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Experimental Physiology – *Research Paper*

Modelflow estimates of cardiac output compared with Doppler ultrasound during acute changes in vascular resistance in women

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We compared Modelflow (MF) estimates of cardiac stroke volume (SV) from the finger pressure-pulse waveform (Finometer®) with pulsed Doppler ultrasound (DU) of the ascending aorta during acute changes in total peripheral resistance (TPR) in the supine and head-up-tilt (HUT) postures. Twenty-four women were tested during intravenous infusion of 0.005 or 0.01 μg kg^{-1} min^{-1} isoprenaline, 10 or 50 ng kg^{-1} min^{-1} noradrenaline and 0.3 mg sublingual nitroglycerine. Responses to static hand-grip exercise (SHG), graded lower body negative pressure (LBNP, from −20 to −45 mmHg) and 45 deg HUT were evaluated on separate days. Bland–Altman analysis indicated that SV_{MF} yielded lower estimates than SV_{DU} during infusion of 0.01 μg kg^{-1} min^{-1} isoprenaline (SV_{MF} 92.7 ± 15.5 *versus* SV_{DU} 104.3 ± 22.9 ml, $P = 0.03$) and SHG (SV_{MF} 78.8 ± 12.0 *versus* SV_{DU} 106.1 ± 28.5 ml, $P < 0.01$), while larger estimates were recorded with SV_{MF} during −45 mmHg LBNP (SV_{MF} 52.6 ± 10.7 *versus* SV_{DU} 46.2 ± 14.5 ml, $P = 0.04$) and HUT (SV_{MF} 59.3 ± 13.6 *versus* SV_{DU} 45.2 ± 11.3 ml, $P < 0.01$). Linear regression analysis revealed a relationship ($r^2 = 0.41$, $P < 0.01$) between the change in TPR from baseline and the between-methods discrepancy in SV measurements. This relationship held up under all of the experimental protocols (regression for fixed effects, $P = 0.46$). These results revealed a discrepancy in MF estimates of SV, in comparison with those measured by DU, during acute changes in TPR.

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The Modelflow method of computing cardiac stroke volume from an analysis of the pulse wave contour of the arterial blood pressure wave (Wesseling *et al.* 1993) has become commercially accessible with the Finometer® device. Several previous investigations have concluded that during supine rest, head-up tilt or exercise, the Modelflow approach correlates well, with little or no discrepancy in the estimation of mean values (Harms *et al.* 1999; Houtman *et al.* 1999; Sugawara *et al.* 2003; van Lieshout *et al.* 2003), although a reference standard is required for quantitative measurements (Harms *et al.* 1999). Recently, stroke volume obtained with Modelflow (SV_{MF}) was compared with stroke volume by Doppler ultrasound (SV_{DU}) to reveal the correspondence of beat-to-beat changes by the two approaches (van Lieshout *et al.* 2003). This study showed no discrepancy between the two methods for the beat-to-beat variability in the supine posture, but did show an offset of about 10%, with the Modelflow estimates being greater than ultrasound, in a 30 deg head-up-tilt (HUT) position. The authors speculated that possible limitations in each method, including a change in heart position that could have affected the ultrasound measurements (van Lieshout *et al.* 2003), might have contributed to this discrepancy, which was greater than the difference observed between thermodilution and model flow at the same tilt angle (Harms *et al.* 1999). However, the estimation of SV_{MF} has underlying assumptions used to derive the interrelationships between aortic characteristic impedance (Z_o), arterial Windkessel compliance (C_w)

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and total systemic peripheral resistance (TPR) that could be influenced by peripheral circulatory factors, including changes in body position.

In the present study, we employed several interventions to test the hypothesis that acute changes in peripheral vascular resistance induced by vasoactive drugs, orthostatic stress and exercise would cause discrepancy in the estimate of SV_{MF} compared with SV_{DU}. To avoid the possible complications in experimental design introduced by changes in body position (van Lieshout *et al.* 2003) or fluid shifts, we kept the subjects in a supine position during static hand-grip exercise (SHG) and during manipulation of vascular resistance by infusions of isoprenaline (IP) or noradrenaline (NA) and sublingual nitroglycerine (NG), and we compared these SV responses with those during passive upright tilt (HUT) and lower body negative pressure (LBNP).

