Correction of cardiac output obtained by Modelflow® from finger pulse pressure profiles with a respiratory method in humans

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ABSTRACT

The beat-by-beat non-invasive assessment of cardiac output ($\dot{Q}$, litre · min^{-1}) based on the arterial pulse pressure analysis called Modelflow® can be a very useful tool for quantifying the cardiovascular adjustments occurring in exercising humans. $\dot{Q}$ was measured in nine young subjects at rest and during steady-state cycling exercise performed at 50, 100, 150 and 200 W by using Modelflow® applied to the Portapres® non-invasive pulse wave ($\dot{Q}_{Modelflow}$) and by means of the open-circuit acetylene uptake ($\dot{Q}_{C_2H_2}$). $\dot{Q}$ values were correlated linearly ($r = 0.784$), but Bland–Altman analysis revealed that mean $\dot{Q}_{Modelflow} - \dot{Q}_{C_2H_2}$ difference (bias) was equal to 1.83 litre · min^{-1} with an S.D. (precision) of 4.11 litre · min^{-1}, and 95 % limits of agreement were relatively large, i.e. from -6.23 to $+9.89$ litre · min^{-1}. $\dot{Q}_{Modelflow}$ values were then multiplied by individual calibrating factors obtained by dividing $\dot{Q}_{C_2H_2}$ by $\dot{Q}_{Modelflow}$ for each subject measured at 150 W to obtain corrected $\dot{Q}_{Modelflow}$ ($\dot{Q}_{corrected}$) values. $\dot{Q}_{corrected}$ values were compared with the corresponding $\dot{Q}_{C_2H_2}$ values, with values at 150 W ignored. Data were correlated linearly ($r = 0.931$) and were not significantly different. The bias and precision were found to be 0.24 litre · min^{-1} and 3.48 litre · min^{-1} respectively, and 95 % limits of agreement ranged from -6.58 to $+7.05$ litre · min^{-1}. In conclusion, after correction by an independent method, Modelflow® was found to be a reliable and accurate procedure for measuring $\dot{Q}$ in humans at rest and exercise, and it can be proposed for routine purposes.

INTRODUCTION

The Modelflow® method for the beat-by-beat assessment of cardiac output ($\dot{Q}$; litre · min^{-1}) makes it possible to reconstruct instantaneous aortic blood flow from arterial blood pressure pulsation by simulating a three-element non-linear and time-varying model of aortic compliance [1]. Numerical integration of flow during systole yields the stroke volume of the heart. $\dot{Q}$ can then be computed by multiplying the stroke volume by the corresponding heart rate.

Application of Modelflow® to pulse pressure profiles obtained non-invasively from finger tip recordings of arterial blood pressure could be of great clinical advantage. In the companion paper by Azabji Kenfack et al. [1a], however, we have shown that the $\dot{Q}$ values obtained from finger-tip pressure profiles are approx. 25 % higher than those obtained invasively from the

Key words: cardiac output, cycling, open-circuit acetylene uptake, pulse pressure analysis, stroke volume, Modelflow®.

Abbreviations: $\dot{Q}$, cardiac output; $\dot{Q}_{C_2H_2}$, $\dot{Q}$ determined by open-circuit acetylene uptake; $\dot{Q}_{Modelflow}$, $\dot{Q}$ determined by Modelflow®; $\dot{Q}_{corrected}$, corrected $\dot{Q}_{Modelflow}$.

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radial artery. These results suggest that Modelflow® $\dot{Q}$ values ought to be corrected by an established method for the measurement of $\dot{Q}$.

The aim of the present study was to test the hypothesis that, after appropriate correction using an independent method, Modelflow® provides reasonably accurate $\dot{Q}$ values at rest and during exercise ranging from moderate to severe intensities. To this end, average steady-state $\dot{Q}$ values obtained by Modelflow® ($\dot{Q}_{Modelflow}$) at rest and exercise were independently corrected using a calibration factor obtained using the open-circuit acetylene technique ($\dot{Q}_{C_2H_2}$) [2].

