A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients†

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In three clinical centres, we compared a new method for measuring cardiac output with conventional thermodilution. The new method computes beat-to-beat cardiac output from radial artery pressure by simulating a three-element model of aortic input impedance, and includes non-linear aortic mechanical properties and a self-adapting systemic vascular resistance. We compared cardiac output by continuous model simulation (MF) with thermodilution cardiac output (TD) in 54 patients (18 female, 36 male) undergoing coronary artery bypass surgery. We made three or four conventional thermodilution estimates spread equally over the ventilatory cycle. In 490 series of measurements, thermodilution cardiac output ranged from 2.1 to 9.3, mean 5.0 litre min^{-1}. MF differed +0.32 (1.0) litre min^{-1} on average with limits of agreement of −1.68 and +2.32 litre min^{-1}. Differences decreased when the first series of measurements in a patient was used to calibrate the model. In 436 remaining series, the mean difference became –0.13 (0.47) litre min^{-1} with limits of agreement of −1.05 and +0.79 litre min^{-1}. When consecutive measurements were made, the change was greater than 0.5 litre min^{-1}, on 204 occasions. The direction of change was the same with both methods in 199. The difference between the methods remained near zero during surgery suggesting that a single calibration per patient was adequate. Aortic model simulation with radial artery pressure as input reliably monitors changes in cardiac output in cardiac surgery patients. Before calibration, the model cannot replace thermodilution, but after calibration the model method can quantitatively replace further thermodilution estimates.

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Clinically, cardiac output is usually estimated intermittently with the thermodilution method. However, a continuous estimate of cardiac output in haemodynamically unstable patients, such as those undergoing cardiac or vascular surgery, would be preferable as continuous monitoring of cardiac output may provide an early warning of changes in circulatory function.

Many methods have been proposed to do this, including arterial pulse contour analysis;[1–3] transoesophageal,[4] transtracheal,[5] and intrapulmonary artery Doppler;[6] the Fick principle;[7] continuous thermodilution;[8–11] and bioimpedance.[12 13] To gain widespread acceptance, however, obstacles must be removed such as physiological limitations, limited reliability, cumbersome maintenance, insufficient precision, and slow responsive have to be overcome.

The 'Modelflow' method maybe suitable.[14–17] This method derives an aortic flow waveform from arterial pressure by simulation of a non-linear three-element aortic input impedance model and integrates stroke volume from

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the flow waveform. The method is now fully automatic, self-recording and has a fast response, and its precision appears substantially improved compared with earlier methods.[2] We studied bias, precision and tracking ability in 54 cardiac surgery patients, in three hospitals, by simultaneous comparison with right heart thermodilution estimates of cardiac output.

Materials and methods

Patients

The departments of Anesthesiology of the Veterans Administration Medical Center, San Diego, CA, USA (San Diego), the University of Leuven Academic Hospital, Leuven, Belgium (Leuven), and the University of Maastricht Academic Hospital, Maastricht, The Netherlands (Maastricht) participated in a prospective study of the bias and precision of the continuous cardiac output method compared with thermodilution, under conditions of routine use during cardiothoracic surgery. With approval of each institution's ethical committee and written informed consent from the patient, we studied 54 patients (18 female, 36 male), undergoing elective coronary artery bypass surgery. All patients had symptomatic coronary artery disease without previous myocardial infarction. We excluded patients with a history of abnormal ventricular function, known tricuspid or pulmonary valve disease, aortic valve abnormality, or aortic aneurysm. None had acute or chronic pulmonary disease.

The anaesthesia regimen differed slightly between the three hospitals. Premedication was with lorazepam (Maastricht, Leuven) or midazolam (San Diego). Anaesthesia was induced with sufentanil and maintained by further continuous infusion of sufentanil (Maastricht), or by injections of midazolam and fentanyl (San Diego), or of etomidate and sufentanil (Leuven) as needed. Complete muscle relaxation was maintained with pancuronium bromide (Maastricht), pipecuronium (San Diego), or vecuronium (Leuven). Patients were ventilated without PEEP, at a rate of approximately 10 bpm. Ventilatory volume and/or frequency were adjusted to maintain between 32 and 42 mm Hg. To control arterial pressure after sternotomy, in some cases during dissection of the internal mammary artery, and after bypass, nitroglycerine or nitroprusside were given. Some of the patients received phenylephrine, dopamine, or dobutamine.

Study plan

Cardiac output was measured continuously from the arterial pressure and thermodilution series were performed at times when identifiable changes in a patient's state occurred. Principally, a few minutes after the induction of anaesthesia, immediately after sternotomy, just before and after bypass, after sternal closure, after changes in drug infusion rate, after cardiac pacemaker rate changes, and after the completion of surgery. No measurements were made during bypass because of the absence of arterial pulsations. The number of measurements made in each patient depended on the duration of surgery and on the complexity of the surgical procedure. The series after induction of anaesthesia, however, was always obtained. Measurements were called and executed by an operator after permission from the anesthetist in charge and a statement of *no objection* from the surgeon. After pressing the start button, the cold liquid injections for the thermodilution estimates and the recording of all data was fully automatic by computer without human intervention thereby removing any operator bias or error. To improve haemodynamic stability, major surgery was suspended during the measurements.

Modelflow method physiologic background

Left ventricular contraction causes inflow of blood into the arterial system, but this inflow is opposed by arterial counter pressure and aortic and peripheral arterial input impedance. The Modelflow method simulates this behaviour. A haemodynamic model of arterial input impedance is used which is known to have realistic properties in computing stroke volume: the extended Windkessel model (Fig. 1).[18 19] The model has three principal components: a characteristic impedance which represents the opposition of the aorta to pulsatile inflow, Windkessel compliance which represents the opposition of the aorta to volume increases, and peripheral resistance which represents the opposition of the vascular beds to blood flow. These components are not constant. Impedance and compliance depend on pressure itself,[20] and total systemic peripheral resistance depends on many factors including circulatory filling, metabolism, sympathetic tone, and vasoactive drugs.

