Finapress arterial pulse wave analysis with Modelflow® is not a reliable non-invasive method for assessment of cardiac output

Jaap J. REMMEN, Wim R. M. AENGEVAEREN, Freek W. A. YERHEUGT, Tjeerd VAN DER WERF, Hans E. LUIJTEN, Anja BOS and René W. M. M. JANSEN
Department of Geriatric Medicine, Heartcenter, Department of Cardiology, University Medical Center Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

ABSTRACT

Non-invasive continuous monitoring of cardiac output could be very useful in clinical care and in research settings, particularly in elderly subjects. We studied whether Finapres arterial pulse wave analysis with Modelflow® is a reliable non-invasive method for the assessment of cardiac output in healthy elderly subjects. We compared Modelflow® cardiac output (MFCO) with thermodilution cardiac output (TDCO) in 28 healthy subjects, aged 70 ± 4 years (mean ± S.D.). TDCO was measured during right-sided heart catheterization, while MFCO was calculated with Modelflow® software from non-invasive arterial Finapres blood pressure, which was measured simultaneously. The two methods were compared using a paired t-test, by Pearson correlation, and by Bland–Altman analysis. TDCO was 6.4 ± 1.1 litres/min (mean ± S.D.) and MFCO was 4.7 ± 1.3 litres/min (P < 0.001). There was no significant correlation between MFCO and TDCO (r = 0.28, P = 0.13). Mean difference (bias) was −1.7 litres/min (S.E.M. 0.27 litres/min), with an S.D. (precision) of 1.5 litres/min. The 95% limits of agreement were −4.6 to +1.1 litres/min. In conclusion, non-invasive MFCO values differed significantly from and showed no significant correlation with invasively determined TDCO values in the normal range. Although simple, non-invasive and patient-friendly, the Modelflow® method is inaccurate for assessment of cardiac output without invasive calibration.

INTRODUCTION

A non-invasive method for the continuous assessment of cardiac output could be useful in clinical care and in research settings. It could monitor the (first-dose) effects of drug therapy and guide treatment of hypertension and heart failure, especially in the elderly, in whom the prevalence of these diseases is high [1].

A promising method for the assessment of cardiac output non-invasively is arterial pulse wave analysis, the main principle of Modelflow® [2–5]. This model is incorporated in the Beatscope® software program, and calculates cardiac output from arterial pressure waves, which can be acquired invasively with an intra-arterial catheter or non-invasively with Finapres [6–11]. Finapres also exists in a portable Portapres® version, which enables long-term ambulatory monitoring of cardiac output [8].

We aimed to study whether Finapres pulse wave analysis with Modelflow® is a reliable non-invasive method for the assessment of cardiac output, by comparing non-invasive Modelflow® cardiac output (MFCO) measurements with thermodilution cardiac output (TDCO) measurements in healthy elderly subjects.

METHODS

In an ongoing study, we are investigating the relationship between pulmonary capillary wedge pressure and the arterial blood pressure (BP) response to the Valsalva...
manoeuvre in elderly subjects. To this purpose, we have performed right-sided heart catheterization in healthy elderly subjects, which has given us the opportunity to compare simultaneously assessed TDCO and MFCO.

Subjects
Volunteers were recruited by means of an advertisement in a local newspaper, requesting participation in an invasive study. A brief medical history was taken by telephone. Suitable volunteers were invited to the outpatient clinic to undergo a screening programme consisting of medical history, physical examination, ECG, blood laboratory analysis, bedside spirometry, bicycle stress ECG and echocardiography. Inclusion criteria for participation were age $\geq 65$ years and ability to give informed consent. Exclusion criteria were: history or signs of myocardial infarction, stable or unstable angina pectoris, rhythm or conduction abnormalities, cardiomyopathy, congestive heart failure, moderate or severe valve stenosis or regurgitation, left ventricular hypertrophy (all according to ACC/AHA Practice Guidelines), history of hypertension (defined as systolic BP at rest $>140$ mmHg and/or diastolic BP $>90$ mmHg or use of anti-hypertensive medication [1]; one-time limits of normal BP were $160/90$ mmHg at screening), any other serious disease, and use of medication with cardiovascular effects. All subjects gave written informed consent. The study was approved by the Ethics Committee for Research on Human Subjects of the University Medical Center Nijmegen, The Netherlands, and conformed with the principles outlined in the Declaration of Helsinki [12].