METHODS

Subjects

Experiments were carried out on nine male healthy subjects (age, 24.6 ± 2.96 years; body mass, 74.6 ± 6.90 kg; and height, 180.4 ± 4.03 cm). All subjects were informed about the procedures and the potential risks of the experiments and they all signed an informed consent form. The study was approved by the Ethics Committee of the School of Medicine of Udine and conformed with the principles outlined in the Declaration of Helsinki [3].

Methods

Reference $\dot{Q}$ ($\dot{Q}_{C_2H_2}$) was measured by means of an open-circuit acetylene technique [2]. At rest and the exercise steady state, the subject inhaled a gas mixture containing 21 % O_2, 6 % helium and 1.5 % acetylene balanced with nitrogen for a total of 20–25 breaths. Gas concentrations during breathing of the mixture were monitored continuously on a mass spectrometer (Airspec 2200, Gillingham, Kent, U.K.). Inspired and expired gas volumes were determined by an ultrasonic flow meter (Tuba; GHG, Zurich, Switzerland). Gas fractions and flow signals were calibrated before each experiment by means of gas mixtures of known composition and by means of predefined inspiratory and expiratory volumes obtained by using a calibrated 3 litre syringe (Hans Rudolph, Kansas City, MO, U.S.A.). At each $\dot{Q}_{C_2H_2}$ measurement, a pneumatic piston operated a shuttle valve (Hans Rudolph) placed between the ultrasonic flow meter and a two-way non-rebreathing valve. The pneumatic servomechanism (Burosoft, Udine, Italy) deviated the inflow from ambient air to the acetylene-containing gas mixture administered from a high-pressure gas cylinder via a Douglas bag. $\dot{Q}_{Modelflow}$ was determined continuously at rest and during exercise from arterial pulse pressure profiles recorded non-invasively by using a Portapres® system (TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). The photoplethysmographic cuff of Portapres® was positioned on the index and middle fingers. The Portapres® signal was calibrated following the procedure indicated by the manufacturer. The height adjustment sensor and the reference were positioned according to the manufacturer's instructions.

Pulse pressure, gas fractions and respiratory flow signals were digitized by means of a 16-bit A/D converter (MP100; Biopac Systems, Santa Barbara, CA, U.S.A.) operated by commercial software (ACK100W; Biopac Systems) running on a PC. Acquisition rate was set at 100 Hz. Exercise was performed on an electromagnetically braked cycle ergometer (Ergomed 840L; Siemens, Erlangen, Germany).

Pulse pressure profiles were then fed to a PC running the Beatscope® 1.0 software (TNO-TPD), implementing the Modelflow® model and making it possible to calculate heart rate and beat-by-beat stroke volumes of the heart. The Modelflow® method for the beat-by-beat assessment of $\dot{Q}$ makes it possible to reconstruct instantaneous aortic blood flow from arterial blood pressure pulsation by simulating a three-element nonlinear and time-varying model of aortic compliance [1]. Numerical integration of flow during systole yielded the stroke volume of the heart. $\dot{Q}$ can then be computed by dividing the stroke volume by the corresponding R-R interval.

Protocol

Subjects were referred to the laboratory after a light meal consumed 2 h before. They were seated on the ergometer and the Portapres® cuffs were positioned. After the calibration procedures were completed, the mouthpiece and the nose-clip were placed in position and the acquisition of the gas fractions, flow and blood pressure signals was started. After 4 min rest, $\dot{Q}_{C_2H_2}$ was measured. Then, the subject started pedalling against a 50 W workload at a constant pedalling rate of 60 revs $\cdot$ min^{-1}. At the fifth minute of exercise, $\dot{Q}_{C_2H_2}$ was measured again. At the end of the measurement, the subject immediately stopped and rested for 5 min. A new exercise run was then performed by increasing the workload by 50 W. Two additional exercise steps, separated by 5 min of rest, were performed up to the highest workload of 200 W.

