Clin Auton Res (2004) 14 : 176–181
DOI 10.1007/s10286-004-0191-1

RESEARCH ARTICLE

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Stroke volume monitored by modeling flow from finger arterial pressure waves mirrors blood volume withdrawn by phlebotomy

Received: 11 February 2004
Accepted: 19 April 2004

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Abstract Rate-controlled blood withdrawal was used to reduce cardiac preload and consequently stroke volume in patients with normal cardiac function. Twelve patients with asymptomatic hereditary hemochromatosis, undergoing regular phlebotomy therapy, volunteered for the study. An average volume of 375 ml was withdrawn in an average period of 6.4 min. Finger pressure was continuously measured by a Finometer® device which includes the Beatscope® software for deriving the stroke volume from the blood pressure waveform. Blood withdrawal resulted in reduction of the stroke volume estimates (from 94.0 ± 5.2 to 80.7 ± 5.3, $P < 0.05$) together with a reduced pulse pressure (from 53.0 ± 3.5 to 47.1 ± 3.2, $P < 0.05$). No significant changes in heart rate (75.2 ± 3.7 versus 78.3 ± 4.5 beats/min) were observed. Calculated cardiac output was reduced while calculated total peripheral resistance was elevated after blood withdrawal. Beat-to-beat analysis demonstrated a significant linear regression between most of the hemodynamic indices and the volume withdrawn. The highest correlation coefficients were found for the stroke volume (0.88 ± 0.01, $P < 0.001$) and the pulse pressure (0.80 ± 0.04, $P < 0.001$) corresponding also to the highest slopes for the lines relating these measures to the relative blood volume withdrawn. The non-invasive estimation of finger blood pressure can be used to derive simple on-line indices (pulse pressure, stroke volume using the Modelflow) of cardiac preload, which are of major interest in the monitoring of cardiovascular status.

Key words hemochromatosis · hemorrhage · hemapheresis · Modelflow · pulse pressure

Introduction

Monitoring cardiac preload is paramount for precise hemodynamic management [21]. Methods for preload determination based on changes in blood pressure (BP) and heart rate (HR) have become accepted in standard practice [14]. Cohn documented a prominent fall in BP that occurs during inspiration when blood volume is reduced [4]. The systolic BP variations related to breathing were shown to be sensitive indicators of reduced preload associated with hypovolemia during mechanical ventilation [20, 27]. Power spectrum analysis was recently used to identify these systolic BP or HR oscillations synchronous with respiration as well as the so-called Mayer waves (0.1 Hz component). Small changes in intravascular volume were assessed in humans following blood donation [5, 28] or plasmapheresis [8] using this frequency domain analysis. Controlled graded normotensive hemorrhage in conscious animals was associated with progressive increases in the respiratory systolic BP variations, estimated from the systolic BP spectrum [1]. More

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recently continuous arterial waveform analysis, based on the algorithm first described by Wesseling, has allowed the monitoring of beat-to-beat stroke volume and has been proposed as a method for measuring continuous cardiac output [13, 25, 31]. Pulse wave form analysis has also been applied to document the effects of hemodynamically active drugs [6, 11, 26].

In the present study, a rate-controlled blood withdrawal was used to reduce cardiac preload and consequently stroke volume in patients with normal cardiac function. This paradigm was used to test whether stroke volume monitored by modeling arterial flow reflected the blood depletion, and to compare these beat-to-beat estimates to the traditional vital signs i. e. instant BP and HR levels. Twelve patients with asymptomatic hereditary hemochromatosis undergoing regular phlebotomy therapy volunteered for the study.

Methods

Subjects

A group of 12 subjects with asymptomatic hereditary hemochromatosis proved by hematologic and genetic study volunteered for this study. This group comprised 8 men, 4 women. Their age was 43.5 ± 2.6 (range 26–56) years; their height was 170.8 ± 2.0 (range 158–182) cm; their weight was 71.4 ± 3.6 (range 53–96) kg. These patients underwent regular phlebotomies with an average number of 40 ± 9 (4–85) sessions. The effectiveness of the therapy was illustrated by the normal serum ferritin levels of 58 ± 24 µg/L (range 9–303). Subjects included had no signs of clinical cardiac or electrocardiographic alteration. None were on medication. All patients gave informed consent to participate in the study which was performed with the approval of the Necker ethics committee (2/7/2002).