Methods

Ethical approval

This project conformed to the standards set by the latest revision of the Declaration of Helsinki and received ethical approval from the Office of Research Ethics at the University of Waterloo. The overall study was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Midi-Pyrénées (France). Each subject gave written informed consent and was aware of her right to withdraw from the study for any reason without prejudice.

Subjects

Twenty-four women (32 ± 4 years old, mean $\pm$ S.D.) enrolled in the Women's International Space simulation for Exploration (WISE) bed rest study gave written informed consent to participate in this experiment. The research was conducted at the MEDES Clinical Research Facility in Toulouse, France.

Measurements

The data for this experiment were collected on the fourth day (hand-grip, LBNP and HUT studies) and the 14th day (drug studies) of the 20 day ambulatory control period prior to the start of the WISE bed rest regimen. All measurements except HUT were performed while the subjects were supine in a quiet, darkened room kept at a relatively constant temperature (21–23°C). Heart rate (HR; Pilot 9200, Colin Medical Instruments, San Antonio, TX, USA), mean arterial blood pressure (MAP) estimated by finger photoplethysmography with height correction on the left arm (Finometer®, FMS, Amsterdam, The Netherlands) and blood velocity in the ascending aorta assessed by pulsed wave Doppler ultrasound (Multigon Industries, Mt Vernon, NY, USA) were collected using a data-acquisition system (PowerLab, ADInstruments, Colorado Springs, CO, USA). The pulsed Doppler 2 MHz probe was positioned in the suprasternal notch and directed towards the aortic root, with the sample volume immediately above the aortic valve to obtain the maximal velocity during systole (Eriksen & Walloe, 1990) and an angle of insonance with forward blood flow within 15 deg (Tibbals *et al.* 1988).

Experimental design

With the subjects supine on an examination table, an intravenous catheter was inserted in the left arm for infusion of isoprenaline and noradrenaline. Following a baseline period of 10 min, isoprenaline infusion was commenceed at two constant rates of 0.005 and 0.01 μg kg^{-1} min^{-1} for 5 min at each dose. At least 10 min was allowed for washout of the isoprenaline and return of heart rate and blood pressure to baseline values before infusion of noradrenaline at 10 and 50 ng kg^{-1} min^{-1} for 5 min at each dose. When measured variables had returned to baseline after the noradrenaline infusion, 0.3 mg of nitroglycerine was administered by sublingual spray. On another day, subjects completed a series of tests. Initially, they were placed in the supine position into an airtight, lower body negative pressure box with a neoprene seal at the level of the iliac crest. Lower body negative pressure was applied at -20, -30 and -45 mmHg for 3 min at each increment. On completion of the LBNP protocol, subjects rested before performing 2 min of static hand-grip exercise at 40% of maximal voluntary contraction. After an additional rest period, subjects were tilted to 45 deg head-up tilt for 5 min.

Data analysis

Beat-to-beat blood velocity in the ascending aorta was obtained by averaging the outer envelope of the Doppler signal between consecutive R waves from the ECG. The diameter of the base of the aorta was measured by echo ultrasound imaging (LOGIQ Book, GE Healthcare, Tours, France) by measuring the distance from the leading edge of the anterior wall to the leading edge of the posterior wall.

Values for SV_{DU} were calculated by averaging aortic blood velocity values over 1 min at baseline, during the final minute of each drug infusion, during the interval between the third and fouth minute following NG administration, and in the final minute of each stage of LBNP, SHG and HUT. The following equation was used:

$$SV_{DU} = V_a \times \pi(D_a/2)^2 \times RR$$

where SV_{DU} is the stroke volume measured by Doppler ultrasound (in ml beat^{-1}), V_a the aortic blood velocity (in

Table 1. Cardiovascular indices during drug administration, static hand grip and orthostatic challenge