Correction of $\dot{Q}_{Modelflow}$ with $\dot{Q}_{C_2H_2}$

In order to correct measured $\dot{Q}_{Modelflow}$ for $\dot{Q}_{C_2H_2}$, a workload was selected and, at the steady state, the average $\dot{Q}_{Modelflow}$ was calculated as the mean of beat-by-beat values over 1 min. A calibration factor was then calculated for each subject as the ratio of average $\dot{Q}_{Modelflow}/\dot{Q}_{C_2H_2}$. The selected workload was 150 W, that is the workload at which this ratio showed the lowest coefficient of variability. The individual calibration factors were then used to recalculate average $\dot{Q}_{Modelflow}$ at rest and at all the remaining workloads.

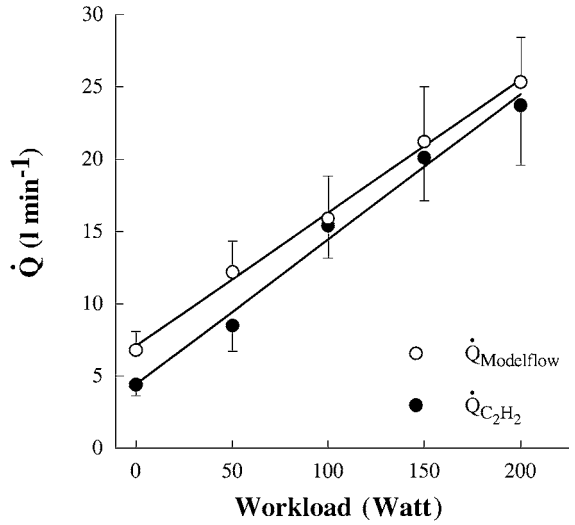

Figure 1 Mean values of $\dot{Q}_{Modelflow}$ and $\dot{Q}_{C_2H_2}$ plotted against workload

Statistics

Correlation between variables was calculated by the least-squares method using the procedure of Brace [4]. Regression parameters were analysed by using the procedures for the comparison of regression lines of the first kind [5]. Significant differences among average values in the different workload conditions were evaluated by means of two-way ANOVA [6]. Student's *t* test for one-sample analysis was utilized to reject the hypothesis of sample mean equal to zero or one. Agreement between the two methods of measurements was assessed by means of Bland–Altman analysis [7]. ANOVA for repeated measurements was applied to identify significant differences between averages related to the different workloads [8].

RESULTS

The average $\dot{Q}_{Modelflow}$ and $\dot{Q}_{C_2H_2}$ values as a function of the workload are shown in Figure 1. Linear regressions were calculated on the entire data in both cases ($n = 45$; $\dot{Q}_{Modelflow}$: $y = 7.09 + 0.092x$, $r = 0.926$; $\dot{Q}_{C_2H_2}$: $y = 4.41 + 0.100x$, $r = 0.937$). These lines had the same slopes, but significantly different y-intercepts. This means that $\dot{Q}_{Modelflow}$ was shifted upward with respect to $\dot{Q}_{C_2H_2}$.

The ratios between $\dot{Q}_{Modelflow}$ and $\dot{Q}_{C_2H_2}$ are shown in Table 1. These ratios varied significantly with the workloads. The ratios at 100, 150 and 200 W were not significantly different from 1. The smallest S.D., and thus the smallest coefficient of variation, was found at 150 W. The average of all the correction factors computed at all the workloads, including rest, was 0.87 (± 0.269).