Aortic compliance decreases substantially when pressure increases. This non-linear behaviour of the aorta would be a

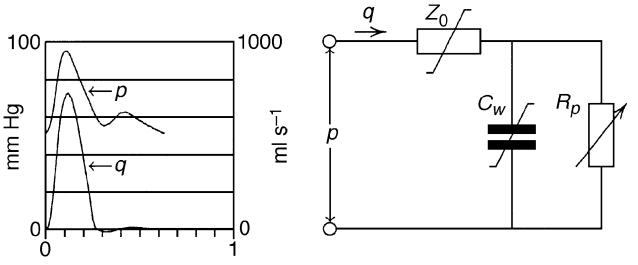

Fig 1 Schematic diagram of the three-element non-linear, self-adapting model (right) and input pressure and simulated flow pulse (left). Arterial pressure p is applied to the model input. Z_0, characteristic impedance of the proximal aorta; Cw, arterial Windkessel compliance; Rp, total systemic peripheral resistance. The non-linear properties of Z_0 and Cw are indicated by a stylized 'S' symbol. Rp has an arrow indicating that it adapts to changes in systemic resistance. The result of the model simulation is a flow curve q. Integrated per beat (the area under the curve) it yields stroke volume.

major source of error if not taken into account. In contrast, aortic characteristic impedance, increases only moderately with pressure. These non-linear relationships were studied *in vitro* by Langewouters and colleagues[20] and described as mathematical functions whose properties depend closely on patient age and gender, and slightly on height and weight. However, the aortic diameter is not known accurately. So, the absolute value of the computed cardiac output is uncertain unless calibration against another method of measurement such as thermodilution can be done. Theoretically, the thoracic aortic diameter could be measured for example with ultrasound, but this possibility was not tested. The tracking of changes in cardiac output, however, is not affected by the uncertainty of aortic diameter.[14]

Use of the Modelflow method

Before the start of surgery the patient's gender, age, height, and weight are entered into the Modelflow computer. These determine pressure-volume, pressure-compliance, and pressure-characteristic impedance relationships using Langewouters' equations, which are population averages. Look-up tables are formed in computer memory for each pressure level from the equations. At each new pressure sample taken at 100 Hz the corresponding values are read from the table and entered into the model. The model is simulated digitally in real-time and supplied with the sampled arterial pressure waveform. The pressure waveform is taken from the monitor in use in the operating room. The simulation result is a sampled continuous aortic flow waveform (Fig. 1). The flow waveform is integrated during arterial systole to deliver stroke volume. Cardiac output is computed for each beat as the product of stroke volume and heart rate. The result is called 'model cardiac output' in the remainder of the paper.

Model total systemic peripheral resistance is obtained as follows. For the first simulated beat, an initial value for peripheral resistance is assumed and mean arterial pressure and cardiac output are computed with this first value in place. The ratio of pressure to cardiac output for this first beat defines a new resistance value, which is used in the model for the next beat, and so forth. Within five beats from the start, the model resistance usually stabilizes to the systemic peripheral resistance value. This self-adaptation scheme remains permanently active so that changes in systemic peripheral resistance that occur are followed by the model. This is possible because systemic peripheral resistance changes slowly, with a time constant which is typically approximately 10 s.

Pressure transducers were clamped to the operating table to keep their correct hydrostatic height with respect to heart level. When height changes occurred they were noted but level correction was not attempted. Continuous flush devices prevented clotting at the catheter tips. The resonant frequency of the system in use at each location was measured in the laboratory and ranged between 15 and 25 Hz. Before each comparison with thermodilution the arterial waveform quality was visually inspected and the catheter was flushed if slow rising upstrokes took more than 100 ms to reach a maximum. The close observation of pressure pulsation quality was facilitated by a static on-screen display similar to the one shown in Figure 1. Damping of the waveform was continuously monitored by software and an alerting message was displayed whenever risetime increased beyond 150 ms. Occasionally, however, a slow rising waveform had physiological causes and led to a false alarm.

Thermodilution method

Thermodilution cardiac output measurements were performed with system controlled by a personal computer, and included an iced injectate container (CO-SET, Baxter-Edwards, Irvine, CA, USA), a proprietary, motor driven injectate syringe, a thermodilution Swan-Ganz catheter (Baxter), and a COM-2 cardiac output computer (Baxter). The start of the ventilatory cycle was read from the ventilator output or, if unavailable, detected from the capnogram waveform. At precisely timed, variable delays from the start of the ventilatory cycle injections of 10 ml of iced glucose solution 5% were triggered automatically. Delays were spread equally over the ventilatory cycle,[21 22] each 25% of the cycle for a series of four injections (Maastricht), each 33% for a series of three injections (San Diego and Leuven). The three or four cardiac output determinations were averaged to obtain one single value for average cardiac output in that period. For this technique to work optimally, the haemodynamic state and respiratory rate must be stable during the series.[21]

Data acquisition

The software we used is an online real-time version of the BEATFAST offline program, called MODELFLO.EXE (TNO, Academic Medical Centre, Amsterdam, The Netherlands) dated May 1997. It automates all actions and records all haemodynamic data relevant to the study. As cardiac output in a patient can be quite variable, it is important to acquire the data from each method simultaneously. Computer storage of the sampled arterial pressure waveform and beat-to-beat derived haemodynamic data for each comparison started one full respiratory cycle before a thermodilution injection, continued for as many respiratory cycles until at least 18 s had passed, and stopped after one additional respiratory cycle. This resulted in an average recording time of 30 s for each single thermodilution measurement. The digital output of the COM-2 device was also stored, including values for cardiac output, blood temperature, injectate temperature, computation constant, and warning and error codes. This procedure was repeated for the remaining injections in a series with a period of five

ventilatory cycles allowed between any two measurements. A series of three or four measurements thus took between 150 and 210 s. Although the MODELFLO monitor ran continuously, waveform samples were recorded only during thermodilution series.