Phlebotomy protocol

Phlebotomy was performed from the antecubital vein in a seated position. The volume withdrawn was adjusted by the hematologist from the last ferritin level, the weight and the height of the subject. The average volume withdrawn was 375 ± 14 ml (range 300–450). The volume depletion corresponded to 8.8 ± 0.3 % of the total blood volume.

The estimation of the total blood volume was obtained using the following formula [12, 30]:

For males: Total blood volume (ml) = Height (cm)*28.5 + Weight (kg)*31.6–2820

For females: Total blood volume (ml) = Height (cm)*16.25 + Weight (kg)*38.46–1369

The average blood volume of the 12 subjects was 4274 ± 166 (range 3237–5230) ml.

The Hemomatic® blood collection monitor (Hemopharm, Gardanne, France) was positioned below the arm to obtain by gravity a regular blood collection rate of about 1 ml/s (average rate 61 ± 5 ml/min) corresponding to an average phlebotomy duration of 6.4 ± 0.3 (range 4.5–7.8) min. The linearity of the blood collection was checked by linear regression of the bag weight every 30 s, versus time (r = 0.98).

Recordings

Finger pressure was measured by a Finometer® device (Finapres Medical Systems, Amsterdam, The Netherlands) which includes the Beatscope® software (Finapres Medical Systems) for deriving the beat-to-beat stroke volume from the BP waveform. The finger cuff and the arm cuff used for calibration were positioned on the side opposite to the venopuncture. Recordings were started 5 min before the beginning of the volume depletion and ended 5 min after completion of the blood withdrawal. Subjects were asked to breathe at a regular rate of 0.25 Hz during the entire session using a metronome.

Analysis

BP values were extracted from the continuous BP signal, the mean BP was integrated from each BP cycle and the instantaneous HR was derived from the pulse intervals as previously described [16]. Pulse pressure was calculated as systolic BP minus diastolic BP. Mean BP, instantaneous HR, and stroke volume were used to calculate cardiac output and total peripheral resistance. Stroke volume index and cardiac index were obtained by normalizing the stroke volume and the cardiac output to the body surface area. Hemodynamic variables were averaged over each 4 s period corresponding to one breathing cycle. Instantaneous blood volume changes were normalized according to the total blood volume, and were expressed as percent of total blood volume (i. e. the ratio of the blood volume withdrawn/total blood volume × 100).

In addition to the study of the dynamic changes, the pre-phlebotomy, phlebotomy and post-phlebotomy levels were averaged over the last 60-s of the corresponding period. Standard deviation of the considered variables was calculated for every 60-s period and was taken as an index of overall variability.

Statistics

Data are expressed as the mean ± SEM. The Pearson's coefficient of correlation and slope were calculated between the normalized blood volume changes and each cardiovascular variable. For the comparison between the pre-phlebotomy, phlebotomy and post phlebotomy periods, a Friedman repeated measure analysis of variance was applied followed by a Tukey post hoc test for multiple comparisons. The Systat® software (SPSS Inc., Chicago) was used for statistical calculations. A value of $P < 0.05$ was considered as statistically significant.

Results

One example of the hemodynamic changes resulting from the phlebotomy is shown in Fig. 1. The most prominent change that occurs is a graded diminution of the beat-to-beat stroke volume during phlebotomy, associated with a reduction in cardiac output. This example shows a moderate reduction in BP. The 4-s period oscillations of the systolic BP, HR, SV and CO levels correspond to oscillations associated with the 0.25 Hz controlled respiration [15].