Table 1 Means, S.D. and coefficient of variation (C.V.) of $\dot{Q}_{Modelflow}/\dot{Q}_{C_2H_2}$ ratios at rest and at the four workloads evaluated

	$\dot{Q}_{Modelflow}/\dot{Q}_{C_2H_2}$		
Workload (W)	Ratio	S.D.	C.V. (%)
0	0.69	0.198	28.7
50	0.72	0.252	35.0
100	1.02	0.320	31.5
150	0.97	0.220	22.6
200	0.96	0.223	23.3

Individual mean $\dot{Q}_{Modelflow}$ plotted as a function of the corresponding $\dot{Q}_{C_2H_2}$ is shown in Figure 2(A). The linear relationship between these two parameters was $y = 0.932x + 2.81$, indicating that the regression line was displaced upward with respect to the equality line (the line on which both sets of data would lie if they were identical). $\dot{Q}_{Modelflow}$ values were significantly correlated with $\dot{Q}_{C_2H_2}$ values ($r = 0.784$, $P < 0.01$).

The results of the Bland–Altman analysis are shown in Figure 2(B). The bias (mean $\dot{Q}_{Modelflow} - \dot{Q}_{C_2H_2}$) was 1.83 litre · min^{-1}. The bias value was significantly larger than 0, thus confirming that the regression line was displaced upward with respect to the equality line. The S.D. (precision) was 4.11 litre · min^{-1} and the 95 % limits of agreement ranged from -6.23 to $+9.89$ min^{-1}.

Corrected $\dot{Q}_{Modelflow}$ values ($\dot{Q}_{corrected}$) at rest and at all workloads, except 150 W, which was used to calculate the correction factor (see the Methods section), are plotted as a function of the corresponding $\dot{Q}_{C_2H_2}$ in Figure 2(C). The regression equation was $y = 1.177x - 3.75$. $\dot{Q}_{corrected}$ values were correlated significantly with $\dot{Q}_{C_2H_2}$ values ($r = 0.931$, $P < 0.01$). The results of Bland–Altman analysis are shown in Figure 2(D). The bias (mean $Q_{corrected} - Q_{C_2H_2}$) was 0.24 litre · min^{-1} and did not differ from 0. This indicated that the line relating $Q_{corrected}$ and $Q_{C_2H_2}$ was equal to the equality line. S.D. (precision) was 3.48 litre · min^{-1} and the 95 % limits of agreement ranged from -6.58 to $+7.05$ min^{-1}.

DISCUSSION

In the present study, the hypothesis that, after appropriate correction with an independent method, Modelflow® provides reasonably accurate $\dot{Q}$ values was tested at rest and during exercise. To this end, non-invasive $\dot{Q}$ values obtained with Modelflow® were corrected for independently established $\dot{Q}$ values measured with the open-circuit acetylene technique. The main finding of the present study is that, after such a correction, Modelflow® applied to the arterial pulse pressure measured non-invasively on the finger did indeed provide a non-biased