Condition	Heart rate (beats min^{-1})	MAP (mmHg)	$\dot{Q}_{DU}$ (l min^{-1})	$\dot{Q}_{MF}$ (l min^{-1})
Baseline drugs	64 ± 8	89.6 ± 9.6	5.2 ± 1.3	5.2 ± 1.2
IP 0.005 μg kg^{-1} min^{-1}	71 ± 8*	87.6 ± 8.1	6.7 ± 1.7*	6.4 ± 1.4*
IP 0.01 μg kg^{-1} min^{-1}	77 ± 8*	88.0 ± 8.8	8.1 ± 1.8*†	7.2 ± 1.5*†
NA 10 ng kg^{-1} min^{-1}	62 ± 8	91.9 ± 13.4	5.3 ± 1.5	5.2 ± 1.2
NA 50 ng kg^{-1} min^{-1}	60 ± 7*	97.5 ± 8.6*	4.7 ± 1.1	5.0 ± 1.0
NG 0.3 mg	74 ± 10*	89.9 ± 7.8	4.7 ± 1.2	4.8 ± 0.8
Baseline SHG	72 ± 9	96.6 ± 9.7	6.6 ± 2.1	5.6 ± 0.8
SHG	88 ± 15*	111.5 ± 12.7*	9.5 ± 1.7*†	6.6 ± 1.1*†
Baseline HUT	72 ± 9	92.8 ± 9.2	5.5 ± 1.4	5.7 ± 1.0
HUT	87 ± 10*	97.3 ± 8.6*	3.9 ± 0.9*†	5.2 ± 0.9*†
Baseline LBNP	69 ± 8	87.7 ± 8.6	5.6 ± 1.3	5.5 ± 1.1
LBNP −20 mmHg	75 ± 9*	86.0 ± 7.7	4.6 ± 1.1	4.9 ± 0.9
LBNP −30 mmHg	79 ± 10*	85.1 ± 8.1	4.4 ± 1.1*	4.7 ± 0.9*
LBNP −45 mmHg	86 ± 11*	86.6 ± 8.2	4.0 ± 0.9*#	4.5 ± 0.9*†

Abbreviations: MAP, mean arterial pressure; $\dot{Q}_{DU}$, cardiac output measured by Doppler ultrasound; $\dot{Q}_{MF}$, cardiac output measured by Modelflow; IP, isoprenaline at infusion rates of 0.005 and 0.01 μg kg^{-1} min^{-1}; NA, noradrenaline at infusion rates of 10 and 50 ng kg^{-1} min^{-1}; NG, nitroglycerine at 0.3 mg sublingual spray; SHG, static hand grip; HUT, head-up tilt; and LBNP, lower body negative pressure. Values are means ± S.D. * Significant difference from baseline, † significant difference between methods, $P < 0.10$.

cm s^{-1}), D_a the aortic root diameter (in cm) and RR the time between R peaks on the ECG (in s beat^{-1}).

Total peripheral resistance was calculated from mean arterial pressure and cardiac output ($\dot{Q}$) using the following equation:

$$\mathrm{TPR} = \mathrm{MAP}/(\mathrm{SV} \times \mathrm{HR}) \times 60$$

where TPRis the total peripheral resistance (in mmHg l^{-1} min^{-1}), MAP the mean arterial blood pressure (in mmHg), SV the stroke volume (in l beat^{-1}) and HR the heart rate (in beats min^{-1}).

Cardiac output by Modelflow was calculated online by the proprietary software of the Finometer® device by analysis of the finger pressure waveform using a three-element [aortic characteristic impedance (Z_0), Windkessel compliance (C_w) and peripheral resistance (R_p)] non-linear equation dependent on the pressure–area relationship of the aorta. Age, sex, height and weight for each subject were entered into the unit prior to testing, and these parameters were used to determine the individual aortic pressure–area relationship. Pressure–area relationship allows for computation of Z_0 and C_w, while R_p is adapted by the model.

$$Z_0 = \sqrt{(\rho/AC)}$$

$$C = \mathrm{d}A/\mathrm{d}P$$

$$C_w = lC$$

where ρ is the density of the blood, A the aortic cross-sectional area, C the compliance per unit length of the aorta and l the effective length of the aorta.

