suction catheters, one dorsal and one ventral, were inserted into the left pleural space. The thorax was closed airtight and both air and fluids were evacuated for 1-2 minutes with -10 cmH\textsubscript{2}O suction while applying a PEEP of 10 cmH\textsubscript{2}O. After surgery and while on continuous pentobarbital infusion, the animals were paralyzed with an intravenous infusion of pancuronium bromide (0.3 mg\textsuperscript{•}kg\textsuperscript{-1}\textsuperscript{•}h\textsuperscript{-1}), after a loading dose of 0.1 mg\textsuperscript{•}kg\textsuperscript{-1} in 3 min.

**Measurements**

The electrocardiogram (ECG), Pao, pulmonary artery pressure (Ppa), Pcv, flow probe signals and tracheal airway pressure (Pt) were simultaneously recorded. Zero level of blood pressures was chosen at the level of the tricuspid valves, indicated by the pulmonary artery catheter during lateral-lateral radiography. The airway pressure transducer was balanced at zero level against ambient air. During the observation periods, ECG, blood flow and pressure signals were sampled in real time for 30-second periods at 250 Hz. The mean of four thermodilution cardiac output measurements equally distributed of the ventilatory cycle was used to obtain the value of COtd (apparatus and method described in).\textsuperscript{16-18} Areas under the pulmonary artery blood flow curve and the aortic flow curves were analyzed online and calibrated by COtd to estimate beat-to-beat cardiac output (COr and COl). Pulse contour cardiac output (COpc) from aortic pressure (for piglets adapted Modelflow method, FMS, Amsterdam, the Netherlands) was calibrated by the same COtd value. After the surgical procedure the animals were ventilated at a rate of 10 min\textsuperscript{-1} with an inflation time of 2.4 seconds and an expiration time of 3.6 seconds. Tidal volume was readjusted to an end-expiratory pCO\textsubscript{2} of approximately 5.33 kPa (40 mmHg), usually corresponding with a slightly higher arterial pCO\textsubscript{2}. The ventilatory settings were kept constant during the observation periods.
We determined Pmsf using inspiratory holds as previously described.\textsuperscript{3,14,15,19} Briefly: During inflation of the lungs venous capacitance is loaded due to an increase in Pcv, which leads to a transient reduction in venous return, in right ventricular output and consequently in left ventricular output (figure 4.1). To avoid transient effects on the relationship between venous return and Pcv, we measured Pcv and right and left ventricular output (CO_r, CO_l and CO_pc) during short periods of end-inspiratory steady state following these initial non-steady-state conditions. CO and Pcv are determined over the final 5 seconds for a set of seven 12-seconds inspiratory hold procedures at seven randomly applied tidal volumes between 0 and 300 ml. The inspiratory hold maneuvers are separated by 5-minute intervals to re-establish the initial hemodynamic steady state. From the steady-state values of Pcv and cardiac output (CO_l and CO_pc) during the seven inspiratory pause periods two venous return curves were constructed by fitting linear regression lines according to the method of least square means through these data points (figure 4.2). Pmsf,l and Pmsf,pc are defined as the extrapolation of these linear regressions to zero flow with CO_l and CO_pc respectively.\textsuperscript{3,14,15,19}

![Figure 4.2 Venous return curves](image)

**Figure 4.2 Venous return curves**
Panel A, the relationship between cardiac output (CO) obtained during the end of the inspiratory hold from the flow probe around the aorta (CO_l,hold) and central venous pressure (Pcv,hold). Panel B, similar relationship obtained by arterial pulse pressure analysis (CO_pc,hold). Mean systemic filling pressure (Pmsf) is obtained by extrapolation of the linear fit to CO is 0. The bold data points are taken from figure 4.1.

**Protocol**
To eliminate the effects of surgery, opening of the pericardium, and applying mechanical ventilation on the hemodynamic measurements, the piglets were allowed to stabilize for 60 to 120 minutes after surgery. Data collection started once heart rate (HR), mean Pao and Pcv were stable for at least 15 minutes. After stabilization, series-1 measurements were performed by applying the seven inspiratory holds. After 50 minutes these measurements were repeated, series-2.
**Data analysis and statistics**