Data analysis

To compare model and thermodilution cardiac output, model cardiac output was first averaged over the beats recorded during an injection. Then the three or four model and thermodilution values per series were each averaged to obtain one single data pair (CO_{mf}, CO_{td}) for further analysis. Both values estimate the average cardiac output during a series.

The same set of comparison data pairs was analysed twice.

1. In a first analysis, model cardiac output (CO_{mf}) was used as is with the model based on the patient's gender, age, height, and weight. This is called uncalibrated.
2. In a second analysis model, cardiac output ($CO_{\kappa 1}$) was made equal to thermodilution cardiac output in the first series after induction, through multiplication by a patient individual calibration factor, $\kappa_1 = CO_{td1}/CO_{mf1}$. This reduces the uncertainty in the patient's aortic diameter, because of the high standard deviation of the age and gender based population average. As the first data pair in each patient, would, therefore, be defined to have zero difference it was excluded from further analysis.

With the second method, we mainly investigated the ability of the model to track changes in cardiac output.

A trend score was computed for each patient and also for the group of patients. The trend score is derived from the changes in consecutive cardiac output values. If both methods simultaneously indicate a positive trend, the changes compare positively and a positive score is counted. If both show a negative trend, they again compare positively. When the changes in cardiac output are in opposite directions they compare negatively and a negative score is counted (see Fig. 6 for examples). Ideally, only positive scores are present. Separate scores were made for all consecutive changes regardless of size, and also for changes where consecutive thermodilution cardiac output values differed by at least 0.5 litre min^{-1}, which is considered clinically relevant.

A trend analysis was performed to spot any systematic trends in cardiac output and in the difference between the methods.[24] This was done by plotting the mean of the model and thermodilution cardiac outputs and their difference averaged over the group and for each half hour of the operation. The calibration pair for each patient was not included.

Haemodynamic stability was verified by analysis of mean arterial pressure and heart rate during a thermodilution series. Stability was considered absent if mean arterial pressure and heart rate averaged per injection period deviated more than 5% from their series average.[22] Severe, persistent arrhythmias during thermodilution measurement was also considered to be absence of stability. If stability was not present, the series was excluded from further analysis. Periods with balloon pump counterpulsation had to be discarded as the model method did not properly recognize the heart beats.

The range ratio of haemodynamic values during an operation was computed as the ratio of the largest to the smallest value that was measured in a patient. Thus, if a lowest mean arterial pressure of 60 and a highest of 120 mm Hg were measured the range ratio was 120/60=2. For two-pressure ranges one 30–90 mm Hg (difference=60, ratio=3) and another 80–140 mm Hg (difference=60, ratio 1.75), the first is more important than the second, because of the non-linear properties of the aorta. The ratio was computed for cardiac output, heart rate, mean arterial pressure, and total peripheral resistance as it has been suggested that these parameters may affect the accuracy of methods such as the model method.

Statistical analysis

We gathered data in three clinical centres in three countries with slightly different anaesthetic regimen, in female and male patients, with changing patient condition during the operation. We studied how these factors might affect cardiac output comparison by testing correlations and differences between cardiac output methods. We used the statistical package BMDP version 7, program 1V and 5V (BMDP, Los Angeles, CA, USA). If either variable is not significantly dependent on centre or patient gender, the data can be pooled to get more reliable statistics.

Computation of limits of agreement was the principal method of analysis with differences in data pairs plotted against their average.[23] The agreement between model and thermodilution cardiac output is computed as the bias (mean), with limits of agreement computed as bias ± 2 SD[23] when differences followed normal distributions. Normality was tested with the Kolmogorov–Smirnov one-sample test. The coefficient of variation was computed as CV=(SD/mean)$\times$100%. Data averages are given as mean (SD). Statistical significance was considered present when $P<0.05$.

Results

In 18 female and 36 male patients a total of 566 thermodilution series were obtained during a median operation time of 4 h 30 min. Inadequate haemodynamic stability caused rejection of 59 thermodilution series. Insufficient pressure signal quality caused rejection of 14 series. Thermodilution problems caused rejection of three series. Thus, 490 series of acceptable quality remained. In