Statistical analysis

All statistical computations were made using statistical analysis software (SAS Institute, Cary, NC, USA). Data are presented as means ± S.D. Absolute values and relative changes for each protocol were plotted as histograms and Q–Q plots to determine normality of the data. The significance of changes in cardiovascular indices from baseline, and between conditions, was determined by fixed effects regression analysis (SAS, using the proc mixed procedure). This model was chosen for its ability to control for all the stable characteristics of the individuals, over repeated measures, by using only within-individual variation to estimate the regression coefficients (Allison, 2006). The significance of differences between measurement techniques was determined using Bland–Altman analysis (Bland & Altman, 1986; Mantha *et al.* 2000). The relationship between change in TPR from baseline and SV measurement bias was fitted using a linear model. A probability of $P < 0.05$ was accepted as statistically significant.

Results

Measures of HR, MAP and $\dot{Q}$ are shown in Table 1. Stroke volume and TPR are shown graphically in Figs 1 and 3, respectively. Both Doppler ultrasound (DU) and Modelflow (MF) methods recorded a significant SV increase from baseline with administration of isoprenaline (Fig. 1). There were no changes in SV with noradrenaline infusion. Both methods also detected decreases from baseline following administration of NG, HUT and LBNP (Fig. 1). There was also an increase in SV_{DU} but not in SV_{MF} during

static hand grip. Bland–Altman analysis (Fig. 2) indicated that the SV_{MF} and SV_{DU} were in good agreement during low-dose IP infusion (confidence interval, CI: −14.7 to +5.0, $P = 0.42$; Fig. 2*A*), 10 ng kg^{-1} min^{-1} noradrenaline infusion (NA_{10}; CI: −14.0 to +8.5, $P = 0.70$; Fig. 2*C*) and 50 ng kg^{-1} min^{-1} noradrenaline infusion (NA_{50}; CI: −3.1 to +13.1, $P = 0.35$; Fig. 2*D*), sublingual NG (CI: −3.2 to +8.6, $P = 0.49$; Fig. 2*E*), LBNP −20 mmHg (CI: −2.3 to +12.3, $P = 0.23$; Fig. 2*H*) and LBNP −30 mmHg (CI: −3.2 to +9.6, $P = 0.37$; Fig. 2*I*). Estimates of SV_{MF} were smaller than those for SV_{DU} during SHG (CI: −39.3 to −3.5, $P < 0.01$; Fig. 2*F*) and high-dose IP (CI: −22.6 to −0.68, $P = 0.03$; Fig. 2*B*) but larger during HUT (CI: +8.3 to +20.0, $P < 0.01$; Fig. 2*G*) and LBNP −45 mmHg (CI: +0.1 to +12.7, $P = 0.04$; Fig. 2*J*).

Total peripheral resistance, as calculated from mean arterial pressure and both the DU and the MF $\dot{Q}$ data, was decreased in a dose-specific manner with IP and increased with the higher dose of NA (Fig. 3*A*). Total peripheral resistance also increased during HUT (Fig. 3*C*) and progressively with LBNP (Fig. 3*D*). Discrepancies between TPR_{MF} and TPR_{DU}, determined from Bland–Altman analysis, were found during HUT (CI: −9.0 to −3.8, $P < 0.01$) and −45 mmHg LBNP (CI: −6.9 to −1.0, $P = 0.02$).

Figure 4 illustrates the relationship between the differences in measured SV_{DU} and SV_{MF} (% change from baseline) and changes in TPR_{DU} due to the drug, hand-grip and orthostatic challenge effects ($r^2 = 0.41$, $P < 0.01$). A fixed effects regression analysis was performed to determine whether there was a difference between two