Materials and measurements
TDCO was determined by right-sided heart catheterization, using a 7.5 French Swan–Ganz FCO/VIP 139HF75 catheter (Baxter, Irvine, CA, U.S.A.), connected to a Baxter COM-1 or Baxter COM-2 computer. To determine TDCO, 10 ml of 0.9% NaCl solution at room temperature was injected manually through the proximal port of the Swan–Ganz catheter in approx. 2 s. Injections were performed at least three times, at random points in the respiratory cycle. Each thermodilution curve was checked visually for shape and appearance time before acceptance. If one TDCO value diverged by more than 10% from the other two, one to three additional injections were performed, and values in the upper and lower range were discarded, after which the mean of the remaining three values was taken as the TDCO.

Non-invasive continuous arterial BP and heart rate were measured beat-to-beat using a Finapres device (Ohmeda 2300, Englewood, CO, U.S.A.) on the index or middle finger on the opposite side to the catheterized arm. MFCO was calculated offline from the Finapres BP waveform by the Modelflow* program that is incorporated in the software program BeatScope, version 1.0 (TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). Modelflow* is a three-element model that uses the arterial input impedance, including continuous correction for variations in the diameter, the compliance of the aorta, and total peripheral resistance, describing the relationship between aortic flow and pressure and computing stroke volume [2]. The parameters age, sex, height and weight are required for the model, and are entered prior to the measurements. MFCO (in litres/min) is computed by multiplying stroke volume and heart rate [2–5].

In order to evaluate a possible effect of the bolus injection on MFCO, we compared MFCO calculated from 15 beats just before the first injection and from 15 beats just after this injection, and we repeated this protocol for the third injection.

Protocol
Subjects refrained from caffeine and nicotine for at least 12 h prior to the experiment. In the catheterization laboratory, the subject assumed a supine position at the catheterization table and the Finapres was applied; subsequently, an experienced cardiologist (W.R.M.A.) inserted an eight French peel-off sheet into the basilic or cephalic vein, using the Seldinger technique under local anaesthesia with lidocaine 2%. A Swan–Ganz catheter was positioned in the left or right pulmonary artery under fluoroscopic guidance. With the subject in the supine position, cardiac output was assessed subsequently by means of bolus thermodilution.

Continuous Finapres BP waves were recorded and stored from the moment of insertion of the Swan–Ganz catheter until the end of the protocol. Offline assessment of MFCO was derived from uninterrupted Finapres BP waves starting 15 s before the first thermodilution injection and ending 30 s after the last injection. Accordingly, all cardiac cycles from which TDCO was derived were also used for derivation of MFCO. However, Modelflow* utilized the cycles between the injections as well, and those cycles were not used for the assessment of TDCO. Therefore not all cardiac cycles used for both methods were identical, and neither was the number of cardiac cycles.

At the end of the protocol, the Swan–Ganz catheter was removed from the arm and a compress was applied. Within 2 h after removal of the catheter, the subject was released from the hospital.

Data analysis and statistics
Data were recorded using a personal computer and sampled with the MID TestOrganizer, version 5.3 (Department of Biomedical Engineering, University Medical Center, Nijmegen, The Netherlands). Statistical analysis was performed with SPSS 10.0 for Windows
Variability of TDCO was expressed as the within-subject S.D., calculated as the square root of the mean variance of the three measurements that were used for comparison with MFCO for all subjects [13]. The coefficient of variation was the within-subject S.D. expressed as a percentage of the group mean TDCO. We divided each period of Finapres curves into portions of 60 beats, which enabled us to calculate the within-subject S.D. and coefficient of variation for MFCO.

Agreement between TDCO and MFCO values was judged by computing Pearson’s correlation coefficient and by plotting the difference between MFCO and TDCO against their mean [14]. The mean difference (bias) and S.D. (precision) between MFCO and TDCO were computed and tested using a paired t-test. Mean difference ± 1.96 S.D. were known as the 95% limits of agreement.

We considered a mean difference of ≥ 1.0 litre/min between MFCO and TDCO (20% of a mean cardiac output of 5.0 litres/min) as clinically important, and assumed an S.D. of 1.0 litre/min for both TDCO and MFCO. We calculated that a sample size of 25 subjects would be sufficient to detect a difference between MFCO and TDCO of 1.0 litre/min at a power of 95%, using a paired t-test.