The results of the data pairs of COr, COl and COpc obtained during each inspiratory hold were compared by linear regression and the difference between them by Bland-Altman analysis. To describe the venous return curve we fitted the set of seven data points of Pcv and COl and of Pcv and COpc by linear regression for series-1 and series-2. We defined Pmsf as the extrapolation of this linear regression to zero flow (figure 4.2), assuming that airway pressure does not affect Pmsf. Repeatability was calculated from the two baseline conditions using Bland-Altman analysis. Hereeto, for each animal the mean and difference of the values of series-1 and series-2 were determined. The upper and lower limits of agreement were calculated as bias ± 2SD. The coefficient of variation (COV) was calculated as 100% x (SD/mean). Differences in variables during series-1 and series-2 were analyzed using paired t-tests. The effect of reduction of the number of inspiratory holds on Pmsf values was studied as follows: 4-holds by selection of holds 1, 3, 5, 7 (see figure 4.2); 3-holds by holds 1, 4, 7 and 2-holds by 1 and 7. All values are given as mean ± SD. A p-value < 0.05 was considered statistically significant.

**Results**

Ten 8–10 week old piglets (all females) bodyweight of 11.0 ± 0.9 kg were studied. The first series of measurements in animal 1 were excluded for analysis because of a technical problem in recording a proper left ventricular outflow signal. Mean hemodynamic characteristics of the animals during series 1 and 2 were: Pao 75.8 ± 6.7 mmHg, Ppa 15.5 ± 3.5 mmHg, Pcv 3.7 ± 0.5 mmHg, heart rate 146 ± 42 min⁻¹, COtd 17.72 ± 3.12 ml·s⁻¹.

The hemodynamic changes during a normal ventilatory cycle and during a ventilatory hold are illustrated in an individual example by plotting Pao, Pcv, Pt and beat-to-beat changes of COr, COl and COpc against time, see figure 4.1. The figure shows that during inflation a rise in Pcv and a concomitant decrease in CO occurs. Also, a shift between the changes in right ventricular cardiac output and left ventricular is observable. However, 8 seconds after start of the inspiratory hold a plateau in COr, COl and COpc occurs. During the normal ventilatory cycle the modulation in right ventricular output is larger than that of left ventricular output. Pooled data during normal ventilation are shown in table 4.1. A Kolmogorov-Smirnov test indicated normal distribution of all data.

**CO during inspiratory hold procedures**

During the inspiratory holds, illustrated in figure 4.1, Pcv increased to a constant level for 12 seconds. This increase in Pcv led to a decrease in Pao, COr, COl, and COpc. Over the last 5 seconds of the hold their CO beat-to-beat values were constant. Over this period in total 133 paired averaged data points were obtained for COr, COl, and
Regression analysis showed that COr, COI and COpc were highly related to each other (COI = 1.002·COR, R² = 0.955; COpc = 0.965·COR, R² = 0.940; and COpc = 0.961·COI, R² = 0.965, figure 4.3A). The result of Bland-Altman analysis for the difference between methods is given in table 4.1 and figure 4.3B. No difference was found between COr and COI, but a small significant difference was present between COr and COpc as well as between COI and COpc. The COV for repeated measurements (series-1 and series-2) of COr, COI and COpc were 12%, 10% and 12% respectively.

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<th>SD</th>
<th>COV</th>
<th>Limits of agreement</th>
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<td></td>
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<td>ml/s</td>
<td>ml/s</td>
<td>%</td>
<td>Lower</td>
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Bland-Altman analysis of cardiac output results by measurements with a flow probe around the pulmonary artery (COR), around the aorta (COI) and arterial pulse contour analysis (COpc). p-value for the difference between bias value and zero is given (n = 133).

**Venous return curves and Pmsf**

An individual example of the Pcv versus blood flow (COI and COpc) relationships, i.e. the venous return curves, is given in figure 4.2. Observable is the linear relationship through the data points obtained from the seven inspiratory holds. For all 10 animals this venous return curve was linear, as can be observed in figure 4.4 for Pcv versus COpc. For all observations the averaged slope of the venous return curve Pcv versus COI is -2.228 ± 0.368 and for Pcv versus COpc is -2.355 ± 0.337 (difference p = 0.03), the averaged squared correlation coefficients (R²) are 0.912 (range 0.887-0.966) and 0.970 (range 0.929-0.993) respectively. The population averaged values of Pmsf with COI and Pmsf with COpc are 10.77 ± 1.00 mmHg and 10.38 ± 1.09 mmHg (difference p = 0.003) respectively. Bland-Altman analysis for the difference between methods (table 4.2) showed that the small difference between Pmsf,l and Pmsf,pc of 0.40 ± 0.48 mmHg (COV = 4.5%) is, however, statistically significant (p = 0.009).