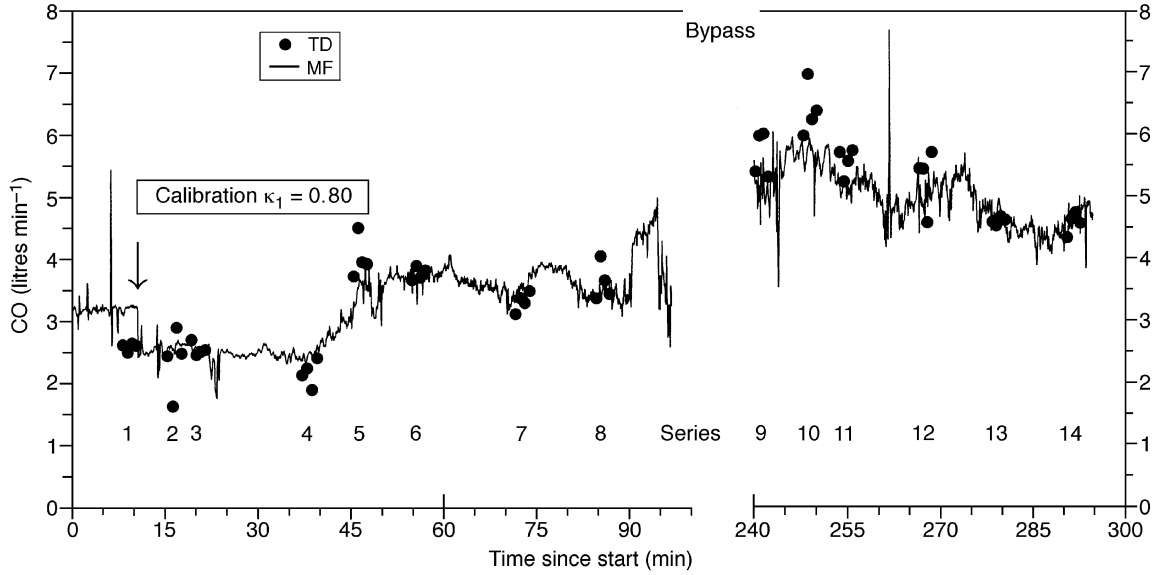

Fig 2 Trend plot in patient 54. This patient was selected because she had a large ratio between highest and lowest cardiac output. The individual thermodilution measurements, not yet averaged over each series of four, are shown as solid dots. Series are numbered from 1 to 14. Continuous model cardiac output is shown as an eight-beat average, which is uncalibrated until the first thermodilution series is completed, at the arrow.

Table 1 Summary of patient details and haemodynamic data. In the columns unit: the unit used to express the numerical values; mean, average values obtained as indicated; SD, standard deviation; range, minimum left and maximum value. Parameters: κ_1, model calibration factor based on first determinations; MAP, mean arterial pressure; HR, hear rate; TPR, total peripheral resistance from MAP/CO_{td}; CO_{td}, thermodilution cardiac output; CO_{mf}–CO_{td}, difference between uncalibrated model and thermodilution cardiac output; $CO_{\kappa 1}$–CO_{td}, difference between calibrated model and thermodilution cardiac output. Above the line the data first averaged per patient and then pooled for the group, below the line all the measurements pooled

Variable	Units	Mean	SD	Range
Patient characteristics, *n*=54				
Age	yr	62	9	43–78
Height	cm	169	8	153–188
Weight	kg	74	8	55–92
κ_1		0.95	0.18	0.62–1.45
Patient means				
MAP	mm Hg	79	7	65–98
HR	min^{-1}	73	11	50–107
TPR	dyn s cm^{-5}	1350	300	817–2534
CO_{td}	litre min^{-1}	4.9	0.9	3.0–7.7
CO_{mf}–CO_{td}	litre min^{-1}	10.3	0.9	–1.5–2.4
$CO_{\kappa 1}$–CO_{td}	litre min^{-1}	–0.1	0.2	–0.7–0.3
Pooled data				
MAP	mm Hg	78	12	39–114
HR	min^{-1}	73	19	39–147
TPR	dyn s cm^{-5}	1332	415	531–2978
CO_{td}	litre min^{-1}	5.0	1.3	2.0–9.3
$CO_{\kappa 1}$–CO_{td}	litre min^{-1}	–0.1	0.5	–2.1–1.6

each patient data from before and after bypass were available.

Figure 2 shows an example of a trend graph of model and thermodilution cardiac output of each injection in patient 54. Although substantial changes in cardiac output occurred between the 14 series, the tracking of thermodilution by model cardiac output was close. Individual thermodilution measurements show scatter within some series of four measurements, but no measurement was rejected.

Table 1 summarizes patient data and selected haemodynamic variables. These include thermodilution cardiac output and the differences between model and thermodilution cardiac output before and after model calibration. Taking averages for each patient and then pooling the 54 patient results, or pooling all 490 series resulted in only marginal differences for the mean values. Standard deviations and ranges were less if patient averages were taken first. Thus, pooling all series, the greatest range ratios for mean arterial pressure, heart rate, thermodilution cardiac output, and systemic peripheral resistance were 3, 4, 5, and 6:1, respectively. Within patients, mean arterial pressure ranged over 2:1 or greater ratios in four of the 54 patients, heart rate in 13, thermodilution in 12, and total peripheral resistance in 20 of the 54 patients. Thus, the haemodynamic state was far from constant within and between patients and peripheral resistance was the least stable.

The mean calibration factor κ_1 was 0.95, which was significantly different from 1.00. The calibration factor was not related to any patient or haemodynamic variable recorded. The cardiac output bias of +0.32 litre min^{-1} before calibration decreased to –0.13 litre min^{-1} and became non-significant. The standard deviation of the differences of 1.0 litre min^{-1} is halved after calibration to 0.47 litre min^{-1}. The differences were not associated with any of the other haemodynamic variables, including systemic peripheral resistance.

The Kolmogorov–Smirnov test for the difference between model and thermodilution cardiac output did not indicate a significant deviation from a normal distribution. No significant differences between clinical centre and between gender were found either before or after once calibrating the model. The data from both patient sexes and from the three clinical centres, could therefore, be pooled. Both methods, however, indicated a highly significant increase in cardiac output towards the end of surgery. This is shown as half hour averages pooled for the group in Figure 3. The difference between the methods is similarly plotted in the bottom trace but shows no significant trend away from zero. Of 436 trends in cardiac output, 354 (81%) were scored in the same direction by both methods. Of 204 trends in thermodilution cardiac output greater than 0.5 litre min^{-1}, 199 (97%) were indicated correctly in direction by model cardiac output.