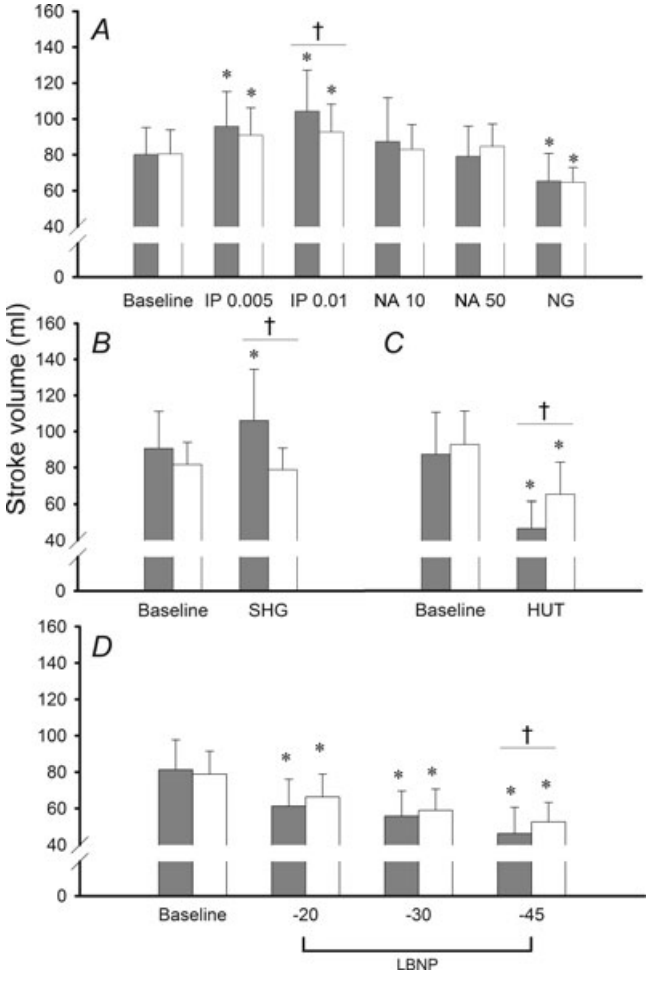

Figure 1. Stroke volume as measured by Doppler ultrasound (grey bars) and Modelflow methods (open bars)
Stroke volume was measured at baseline and during infusion of isoprenaline (IP) and noradrenaline (NG) and sublingual nitroglycerine (NG; *A*), during static hand-grip exercise (SHG; *B*), during head-up-tilt (HUT; *C*) and during lower body negative pressure (LBNP; *D*). Values are means + S.D. * Significant difference from baseline, † significant difference between methods, $P < 0.05$.

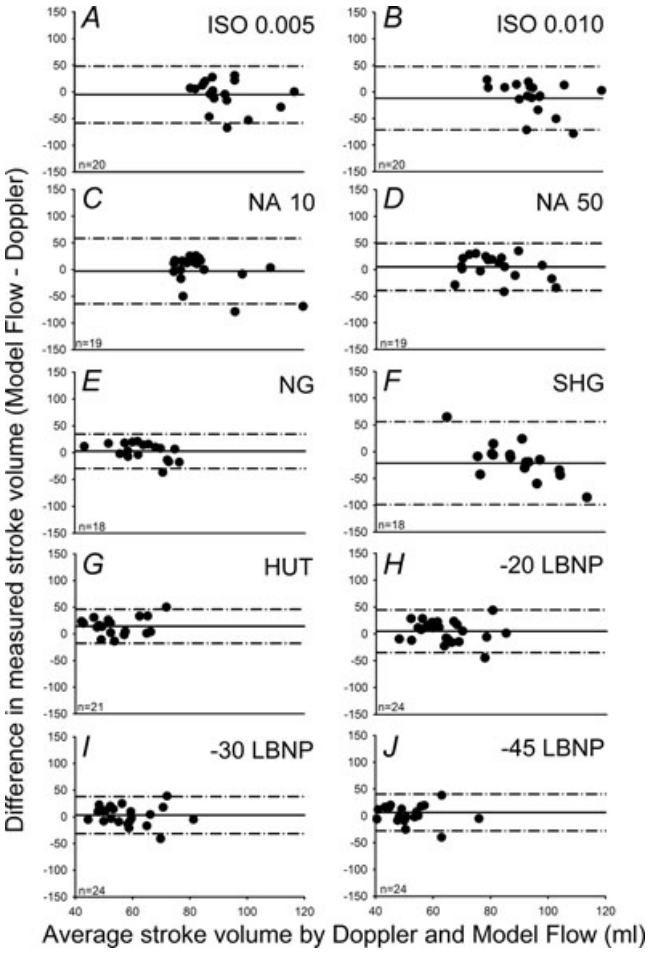

Figure 2. Bland–Altman plots comparing stroke volume estimations by Doppler ultrasound and Modelflow methods during drug administration, static hand-grip exercise and orthostatic challenge
The plots indicate good agreement between the methods; however, SV was underestimated by MF during IP infusion at 0.01 μg kg^{-1} min^{-1} and overestimated during HUT and −45 mmHg LBNP compared with DU. —, mean; –·–, ±2 S.D.