The 60-s average hemodynamic levels before phlebotomy, at the end of the blood withdrawal and after phlebotomy are shown in Table 1. The main change that followed phlebotomy was a stroke volume (and stroke volume index) diminution which was still significant at the end of the recovery period. Cardiac output (and car-

diac index) was reduced as a consequence of this stroke volume diminution. A slight elevation in total peripheral resistance was observed during phlebotomy. Systolic BP decreased and as a result, there was a reduction in pulse pressure during and after phlebotomy. HR changes were transient and did not reach significance.

No significant changes in the overall variability of systolic BP or HR were observed (4.5 ± 0.3, 4.9 ± 0.4 and 4.6 ± 0.3 mmHg for the average systolic BP standard deviation of the three periods and 3.1 ± 0.3, 2.8 ± 0.3 and 3.0 ± 0.3 beats/min for the average HR standard deviation of the three periods). This was also true for the other hemodynamic variables (results not shown).

An example of the relationship between the volume withdrawn and the different hemodynamic indices, corresponding to the data shown in Fig. 1 is shown in Fig. 2. The hemodynamic variables are normalized to the pre-phlebotomy levels calculated over 60 s. The abscissa represents the volume withdrawn as a percentage of the estimated total blood volume of the subject.

The average correlation coefficients and the slopes of the regression lines between each variable and the volume withdrawn are shown in Table 2. The highest correlation coefficients were found for the stroke volume (0.88) and the pulse pressure (0.80) also corresponding to the highest slopes of 2.15 for the stroke volume changes and 2.70 for the pulse pressure changes. The stroke volume changes exhibited the most homogenous results, illustrated by the smallest SEM. The significance of the linear regression, obtained with an average number of 95 pairs of values was observed in the 12 subjects for the following variables: systolic BP, pulse pressure, stroke volume and cardiac output. One regression out of 12 did not reach significance for mean BP, two for HR, 5 for total peripheral resistance and 6 for diastolic BP.

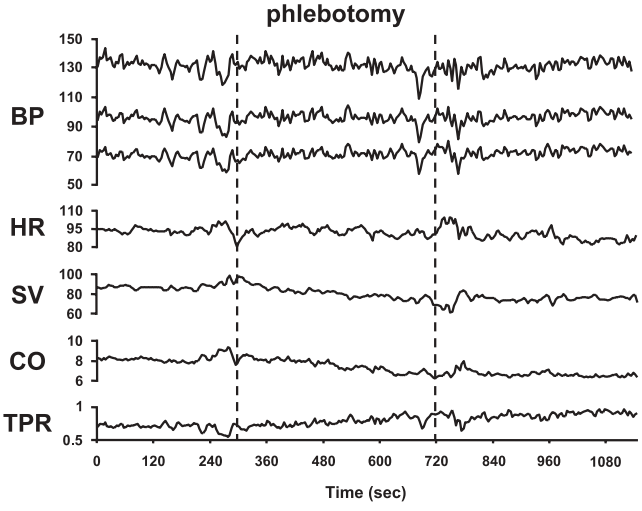

Fig. 1 Example from one patient of the effects of phlebotomy on the hemodynamic indices. *BP* blood pressure (mmHg); *HR* heart rate (beats/min); *SV* stroke volume (ml/beat); *CO* cardiac output (L/min); *TPR* total peripheral resistance ($mmHg \cdot min \cdot L^{-1}$)

Discussion

A reduced stroke volume was detected during phlebotomy, using the Modelflow. The first consequence of blood withdrawal occurs on the low pressure side of the circulation, and is reduction of the venous return. This could well explain the reduced stroke volume. Using impedance cardiography, Kosowsky et al. showed that the stroke volume index measured after a controlled hemorrhage (500 ml) was reduced when compared to its predonation levels [14]. A reduced thoracic blood volume which inhibits the low pressure cardiopulmonary baroreceptor discharges would result in sympathetic activation, with an additional contribution from the arterial (high pressure) baroreceptors when the systemic BP is diminished [23]. BP is not always reduced when the fall in stroke volume is compensated by a HR increase which maintains the cardiac output. However, the present protocol of phlebotomy did not significantly increase HR and the cardiac output was consequently reduced. Similarly, Fortrat et al. [5] did not observe any HR