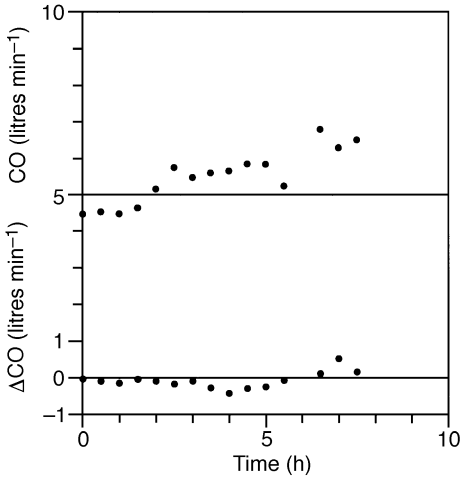

Fig 3 Trend plots of cardiac output and cardiac output difference *vs* time from induction of anaesthesia. Cardiac output is the mean of model and thermodilution values. The data of all patients are pooled per half hour and plotted at the start of each half hour. Data points are plotted only when at least three values were available for that half hour. Cardiac output increases significantly with time and post bypass. Cardiac output difference showed no significant trend.

Figure 4 shows uncalibrated model *vs* thermodilution cardiac output for the calibrating cardiac output pair of each patient. Clear differences in the absolute level of cardiac output were present up to +2 and –1.5 litre min^{-1}. In the scattergram four patients are marked with a '×' symbol. They had the greatest cardiac output and systemic peripheral resistance range ratio, and smallest and largest cardiac output and are shown individually in Figure 5, demonstrating the marked variability of cardiac output between and within patients. In Figure 5, the line through the origin and the calibrating point is also shown for the two patients with the highest range ratios. Clearly, individual estimates are closer to this line than to the line of identity, which shows that differences from thermodilution are largely systematic. They can thus be corrected by a calibration factor that alters the slope of the line towards unity.

The cardiac output of patient 31 is plotted as a trend chart in Figure 6a, with mean arterial pressure, heart rate, and total peripheral resistance included. Again, the model method bias appears insensitive to changes in these variables even though the systemic peripheral resistance range ratio is 3.4:1. This patient also has one of the lowest calibration factors, κ_1=0.66, yet tracking was not affected. The duration of the operation on patient 45 in Figure 6b is unusually long. The calibration factor, κ_1=0.97, but the plot is of values before calibration. After bypass, the cardiac output increases are associated with infusions of 450 ml of autologous whole blood and 250 ml of packed cells nitroglycerine and dopamine

Figure 7 summarizes in four panels the pooled results before and after calibration of the model. The two left hand panels show scatter plots of the 490 (top panels) and 436 series (bottom panels). The points lie closer to the line of identity after calibration. The right hand panels show Bland–Altman plots. The 15 largest negative differences, those below the –2 sd line in the bottom right diagram, were obtained in eight patients and were all recorded immediately after bypass. They do not depend on the value of cardiac output.

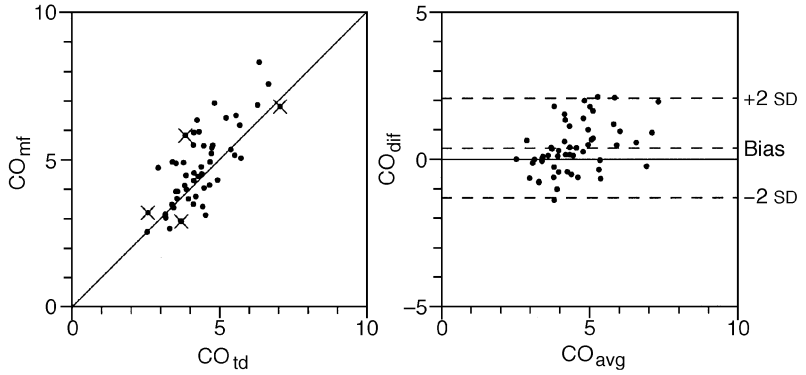

Fig 4 The model *vs* thermodilution cardiac output pairs for the calibration (the first) series in the 54 patients. In the Bland–Altman plot CO_{dif} is CO_{mf}–CO_{td}, CO_{avg} is their mean. The crosses indicate four patients shown in full in Fig. 5.

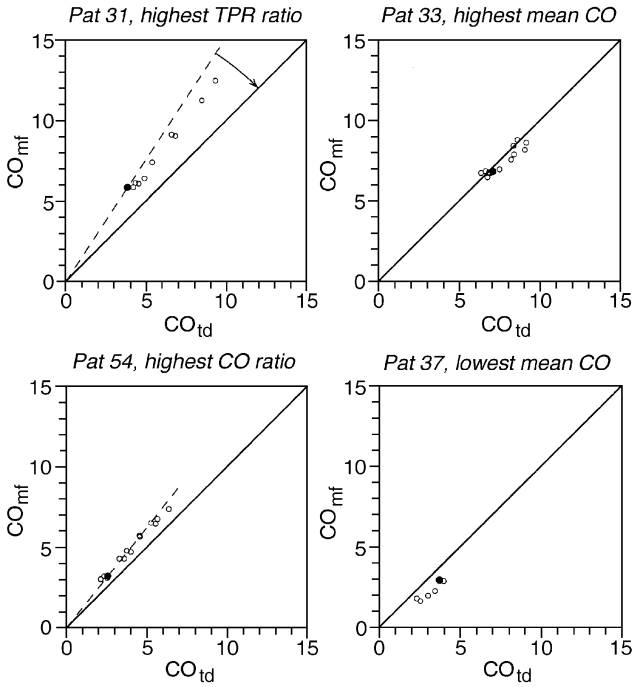

Fig 5 Scattergram of uncalibrated model and thermodilution cardiac output in four patients selected for lowest (3.2) and highest (7.6 litre min^{-1}) mean cardiac output and greatest cardiac output (3.0:1) and systemic peripheral resistance (3.4:1) range ratio. Calibration turns the dashed line for patient 31 in the direction of the arrow onto the line of identity. In this patient the other points move below the line of identity which will result in a negative bias after calibration. The solid dot (●) indicates the calibration pair.