sets of conditions, one where subjects were always in quiet supine rest so that no displacement of the Doppler probe to the heart would be expected (drug tests and SHG; filled circles in Fig. 4) and one where the subjects' hearts might have moved relative to the Doppler probe due to gravity or fluid shifts (LBNP and HUT; open triangles in Fig. 4). There were no differences in the relationship between discrepancies in ΔSV_{DU} and ΔSV_{MF} and ΔTPR ($P = 0.46$) whether the subjects were in the quiet supine position (no displacement) or under orthostatic challenge (possible displacement of heart relative to Doppler probe).

Discussion

This is the first study to explore the ability of the Modelflow method of SV estimation to track SV during periods of acute changes in TPR in both the supine and HUT postures. Previous discrepancies between stroke volume values measured by Doppler ultrasound and Modelflow calculations from finger pulse contour analysis were attributed to changes in heart position during HUT that could introduce error in the Doppler measurement (van Lieshout *et al.* 2003). van Lieshout *et al.* (2003) found that Doppler measurements diverged from the more direct measure of thermodilution at 30 deg of passive tilt. However, in the present study continuous attention was paid, by both audio and visual techniques, to ensure the correct direction of the ultrasound beam, thus limiting the effect of blood pooling or heart displacement. Indeed, our results have revealed between-methods discrepancies independent of postural changes. We suggest that the measurement bias relative to Doppler measurements results from a failure of the Modelflow mathematical algorithm to track cardiac stroke volume changes accurately during conditions that result in acute changes in vascular resistance. We observed a consistent pattern of bias, with an overestimate of SV_{MF} compared with SV_{DU} when TPR increased (HUT and LBNP −45 mmHg), and an opposite underestimate of SV_{MF} compared with SV_{DU} when TPR decreased (IP 0.01 μg kg^{-1} min^{-1}).

It has been reported that Modelflow calculation of cardiac stroke volume derived from the finger pressure-pulse waveform can yield accurate continuous measurements of cardiac minute volume ($\dot{Q}$) if an initial calibration is made using a gold standard method such as the direct Fick or thermodilution method (Sugawara *et al.* 2003; Matsukawa *et al.* 2004; Bogert & van Lieshout, 2005). The Modelflow calculation used by the Finometer®