Table 1 Hemodynamic values averaged over 60 s before phlebotomy, at the end of the blood withdrawal and during recovery periods, obtained in the 12 subjects

	Pre-phlebotomy	Phlebotomy	Post-phlebotomy
Systolic BP mmHg	127.8±3.6	122.1±3.8	121.2±3.9*
Diastolic BP mmHg	74.8±2.2	75.0±2.3	73.5±2.1
Mean BP mmHg	96.4±2.3	94.0±2.4	92.6±2.4*
Pulse pressure mmHg	53.0±3.5	47.1±3.2*	47.7±3.5*
HR Beats/min	75.2±3.7	78.3±4.5	75.9±3.8
Stroke volume ml/beat	94.0±5.2	80.7±5.3*	83.5±5.1*
Stroke volume index $ml/beat \cdot m^2$	51.5±2.6	44.1±2.4*	45.6±2.3*
Cardiac output L/min	6.9±0.4	6.1±0.3*	6.2±0.3*
Cardiac index $L/min \cdot m^2$	3.8±0.2	3.4±0.2*	3.4±0.2*
Total peripheral resistance $mmHg \cdot min \cdot L^{-1}$	0.73±0.06	0.79±0.08*	0.76±0.09

Values shown are means ± SEM. * $P < 0.05$ versus pre-phlebotomy levels

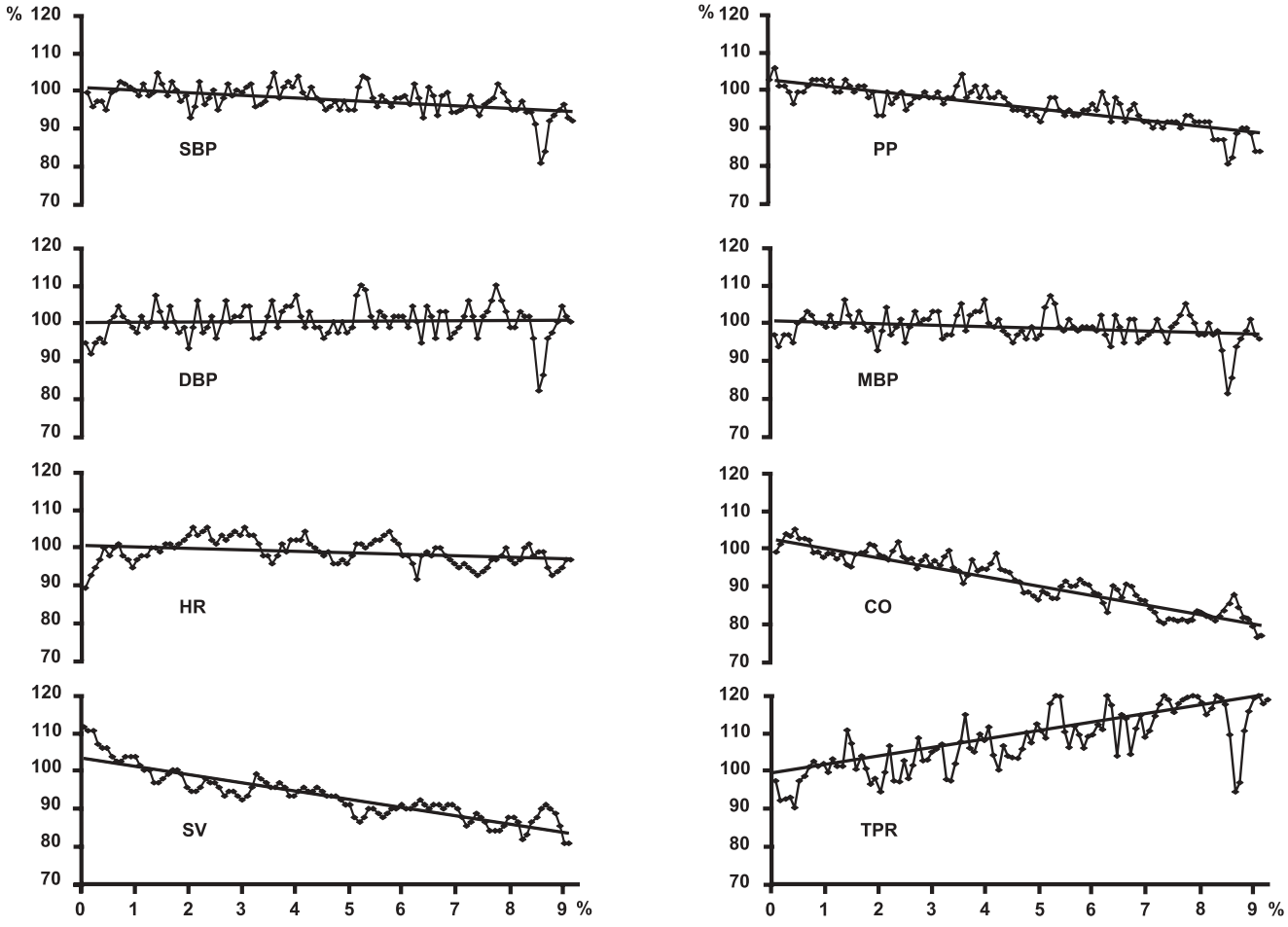

Fig. 2 Relationship between the volume withdrawn and the different hemodynamic indices, corresponding to the data from the patient shown in Fig. 1. The hemodynamic variables (ordinates) are normalized to the pre-phlebotomy levels. The abscissa represents the volume withdrawn as a percentage of the estimated total blood volume of the subject. *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *HR* heart rate; *SV* stroke volume; *PP* pulse pressure; *MBP* mean blood pressure; *CO* cardiac output; *TPR* total peripheral resistance

Table 2 Average correlation coefficients of the regression between the different hemodynamic variables and the normalized blood volume changes (in percent) obtained in the 12 subjects

	Correlation coefficient	Slope
Systolic BP	0.68 ± 0.05	−1.44 ± 0.20
Diastolic BP	0.39 ± 0.09	−0.58 ± 0.18
Mean BP	0.57 ± 0.07	−1.01 ± 0.17
Pulse pressure	0.80 ± 0.04	−2.70 ± 0.29
HR	0.52 ± 0.09	+1.01 ± 0.25
Stroke volume	0.88 ± 0.01	−2.15 ± 0.17
Cardiac output	0.64 ± 0.05	−1.25 ± 0.17
Total peripheral resistance	0.31 ± 0.05	+0.55 ± 0.30

Values shown are means ± SEM