Discussion

We found that the Modelflow method can reliably track directional changes in thermodilution cardiac output in cardiac surgery patients. Cardiac output can be monitored quantitatively and continuously with little error *only* after an initial calibration of the model to an individual patient. Acquiring such relatively precise data required several precautions.

A precise thermodilution method

An important factor in this research was a good reference for comparison. Individual thermodilution cardiac output estimates show substantial scatter in their values even under stable haemodynamic and ventilatory conditions.[25] Four quickly repeated thermodilution estimates of cardiac output may differ more than 1 litre min^{-1}. In such circumstances, an average of a number of random injections does not allow a true mean cardiac output estimate. When injections are synchronized with ventilation, however, not by a fixed or a random but by a systematically varied phase equally spread over the ventilatory cycle, much closer estimates of true mean cardiac output can be obtained[21] by eliminating ventiliation effects. Precise timing of the injections requires a trigger synchronized with ventilation, and computer control. Precisely measured injections over a repeatably short time period requires a motor driven syringe.[26] We used a system for thermodilution cardiac output that is simple but not generally available.

Quality control of arterial pressure measurement

A second important factor was adequate control of the quality of measurement of intra-arterial pressure. All pressure transducers were calibrated against the same standard. Zeroing was done semi-automatically and occasionally checked, although never adjusted during a surgery. The pressure pulsation risetime was constantly monitored with a simple computer algorithm. Visual inspection before each thermodilution series was also the rule. Changes in the hydrostatic level of the pressure transducer with respect to the heart affect model cardiac output. Theoretically, when arterial pressure is artificially high because of a low position of the transducer, model cardiac output is slightly but measurably reduced, and vice versa. Tilting of the operating table caused height changes up to ± 15 cm, or approximately 10 mm Hg, and which we did not correct. As height changes were in both directions, and as the errors introduced are small, they have little effect on overall statistics in view of the other sources of error.[14]

Patient selection

A third important factor was patient selection. All patients probably had patent aortic valves and no aortic aneurysms. An aneurysm affects a patient's aortic compliance. A patent aortic valve is required for proper model cardiac output computation as the model computes forward flow into the aorta and in regurgitation ignores backward flow. Thus, model cardiac output will be systematically larger than thermodilution which estimates the net flow as forward minus backward flow. We cannot exclude the possibility that some patients had a small undetected valve leakage, or that such leakage occurred at some times during surgery. If so, this will increase the inaccuracy of the comparison.

Haemodynamic stability

Suspension of major surgery during a series was been a fourth important factor. Haemodynamic stability, however, is not a prerequisite for a correct model cardiac output. Changes in cardiac output are as reliably estimated by the model during arrhythmias and various cardiovascular manoeuvres as when heart rate and rhythm and circulatory volume distribution were stable (J.J. van Lieshout, personal communication).