**Repeatability**

Bland-Altman analysis for repeated measurements for Pmsf,l showed a bias of -0.18 mmHg and a precision of 0.67 mmHg (COV = 6.2%) and for Pmsf,pc these values were -0.27 mmHg and 0.63 mmHg (COV = 6.1%). There was no difference between the first and second series of Pmsf,l and Pmsf,pc (p = 0.58 and 0.22 respectively).

**Data reduction**

The results of reduction of the number of data points per venous return curve from 7 to 4, 3 and 2 inspiratory holds is shown in table 4.2. A remarkable good agreement
between Pmsf with COl and Pmsf with COpc was found for Pmsf with 7, 4, 3 and 2 inspiratory holds per venous return curves. The difference between the techniques was statistically significant but was maximally 4.5%. No difference between the first and second series per animal was found and the COV for repeated measurements of Pmsf ranged from 2.2 to maximally 6.5% (table 4.2).

Figure 4.3 Cardiac output by aortic probe and pulse contour cardiac output
Cardiac output measured during the end of the inspiratory hold by the aortic probe (COl) and pulse contour cardiac output (COpc). In panel A, regression between COl and COpc is given. Noticeable is the small underestimation of COpc in the low output range. In panel B, Bland-Altman analysis of COl and COpc is shown.

Figure 4.4 Venous return curves of the 10 individual animals.
COpc is cardiac output (ml·s⁻¹) measured by pulse contour and Pcv is central venous pressure (mmHg).
Evaluation of mean systemic filling pressure from cardiac output and central venous pressure

<table>
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<th>SD</th>
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Bland-Altman analysis for the difference between mean systemic filling pressures (Pmsf) measured with a flow probe around the aorta (Pmsf,COl) and with arterial pulse pressure analyses (Pmsf,COpc) as well as Bland-Altman analysis for repeated measurements. Both analyses were done for 7, 4, 3 and 2 inspiratory hold maneuvers (n,h). p-value for the difference between bias value and zero is given.

Discussion

Our analysis shows clearly: 1. COr equals COl equals COpc at the end of the inspiratory holds; 2. the feasibility of pulse contour analysis to estimate the venous return curve and the unambiguous determination of mean systemic filling pressure; and 3. Pmsf can be estimated with 2-7 inspiratory holds.

The measurement of Pmsf under clinical conditions was limited to the availability of planned, unavoidable circulatory arrest for instance during testing of ICD. But, recently we showed the feasibility of bedside determination of effective volume-status, Pmsf, by the application of 4 inspiratory holds and measurement of Pcv and pulse contour cardiac output during these holds. In this and former animal studies we made several assumptions for the determination of mean systemic filling pressure: 1, we assumed venous return to the heart to be equal to the left ventricular output during the end of the inspiratory holds; 2, we expected pulse contour cardiac output to be equal to left ventricular output; and 3, we reasoned that three or four inspiratory holds were enough to reliably describe the venous return curve.

Venous return equals left ventricular output

In comparing CO techniques, the limits of agreement of COr with COl (2SD/mean) were 9%. Together, with a bias for the difference between techniques which was not significantly different from zero and a COV for repeated measurements of 12% and 10% for COr and COl, the two methods are interchangeable. Thus, measurement of left ventricular output during inspiratory holds allows the estimation of right ventricular output. 
output and most presumably also from right atrial input, as the right heart has a limited storing capacity for blood.

**Left ventricular output equals arterial pulse contour cardiac output**

The technical set-up with a flow probe around the pulmonary artery or aorta is not generally applicable in humans. Therefore we have chosen to evaluate a beat-to-beat determination of cardiac output by arterial pulse contour analysis. Most commercial pulse contour methods (PiCCO, LiDCO, FloTrac-Vigileo and Modelflow) use a pressure to volume conversion based on *in vitro* measurements of the human aorta. From a comparative study it became clear that there are differences in aortic compliance between humans and pigs.\(^{22}\) In humans the compliance of the aorta decreases non-linearly with increasing pressures between approximately 30 and 200 mmHg.\(^{23}\) This relation is age dependent. For pigs the compliance first increases in the lower pressure range and next decreases in the higher pressure range. This increase and decrease in pigs is less pronounced than the decrease in compliance in humans. No information is available about age dependency in pigs. In our present study we approximated the pressure-dependent compliance in the pig with a constant compliance. This might lead to a slightly underestimated pulse contour cardiac output in the lower arterial pressure range. Indeed in this range the actual compliance is slightly larger than the used constant compliance leading to an underestimated stroke volume and CO (figure 4.3A). Still, Bland-Altman analysis showed a good agreement between CO\(_l\) and CO\(_{pc}\) with limits of agreement of -0.90 to 1.58 ml·s\(^{-1}\) and a COV of 5.6%. This was accompanied by a small, although significant, mean difference (bias = 0.34 ml·s\(^{-1}\)) and a low coefficient of variation for repeated measurements. We conclude that our pulse contour CO measurement can replace the measurement of LV output with a probe around the aorta.