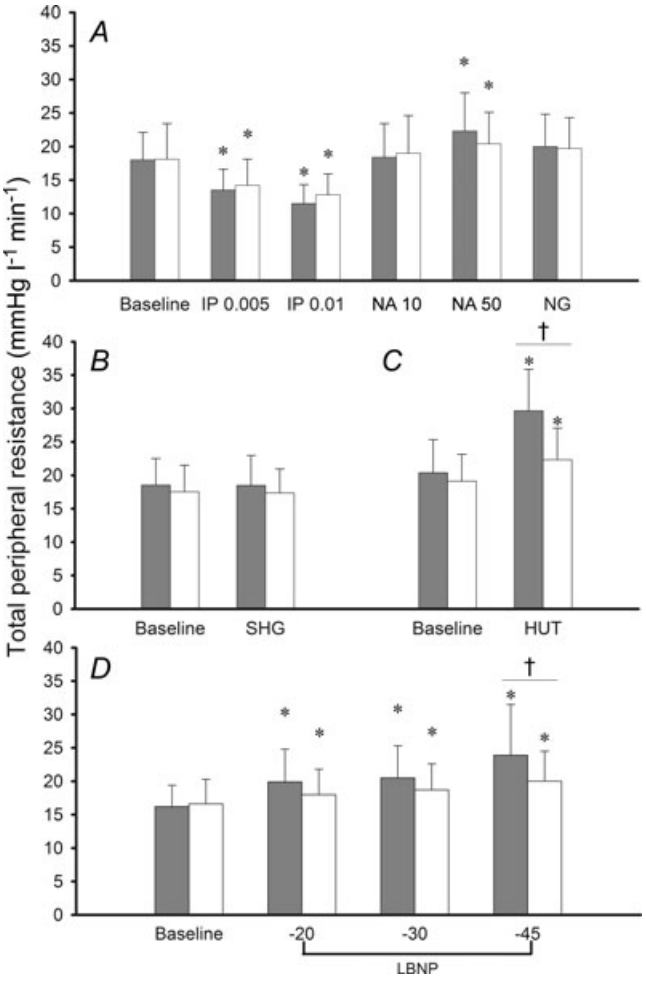

Figure 3. Total peripheral resistance as calculated from Doppler ultrasound (grey bars) and Modelflow (open bars), at baseline and during drug administration (*A*), SHG (*B*), HUT (*C*) and LBNP (*D*)

See Fig. 1 for abbreviations. Values are means + S.D. * Significant difference from baseline, † significant difference between methods, $P < 0.05$.

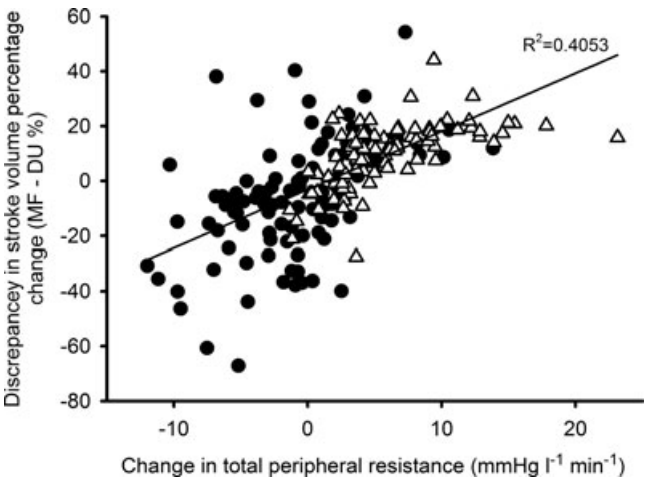

Figure 4. Discrepancy in measurement of stroke volume percentage change between Doppler ultrasound and Modelflow methods in relation to the change in TPR calculated from Doppler stroke volume and mean arterial pressure with (△, HUT and LBNP) and without (●, drug administration and hand-grip) and orthostatic challenge

is comprised of blood pressure measurements made at the finger (calibrated at the brachial artery) and assumed values for aortic diameter, Windkessel compliance and (TPR). Total peripheral resistance in this model is defined as the total of aortic characteristic impedence (Z_0) and the Poiseuille resistance of all vascular beds (R_p; Wesseling, 1977). The value of R_p is assumed to change relatively slowly compared with the heart beat interval, and thus the current computed value is used to simulate the flow over the next beat; a reasonable initial value is assumed, the ratio of 100 mmHg mean pressure and 3 l min^{-1} cardiac output are assumed, and from true mean pressure and computed mean flow the next approximation is computed. As such, R_p can converge from the initial value to the correct value in a few heart beats (Wesseling, 1977). However, it is possible that acute changes in TPR will not allow the model to converge adequately upon a reasonable R_p value for inclusion in the derivation of volume flow for subsequent beats. It is beyond the scope of this article to perform a thorough critique of the Modelflow equations; however, we have shown that there is significant discrepancy in the cardiac output derived by the method, when compared with Doppler ultrasound, during periods of dynamic changes in peripheral vascular resistance.

Non-linear modelling by the Modelflow method and periodic servo-loop calibrations performed by the Finometer® device have improved the accuracy of cardiac stroke volume computation by pressure-pulse analysis (Wesseling *et al.* 1993). The periodic Finometer® finger volume-clamp servo loop adjusts to changes in arterial tone in the finger (Langewouters *et al.* 1998), assuring consistent monitoring of the pressure waveform at the finger. When calibrated by the direct Fick or thermodilution method (Sugawara *et al.* 2003; Matsukawa *et al.* 2004; Bogert & van Lieshout, 2005) or monitoring of aortic diameter (de Vaal *et al.* 2005), Modelflow reliably and accurately provides cardiac output data, validated during exercise and active postural change (Matsukawa *et al.* 2004), in cardiac surgery (Bolt *et al.* 1994) and in the intensive care unit (de Vaal *et al.* 2005). However, the results of the present analysis have exposed experimental, and potentially clinical, situations in which the effectiveness of these improvements is limited. Our results reveal that during administration of vasoactive drugs or the initiation of static exercise or passive orthostatic challenge causing changes in the peripheral vascular resistance there was discrepancy in Modelflow estimation when compared with Doppler ultrasound.