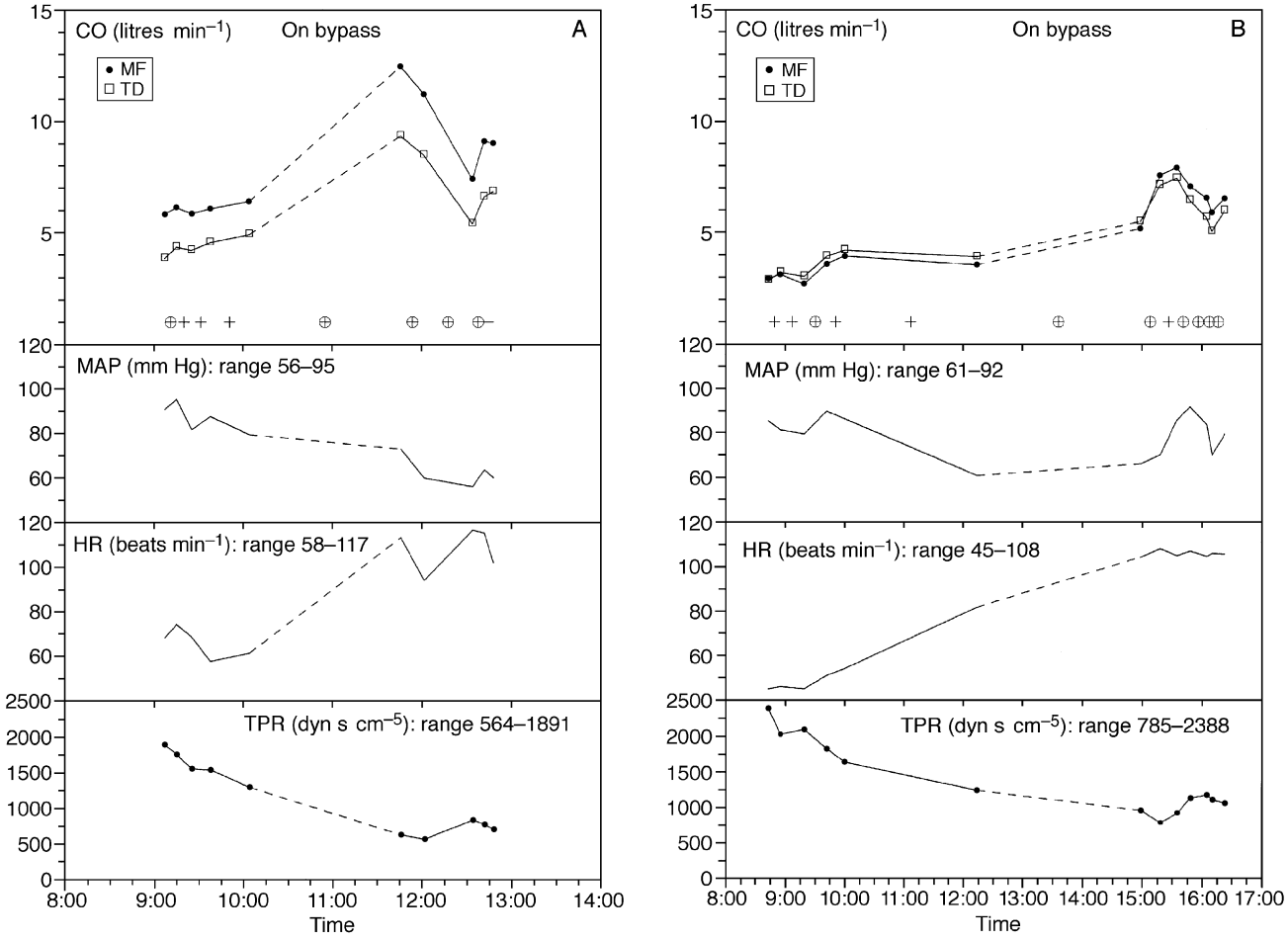

Fig 6 (A) Trendplot of patient 31 with the highest systemic vascular resistance range ratio, and (B) trend plot of patient 45 with a long operation. MF, uncalibrated model cardiac output; TD, thermodilution cardiac output; MAP, mean arterial pressure; HR, heart rate; TPR, total systemic vascular resistance computed as MAP/TD. The + signify correct, the – incorrect indication of thermodilution trend by the model method. The ⊕ signify correct and ⊖ incorrect, trends for thermodilution trends greater than 0.5 litre min^{-1} between consecutive determinations. (A) The trendscore is 9 trends of which 8 are indicated correctly (9/8), 5 trends greater than 0.5 litre min^{-1} which are all correct (5/5). (B) These scores are (12/12) and (7/7).

Model calibration

Differences between uncalibrated model and thermodilution cardiac output in individual patients are small in most but substantial and unreliable in some. The standard deviation of the difference, 19%, is similar to that of a single thermodilution estimate,[22] to that of bioimpedance,[13] or ultrasound Doppler flow velocity in the aorta,[1–6] or continuous thermodilution,[10 11] but the differences are largely systematic, as this study shows (Figs 5 and 6). Thus, averaging a number of measurements tends not to improve the precision of model cardiac output much. When interest is in monitoring percentage changes in cardiac output from a control level, calibration is not needed and the fact that model errors are principally systematic is an advantage.[16] In other circumstances calibration is necessary. As the trend plot of differences between the methods (Fig. 3) does not show a trend away from zero a single calibration per operation seems adequate. The calibration does not change on the second day of monitoring compared with from the first.[17]

Pharmacological agents

The administration of fluids, vasoactive drugs, and cardiac stimulants was not changed from normal routine for this study. These will change arterial pressure, heart rate, ejection time, contractility, cardiac output, and peripheral resistance. As a consequence, the variations in heart rate, cardiac output, and peripheral resistance were substantial (Table 1), yet tracking precision of model cardiac output appeared unaffected. Nitroglycerine or sodium nitroprusside were administered principally after sternotomy and after cardiopulmonary bypass. Thus, if these agents affected model error, it should be evident in these parts of the operation. No important trend in the differences away from zero is seen in Figure 3, and is confirmed by the absence of significance in the differences analyses (see Statistics methods).

In another study[3] changes in total peripheral resistance were suggested to reduce the tracking ability of a commercial device. The close tracking of our model method during

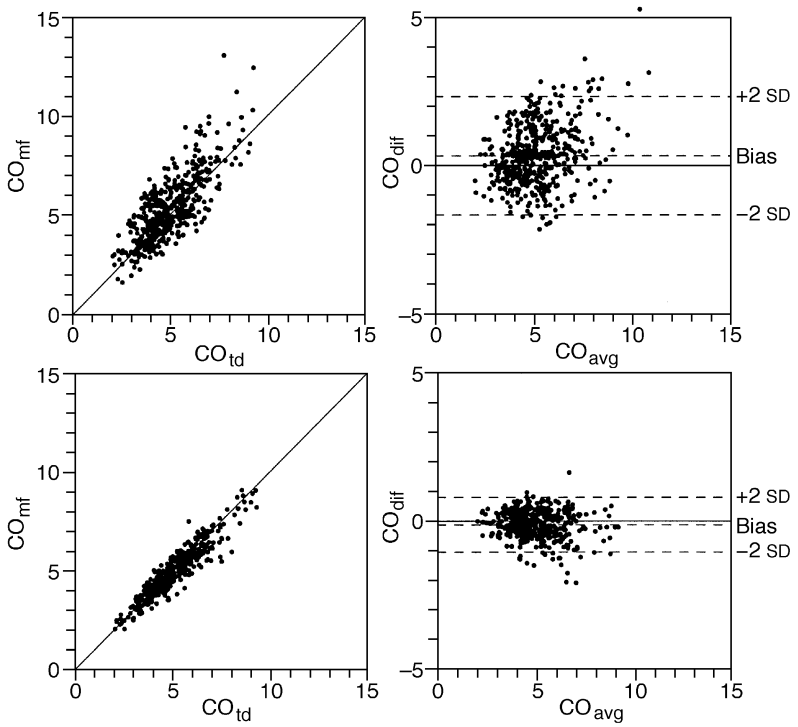

Fig 7 Diagrams showing the data pairs in all 54 patients before (top, *n*=490) and after (bottom, *n*=490–54=436) calibration on the first series after induction of anesthesia. In the Bland–Altmanplot CO_{dif} either CO_{mf}–CO_{td} before, or $CO_{\kappa 1}$–CO_{td} after calibration; CO_{avg} is their mean. The dashed lines indicate the bias and limits of agreement between methods.

changes in peripheral resistance might have been facilitated by the self-adapting model peripheral resistance, as explained under Methods.