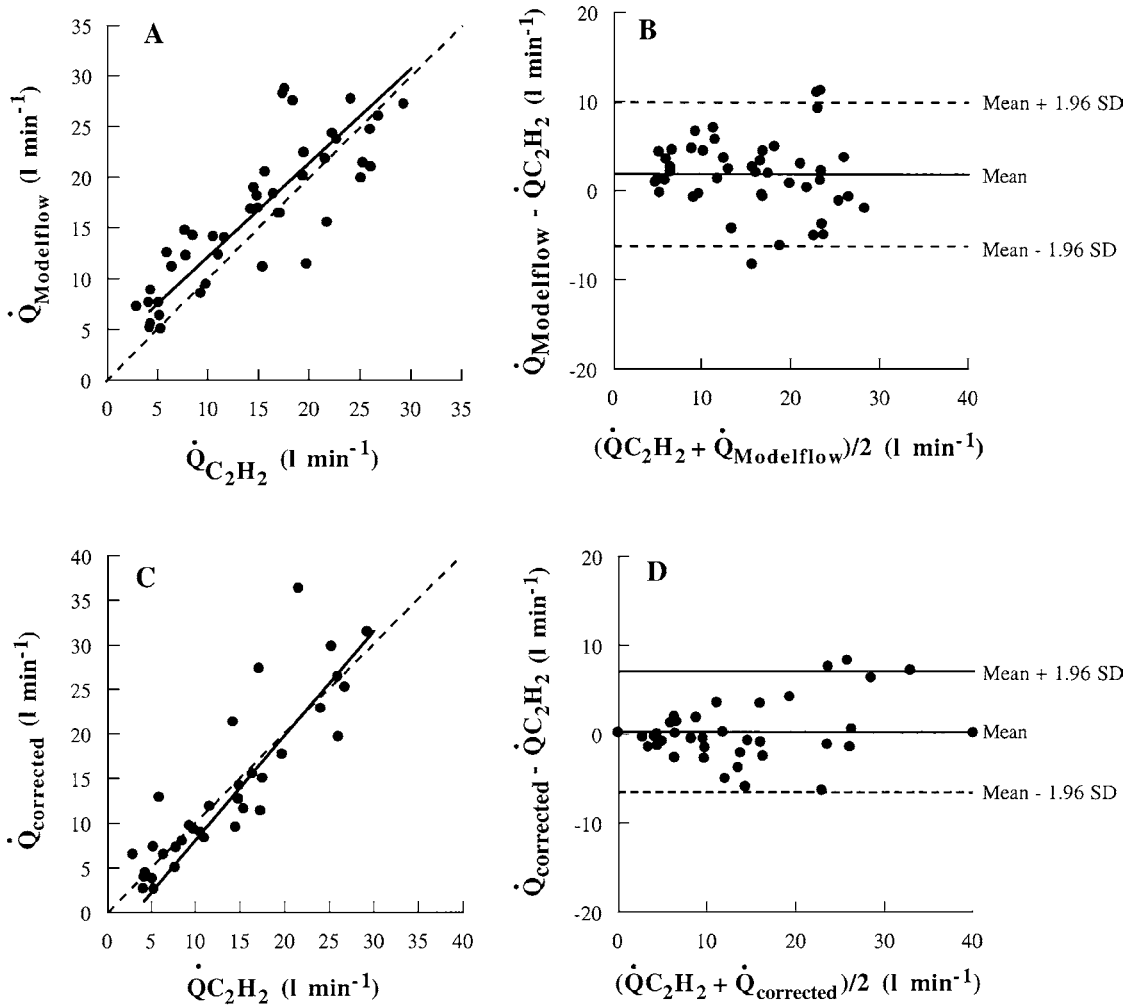

Figure 2 **Relationship between $\dot{Q}_{Modelflow}$, $\dot{Q}_{C_2H_2}$ and $\dot{Q}_{corrected}$**

(A) $\dot{Q}_{Modelflow}$ determined for each subject plotted against the corresponding $\dot{Q}_{C_2H_2}$ values. (B) Difference between $\dot{Q}_{C_2H_2}$ and $\dot{Q}_{Modelflow}$ values plotted against their mean. (C) $\dot{Q}_{corrected}$ values determined in each subject plotted against the corresponding $\dot{Q}_{C_2H_2}$ values. (D) Difference between $\dot{Q}_{C_2H_2}$ and $\dot{Q}_{corrected}$ values plotted against their mean. In (A) and (C), the broken lines correspond to the lines of equality, and the solid lines are the regression lines. In (B) and (D), broken lines represent the 95% limits of agreement.

and reliable measure of $\dot{Q}$ in healthy subjects at rest and during exercise, ranging from moderate to severe intensities, whereas uncorrected Modelflow® $\dot{Q}$ values ($\dot{Q}_{Modelflow}$) were significantly different from the corresponding $\dot{Q}_{C_2H_2}$ values.

To our knowledge, the present study is the first in which $\dot{Q}_{corrected}$ values were compared with those measured with a respiratory method ($\dot{Q}_{C_2H_2}$) during high-intensity exercise at steady state in humans. As such, the method offers a valid non-invasive approach for the assessment of $\dot{Q}$ on a beat-by-beat basis to exercise physiologists that is applicable not only at the exercise steady state, but also during exercise transients.