change following blood donation (480 ml) in experienced blood donors (as the present patients are) although elevation in plasma catecholamines indicated sympathetic activation. A rise in total peripheral resistance was observed during blood withdrawal in our study. This reflex increase in peripheral resistance might buffer the mean BP changes and probably explains why the BP changes following a 14 % reduction in stroke volume were small (Table 1). Burke and Dorward also showed in rabbits that reduction of up to 18 % blood volume doubled renal sympathetic nerve activity with virtually no change in BP [2]. Nevertheless, continuous BP measurements from the finger allowed the detection of these small graded changes concomitant to the blood withdrawal (Table 2), which are rarely observed with an automated cuff device [14].

Thus, the relationship between the stroke volume estimates and the other variables (BP, HR levels) may predominantly result from the baroreflexes. Other hemodynamic factors may also link these variables. The interesting finding of a reduced pulse pressure associ-

ated with the blood volume diminution is not surprising since the pulse pressure is largely dependent upon the stroke volume [3, 9]. Indeed pulse pressure is often used to reflect cardiac preload [17, 18]. The pulse pressure reduction during phlebotomy was mainly due to a diminished systolic BP, as a consequence of a reduced cardiac ejection. Compared to the stroke volume estimates derived from the Modelflow, the pulse pressure appeared to be equally able to estimate blood volume withdrawn since it was as well correlated to the blood volume withdrawn. Also the slope obtained for stroke volume versus the volume withdrawn was in a similar range as that obtained for the pulse pressure versus the volume withdrawn. One theoretical advantage for using the stroke volume is its causal role in the hemodynamic changes. However stroke volume is calculated (see below) while pulse pressure is directly measured.