RESULTS

Patient enrolment
The flow diagram in Figure 1 shows the enrolment of healthy elderly subjects in the study protocol. More men
Table 1  Subject characteristics at screening
Data are expressed as means ± S.D. (n = 28).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>22/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70 ± 4</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>143 ± 16</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>83 ± 3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64 ± 6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175 ± 9</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.93 ± 0.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 ± 12</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>Bicycle stress ECG</td>
<td></td>
</tr>
<tr>
<td>Maximum heart rate (% of predicted)</td>
<td>105 ± 9</td>
</tr>
<tr>
<td>Maximum workload (% of predicted)</td>
<td>141 ± 18</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
</tr>
<tr>
<td>Peak velocity early diastolic rapid filling (E) wave (m/s)</td>
<td>0.62 ± 0.15</td>
</tr>
<tr>
<td>Peak velocity late diastolic atrial contraction (A) wave (m/s)</td>
<td>0.75 ± 0.15</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.84 ± 0.15</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>233 ± 50</td>
</tr>
<tr>
<td>End-systolic volume (ml)</td>
<td>50 ± 16</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td>127 ± 41</td>
</tr>
<tr>
<td>Ejection fraction (Simpson) (%)</td>
<td>53 ± 7</td>
</tr>
</tbody>
</table>

(78%) than women (22%) completed the protocol: more men (74%) responded to the advertisement, and since respondents were invited to the screening in order of response, more men (63%) than women (37%) were included. In addition, due to spasms of the antecubital veins, the insertion of the catheter failed in five women. The data for the 28 elderly subjects who completed the study protocol were suitable for analysis. Subject characteristics are presented in Table 1. None of the subjects used medication. BP was assessed sphygmomanometrically; minimum, maximum and median BP values were 110, 170 and 75, 90 and 85 mmHg respectively for systolic BP and diastolic BP. One subject with a systolic BP of 170 mmHg was not excluded, because later on the BP was 150 ± 70 mmHg. At the bicycle stress ECG, all subjects performed well, and exceeded the predicted age- and sex-adjusted maximal heart rate and workload. Echocardiographic findings were in the normal, age-adjusted range [15]. All cardiac output measurements were performed between 22 March 2000 and 24 November 2000.

Cardiac output measurements
In the 28 subjects, the mean (±S.D.) recording time of Finapres BP used for Modelflow® analysis was 197 ± 76 s (range 96–456 s). From the monitor, all Finapres signals appeared of good quality. The mean number of cardiac cycles per subject, used for calculation of MFCO, was 229 ± 102 (range 88–536). Finapres heart rate was 69 ± 8 beats/min, systolic BP was 163 ± 21 mmHg, diastolic BP was 82 ± 11 mmHg and mean arterial BP was 108 ± 13 mmHg. From these Finapres signals, MFCO was calculated; mean MFCO was 4.7 ± 1.3 litres/min. The within-subject S.D. of MFCO was 0.17 litre/min and the coefficient of variation was 3.6%.

For TDCO measurements, at least three injections were performed in each subject. In 12 out of 28 subjects (42%), more than three injections were carried out, due to diverging values or unreliable temperature curves: four injections were carried out in five subjects, five injections in three subjects, and six injections in four subjects. Group mean TDCO was 6.4 ± 1.1 litres/min. The within-subject S.D. was 0.30 litre/min and the coefficient of variation was 4.7%.
The mean difference in MFCO calculated from 15 beats just before and 15 beats just after the first bolus injection was 0.058 litre/min (not significant; 95% confidence interval −0.005 to 0.121 litre/min). For the third injection, the difference was 0.062 litre/min (not significant; 95% confidence interval −0.005 to 0.131 litre/min).

Figure 2 shows MFCO plotted against TDCO assessed simultaneously in each subject. There was no significant correlation between MFCO and TDCO (r = 0.29, P = 0.13). The mean difference (MFCO−TDCO) expressed as a percentage of TDCO was −32% (95% confidence interval −43% to −22%). The difference between MFCO and TDCO plotted against their mean is shown in Figure 3. MFCO and TDCO differed significantly (P < 0.001). The bias was −1.7 litres/min (S.E.M. 0.27 litre/min), with a precision of 1.5 litres/min. The 95% limits of agreement were −4.6 to +1.1 litres/min.

DISCUSSION

The main findings of the present study in healthy elderly subjects are that MFCO values differed significantly from TDCO values, and that there was no significant correlation between MFCO and TDCO. Modelflow® mostly underestimated cardiac output compared with TDCO. In addition, Bland−Altman plots showed that the error between the two methods was not confined to a certain range of cardiac output. The range between the 95% limits of agreement was large, from −4.6 to +1.1 litres/min (more than 5 litres/min). Taking into account a mean TDCO in our subjects of approx. 6 litres/min, this range is unacceptable large from a daily clinical perspective. Therefore Modelflow® seems inaccurate for non-invasive assessment of cardiac output.

To our knowledge, this has been the first study comparing MFCO with invasive TDCO in healthy elderly subjects. In combination with the portable Finapres® recordings, Modelflow® could enable continuous, long-term and ambulant non-invasive monitoring of cardiac output. Especially in the elderly, it could be of great use for diagnosis and guidance of treatment of heart failure and hypertension, if it were an accurate method for the non-invasive assessment of cardiac output. Within that framework, our findings are disappointing.