The results presented in Figures 1, 2(A) and 2(B), showing uncorrected $\dot{Q}_{Modelflow}$ values, are consistent with those obtained by others. Remmen et al. [9] compared Modelflow® applied to peripheral pulse pressure profiles with thermodilution and showed that Modelflow® did not yield accurate $\dot{Q}$ values in healthy elderly subjects at rest. Houtman et al. [10] showed that Modelflow® did not accurately predict $\dot{Q}$ during cycling exercise of moderate intensity compared with the CO_2 rebreathing procedure. Taken together, these results underline the need for correcting $\dot{Q}_{Modelflow}$ values with a calibration factor obtained by an independent method if the accuracy of the method is to be improved. At rest, such a correction was indeed shown to substantially improve the accuracy of $\dot{Q}_{Modelflow}$ values [11]. The accuracy at rest was also increased when haemodynamic conditions were modified either pharmacologically or during surgery [1]. In none of the cited studies, however, was such a correction applied during exercise. This was

done in the present study, and this is of novelty in our study.

In order to proceed with this correction, the $\dot{Q}_{C_2H_2}$ assessed at 150 W was taken as the reference. The rationale of this choice was based on the results obtained from a post-hoc analysis performed on the $\dot{Q}_{Modelflow}/\dot{Q}_{C_2H_2}$ ratios at the various workloads. This analysis showed that $\dot{Q}_{Modelflow}/\dot{Q}_{C_2H_2}$ ratio at 150 W was closest to, and not significantly different from, 1 and had the lowest coefficient of variation.

The open-circuit soluble gas method [2,12–14], used for correction in the present study, is a well-established method for $\dot{Q}$ computation. It showed fairly good agreement with the direct Fick method both at rest and during exercise up to 90 % of maximal O_2 uptake ($V_{O_2}max$) [2,12,14]. A comparison of the open-circuit acetylene uptake compared with the closed-circuit acetylene rebreathing method at exercise was recently carried out [13], showing a very good agreement between the two methods. However, investigators are not compelled to use this method for the correction of $\dot{Q}_{Modelflow}$ values: any steady-state method, either invasive or non-invasive, may be conveniently used, provided it is at least as accurate and precise as the respiratory method used in the present study.

The present study showed that $\dot{Q}_{Modelflow}$ was significantly larger than $\dot{Q}_{C_2H_2}$, consistent with the results of the companion paper by Azabji Kenfack et al. [1a] and with the data from Houtman et al. [10] during cycling exercise. This overestimate of $\dot{Q}$ is at least partially explained by the peripheral site of signal sampling, as demonstrated in the companion paper by Azabji Kenfack et al. [1a]. It is noteworthy, however, that Modelflow® relies on data from the elastic properties of thoracic and abdominal aortas obtained from *post-mortem* examinations of patients from 30- to 88-years old [15]. The age of our subjects is below this range, thus introducing a further potential source of error. However, correction was carried out with a respiratory technique and this allowed circumvention of all the problems brought about by the assumption of the given elastic characteristics of the aorta.

In conclusion, Modelflow® applied to non-invasive recordings of pulse pressure profiles from small peripheral arteries can be considered a reliable procedure for measuring $\dot{Q}$ on a beat-by-beat basis in resting and exercising humans, but only if a correction by a well-established independent steady-state method (open-circuit acetylene uptake in the present case) is carried out. Therefore, applied in combination with such a method, it could be accepted as an excellent alternative to invasive approaches for measuring $\dot{Q}$ in dynamic conditions and exercise transients both in healthy subjects and cardiovascular patients.

The need for an independent individual recalibration of the method, however, does not allow us to apply Modelflow® to the monitoring of large cohorts of patients in the clinical environment. Its utilization must be restricted to the study of specific highly monitored situations, such as research protocols on a limited number of subjects, but only if access to a calibration procedure is possible.

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