The hemodynamic changes associated with a rapid and moderate blood withdrawal, 375 ml in 6.4 min in this study, may differ from those occurring over longer periods of time such as 30 min. The autonomic nervous system might be the main factor compensating BP on a short-term basis. The changes in stroke volume and pulse pressure observed during the phlebotomy were still present 4–5 min after completion of the blood withdrawal, indicating that long-term regulatory processes were not efficient within this time range to restore the blood volume. The activation of humoral systems and the shift of fluid from an extravascular compartment to the blood also dampen these changes during longer bleedings [1, 22]. However, a recent study showed fluid replacement occurs rapidly, within the time range of the present study i. e. 6–7 min [12]. Alltogether, these compensatory mechanisms explain why a 10 % blood volume reduction does not markedly affect BP [5, 9, 28, 32].

The main result of this study is the observation that the Modelflow appears to be sensitive enough for tracking a graded and moderate blood loss on a beat-to-beat basis. This BP waveform modeling was shown to be able to quantify the cardiac output decrease associated with an orthostatic maneuver [7, 10, 29]. This procedure of instant stroke volume determination was considered correct according to the validation studies comparing this method to thermodilution and Doppler ultrasound velocity [10, 29, 31]. The Modelflow method computes an aortic flow waveform from a peripheral arterial pressure signal. It uses a nonlinear, time-varying, three-element model of the aortic input impedance. The three elements correspond to the characteristic impedance of the aorta, the total arterial compliance, and the total peripheral vascular resistance. The flow pulsation is integrated for each beat to obtain stroke volume, and finally cardiac output is calculated by the product of stroke volume and instant HR. Aortic pressure is theoretically preferred in the model, but is not routinely available in clinical practice. Therefore, peripheral (finger) arterial pressure was used. However, peripherally measured arterial pressure is distorted compared with aortic pressure and although the calculated flow waveform is also distorted, the area under the flow wave, which equals the stroke volume, was shown to be minimally affected by such distortion. Nevertheless, within-subject changes in stroke volume are more accurate than the between subject stroke volume differences. Under our conditions the within-subject changes in stroke volume closely mirrored the blood withdrawal. However, in a study performed in the elderly, the validity of Modelflow has been questioned [24]. It has been shown that a calibration factor using one concomitant thermodilution cardiac output measure should be used to obtain accurate estimates of cardiac output with the Modelflow [24]. One consideration which may affect stroke volume estimation by the Modelflow is the effect of HR on the aortic impedance, which reflects cardiac afterload faced by the left ventricle. Aortic impedance has been shown to decrease while HR increases [19]. The aortic impedance is taken into account in the Modelflow calculation of the stroke volume. This factor may affect the stroke volume estimates when HR is changing with the blood withdrawal. However, the stroke volume estimates were better correlated to the blood loss than the HR changes, which were of small amplitude (4 %). Moreover the example shown in Fig. 1 clearly shows a stroke volume diminution without concurrent HR increases. This confirms the marginal influence of the HR changes on the calculation of stroke volume.

In conclusion stroke volume monitored using the Modelflow adequately mirrored the blood volume withdrawn during therapeutic phlebotomy performed in subjects with asymptomatic hemochromatosis. Pulse pressure was also sensitive enough to reflect the blood volume diminution. Thus, the noninvasive estimation of finger BP can be used to derive simple on-line indices (pulse pressure, stroke volume) of cardiovascular status, particularly useful in the monitoring of cardiac preload in the critically ill patient. Another potential application of this study could be the description of stroke volume changes resulting from an acute drug administration. The effects of drugs modifying blood volume (diuretics), cardiac inotropy or venous return could be tested in the future using this approach.

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