**Mean systemic filling pressure by LV output and arterial pulse contour CO**

The venous return curve constructed with the results of measurement of Pcv and CO\(_l\) or CO\(_{pc}\) during the inspiratory holds was linear in all 10 animals. The correlation coefficients with CO\(_l\) or CO\(_{pc}\) in the fit were high (mean R\(^2\) = 0.971 and 0.984 respectively). The extrapolation of the linear fit to zero flow resulted in a mean Pmsf,\(_l\) of 10.77 ± 1.00 mmHg and of Pmsf,\(_{pc}\) of 10.38 ± 1.09 mmHg. Also the repeatability or precision of the results of the two series of measurements per animal is good, mean difference between the first and second series of measurements is -0.18 ± 0.67 mmHg for Pmsf,\(_l\) and -0.27 ± 0.63 for Pmsf,\(_{pc}\). The small COV (6.2% and 6.1% for Pmsf,\(_l\) and Pmsf,\(_{pc}\) respectively) clearly indicates the unambiguous validity of our method with inspiratory holds to determine Pmsf.

Bland-Altman analysis for the difference between Pmsf,\(_l\) and Pmsf,\(_{pc}\) showed a small but significant mean difference of 0.40 ± 0.48 mmHg. Detection of this small mean difference can be explained largely by the high correlation coefficient of the linear fit. With small limits of agreement and with a small mean difference we concluded
that the two methods are interchangeable. Thus, pulse contour analysis can be used to determine the venous return curve and Pmsf.

**Number of inspiratory holds to describe the venous return curve**

Application of 7 inspiratory holds and recovery to baseline value takes approximately 35 – 40 minutes. Reduction of 7 to 4, 3 or even 2 inspiratory holds will shorten the time needed to determine the venous return curve and Pmsf, which makes the method more clinically feasible. The results given in table 4.2 indicate that already 2 inspiratory holds (i.e. the hold with inflation of 0 and 300 ml) allow an accurate estimate of Pmsf. The use of four inspiratory holds in our previous clinical study\textsuperscript{12} seems thus more than sufficient.

**Comparison with Pmsf values found in literature**

We found difference in Pmsf values of approximately 8 mmHg between the experimental settings with our animals (10.4 mmHg) and the clinical setting with postoperative cardiac patients (18.8 mmHg)\textsuperscript{12} using the same measurement technique. This can be explained partly by: the difference in filling status; all postoperative cardiac patients had a positive fluid balance whereas in our animal study only fluid was given to compensate for blood loss during surgery; and a difference in positive end-expiratory pressure (patients 5 cmH\textsubscript{2}O and in our piglets zero cmH\textsubscript{2}O). These differences during baseline condition are reflected in different Pcv values (patients 6.7 mmHg and our piglets 3.7 mmHg). Furthermore, the Pmsf may be patient population and species dependent. For animals Pmsf values between 7\textsuperscript{24} and 30 mmHg\textsuperscript{25} are reported.

We based our analysis on the assumption that the venous return curve is linearly dependent on applied central venous pressure. Except for a minor inflection at low or negative values of Pcv such linearity was demonstrated by Guyton *et al.*\textsuperscript{10} in open chest experiments. Pinsky\textsuperscript{26} in dogs and Versprille and Jansen\textsuperscript{3} in pigs confirmed this linearity in closed chest circumstances after thoracotomy. Furthermore, Pinsky\textsuperscript{26} demonstrated that Pmsf obtained by linear extrapolation of the venous return curves did not differ from the value measured during circulatory arrest. The Pmsf-values calculated from Pcv and COI or COpc are in agreement with the Pmsf-values determined by the inspiratory hold procedure\textsuperscript{3,13-15} and stop-flow measurements.\textsuperscript{27}

**Conclusions**

During an inspiratory hold pulmonary flow and aortic flow equilibrate. Cardiac output estimates by the pulse contour method and by a flow probe around the aorta are interchangeable. Therefore, venous return can be estimated by pulse contour methods. Mean systemic filling pressure can be estimated with equal precision with both blood flow measurement methods. Four, three or even two inspiratory holds satisfy to construct a venous return curve and to estimate Pmsf.
References


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