There was no change in TPR with sublingual nitroglycerine administration or the low-dose infusion of noradrenaline. Total peripheral resistance was found to be decreased during the administration of isoprenaline. The significant discrepancies in SV derivation between methods during IP 0.01 μg kg^{-1} min^{-1} and during HUT can probably be explained by the significant changes in TPR witnessed during these protocols. The reduced vascular resistance during IP infusion and increased TPR during HUT mirror the discrepancy in stroke volume measured by the Modelflow method. It is more difficult to resolve the findings of between-methods SV discrepancies during SHG and the agreement during NG, both conditions in which TPR was found not to change from baseline. These findings may indicate that it is not the change in TPR *per se* that is responsible for the discrepancy, but more local resistance changes that in some conditions underlie a change in TPR (IP and HUT), while in others do not change TPR (SHG).

It is well established that isoprenaline and noradrenaline alter TPR via sympathetic activation in resistance arterioles; isoprenaline via the dilatory β-adrenergic receptors and noradrenaline via the constrictive α-adrenergic receptors (Dixon *et al.* 1979). Nitroglycerine, in contrast, is proposed to act as a nitric oxide donor at the smooth muscle, causing conduit vessel dilatation (Lippton *et al.* 1982; Brien *et al.* 1988). Total peripheral resistance did not change with administration of NG, suggesting that there was vasoconstrictor compensation in the peripheral vasculature, probably mediated by the sympathetic nervous system (Gisolf *et al.* 2004). Lower body negative pressure has consistently been shown to increase TPR in a dose-specific manner (Stevens & Lamb, 1965), which can be explained by increases in sympathetic tone (Shoemaker *et al.* 1997). Total peripheral resistance has been reported not to change or to increase slightly during static hand-grip exercise (Sakakibara & Honda, 1990). Although sympathetic nerve activity has been shown to increase during static exercise (Sakakibara & Honda, 1990; Shoemaker *et al.* 2000) the effect of this on total peripheral resistance has not fully been explored. Our finding that TPR did not change during the SHG is due to the increase in SV (measured by Doppler ultrasound) being met with a compensatory rise in MAP.

The trend line generated in the regression analysis (Fig. 4) indicates that there was a tendency for the Modelflow method to overestimate changes in SV when TPR is increased (NA, HUT and LBNP), and to underestimate changes in SV when TPR is decreased (IP). We acknowledge that Doppler ultrasound is not a gold standard method of measuring cardiac stroke volume; however, it is unlikely that there would be a systematic bias of Doppler measurements across the experimental models used in this experiment. The discrepancies in measurements were not likely to be due to heart position or blood volume shift artifacts, because the drugs and hand-grip protocols would not have caused movement of the heart relative to the Doppler probe that may occur during postural change or LBNP. Also, fixed effects regression analysis indicated that the relationship between the change in TPR_{DU} and between-methods SV discrepancy was independent of the protocol.

Conclusion

Although both Doppler ultrasound and ModelFlow were able to track changes in cardiac output adequately in 10 of the 14 tests performed, we showed a significant discrepancy between the methods that was associated with acute changes in TPR during the administration of vasoactive drugs or orthostatic challenge. Factors that decreased TPR were associated with an underestimate of SV_{MF} compared with SV_{DU}, while factors that increased TPR were associated with an overestimate of SV_{MF} compared with SV_{DU}. In one case, SHG, there was a discrepancy without a change in TPR. However, the complex nature of haemodynamic changes (central and peripheral) during SHG could have contributed to miscalculation by Modelflow. These data indicate that while the Modelflow method provided a non-biased estimate of SV in baseline conditions for our healthy young female subjects, caution should be applied in the interpretation of changes in SV if the subject under investigation exhibits large changes in TPR.

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