Several factors could account for our findings. One of these might be the fact that we did not calibrate Modelflow® with an invasively assessed cardiac output value. Based on data from a study on the elastic properties of human aortas obtained at autopsy [16], Modelflow® uses the maximal cross-sectional area of the aorta at high pressure. However, the patient’s true aorta area deviates from the mean value that is used by Modelflow®. Accurate measurement of the aortic diameter or a dilution estimate of cardiac output was reported to improve accuracy [2]. In several studies, a calibration factor (initial TDCO divided by initial MFCO) was multiplied by MFCO, after which 95% limits of agreement with TDCO were small [2,4,5,17]. In only one study were the pre-calibration 95% limits of agreement reported [5]. In that study, in septic patients on an intensive care unit, the 95% limits of agreement were −6.5 to +2.6 litres/min, even larger than in our present study, although with a range of cardiac output of 4.1–18.2 litres/min. Because of its invasive nature, calibration by using right-sided catheterization means that the Modelflow® method is not strictly non-invasive and limits its use. If the Modelflow® method were also accurate without invasive calibration, this could make it a truly non-invasive and far more easy to use method. For this reason, we decided to assess MFCO without initial invasive calibration.

The advanced age of our subjects seems not to be an explanation for the large differences between MFCO and TDCO values. As mentioned above, Modelflow® uses data derived from a study on 45 human thoracic and 20 abdominal aortas. The age of the patients at autopsy ranged from 30 to 88 years; 54% of the patients were over 65 years old [16]. Whether our results can be extrapolated to younger subjects remains unanswered, but it is unlikely that age is responsible for the differences found in the present study.

Unlike our present study, most other studies have used intra-arterial BP curves for Modelflow® analysis. Since Finapres recordings were reported to be even better for Modelflow® analysis than intra-arterial BP curves [4], the use of Finapres instead of intra-arterial BP is also unlikely to be responsible for the large differences between MFCO and TDCO values in the present study.

The bolus thermodilution method, achieved by right-sided heart catheterization, has been accepted as the gold standard for measurement of cardiac output [18,19], and was therefore used in the present study for comparison with the Modelflow® method. Large variability in TDCO values could, at least partially, account for the difference between MFCO and TDCO. For TDCO, the S.D. of the mean of three injections has been reported from 3.5% to 11%, and when the injectate used was colder the S.D. became smaller [19,20]. In our present study, using room-temperature injectate, we achieved a very small within-subject S.D. of less than 5%. It is therefore unlikely that variability in our TDCO values was a main cause of the difference between MFCO and TDCO. We recognize that variability is more a measure of reproducibility than of accuracy. The small variability of our TDCO values is probably due to a number of reasons: values diverging more than 10% from the other two were discarded; all subjects were healthy, without any cardiac abnormality; the range of measured cardiac output was relatively small; and all measurements were performed by the same experienced cardiologist. The variability of MFCO was even smaller than that of TDCO, and this cannot explain
the large differences between the values derived from the two methods either.

MFCO values measured before and after bolus injection did not differ significantly. Therefore bolus injection of 10 ml of ambient-temperature saline solution appeared to have little or no influence on MFCO, and also cannot explain our findings.

In several reports, invasive calibration was not performed for Modelflow® assessment of cardiac output, and therefore cardiac output was not expressed as an absolute value but solely as (relative) change in cardiac output [21–26]. In other reports, however, MFCO has also been expressed as absolute values [27–29]. Based on our findings, we believe that absolute MFCO values, determined without invasive calibration, should be interpreted cautiously and should not be used to guide clinical treatment. Additionally, changes in MFCO expressed as absolute values might not correctly reflect changes in true cardiac output either. Relative changes in MFCO might give a correct reflection of relative changes in cardiac output, since the calibration factor is then present in both the numerator and the denominator. To assess the ability of Modelflow® to detect relative changes in cardiac output without previous invasive calibration, further studies are needed comparing relative changes in MFCO with relative changes in TDCO.

The present study was subject to certain limitations. First, we compared absolute MFCO values with TDCO values at just one time point, and not at different times with different values of cardiac output. Therefore we could not assess the ability of Modelflow® to detect changes in cardiac output. Furthermore, our findings are restricted to the normal physiological range of cardiac output. Whether these findings can be extrapolated to pathologically low or high cardiac output ranges remains unanswered.

In conclusion, in healthy elderly subjects, non-invasive MFCO values differed significantly from and showed no significant correlation with invasively determined TDCO values in the normal range. Therefore, although the Modelflow® method is easy to use, non-invasive and patient-friendly, it is inaccurate for the assessment of cardiac output without invasive calibration.

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