Exclusion of data

We performed 566 series of thermodilution estimates and rejected 76, based on pre-set criteria. This study was set up to investigate bias and precision of the model method. To achieve this goal the precision of the comparisons should not be impaired by a poor reference value or by inadequate arterial pressure recordings.

Single thermodilution estimates are inaccurate as they are strongly affected by baseline temperature changes and the waxing and waning of right heart cardiac output with ventilation.[27] Thus, averaging of several random estimates is needed to obtain reasonable accuracy. Our goal for the cardiac output reference was to achieve near 5% precision. Given the precision of single estimates of 17%[22 25 28 31] we would have to average some nine estimates as inaccuracy decreases in proportion to the square root of the number. However, using the ventilatory phase-spreading technique, inaccuracy reduces in proportion to the number of estimates and three estimates would improve precision from 17 to 6%.[21 22] For the averaging technique to work, the haemodynamic, conditions should be stable during the series. To judge stability we could have used model cardiac output but this method was under test. We, therefore, used mean arterial pressure and heart rate as easily obtainable measures. Between the thermodilution estimates in a series, we allowed each parameter to deviate maximally 5% from the series average. Inspection of the rejected series suggest that the 5% criteria might have been too strict, as we rejected some apparently adequate series in terms of cardiac output comparison. In another study, under different circumstances, the limit was relaxed to 10% deviation, and acceptable results were still obtained.[16]

The arterial pressure waveform used as input for the haemodynamic model should ideally have been aortic pressure. This waveform differs from radial artery pressure in shape. As radial artery pressure is what is used clinically the model had to accept this. As shown in another study[14] the use of radial artery pressure modifies the model flow waveform but by integrating the flow over systole, to obtain stroke volume, waveform purity becomes less relevant. Radial artery pressures in some patients, however, may deteriorate in mean level and pulse amplitude for a period after bypass in comparison to aortic pressures.[29] The pressure difference between aorta and radial artery is usually almost negligible at 0–2 mm Hg. After bypass it can become as great as 10 mm Hg for mean and more than twice that for systolic pressures in six of 38 patients,[29] caused by an increase in pressure gradient in the proximal arteries of uncertain cause. With 15 outliers in eight patients all recorded immediately after bypass, this emphasizes importance of a reliable arterial pressure as input for the

model method. Due to warming of the patient post bypass, with substantial changes in thermal baseline, thermodilution may also be unreliable in this critical period.

Discussion of errors

In an editorial Gardner[30] proposed that objective criteria be established for judging the precision of cardiac output measurement methods. Critchley and Critchley,[31] in trying to establish such objective criteria state that: if a 'new' method is to replace an older, established method, the new method should itself have errors not greater than the older method.

Thermodilution is the reference cardiac output method in almost all studies, as in the present one. A single thermodilution estimate of cardiac output has a probable percentage error standard deviation or coefficient of variation, further called 'error', of 15–20%.[22 25 28 31] A triplicate, randomly injected thermodilution has an error of 10% as the result of averaging.[31] When the new method's error, n, is acceptable if it is the same as that of the method to be replaced, r, the error of the comparison, c, can be computed with Pythagoras' law as $c^2=n^2+r^2$ or $c=\sqrt{n^2+r^2}$.[31] This computation requires the errors to be statistically independent of each other. Usually, however, we have the error of the comparison and an estimate of the error of the reference method. The error of the new method is then computed as $n=\sqrt{c^2-r^2}$.

Approximately, the error we found between the uncalibrated model and thermodilution cardiac output is 19% (Table 1). Our reference cardiac output used the phase-spreading injection technique, which has only 17/3~6% error. The conclusion is that uncalibrated model cardiac output has an error of $\sqrt{19^2-6^2}=18\%$. If a triplicate random thermodilution is to be replaced by another technique, uncalibrated model cardiac output is not the method of choice as it is not sufficiently precise (18 *vs* 10% required) as a standalone method.

After model calibration, the error of subsequent comparisons decreases to 9% (Table 1). With 6% error of the thermodilution reference, the calibrated model cardiac output has a probable error of $\sqrt{9^2-6^2}=7\%$. This is almost as good as a triplicate phase-spreading thermodilution (7 *vs* 6%) and could thus almost replace it.[31] It is definitely better than a triplicate random thermodilution (7 *vs* 10%).

Positioning of the model method

Response time is a variable to be specified for a continuous cardiac output method.[30] For the model method it is the duration of one beat, and even after eight-beat averaging, response time is measured in seconds, not minutes.[9]

Invasiveness is another aspect to be considered.[27] Clearly, the model method as studied here, requires an invasive signal: radial artery pressure. Thus, although as a method it is not more invasive, it is not non-invasive. In a remarkable study, however, Hirschl and colleagues[15] used non-invasive finger arterial pressure as input to the same model as used in the present study in critically ill patients in an emergency department. They also used the phase-spreading thermodilution technique as a precise reference although no mention is made of rejection of data if haemodynamic conditions were unstable. No mention is made of the possibility of calibration on the first series. Expressed as cardiac index, their results are quite similar to ours before calibration, including a similar bias and a small number of outliers beyond the limits of agreement.

The present study adds to Hirschl and co-workers' results the use in cardiac surgery patients; emphasizes the tracking ability of the model method after calibration; indicates the insensitivity of the model method to changes in mean arterial pressure, heart rate, and systemic peripheral resistance as caused by vasoactive agents, cardiac stimulants or improved heart function after surgery; and confirms that differences between model and thermodilution cardiac output before calibration are not related to age, gender, underlying diagnosis, or body mass index. Differences are because of uncertainty about the diameter of the individual patient's aorta, not apparently related to any obvious patient characteristic.[20] By using invasive arterial pressure in the present study we avoided uncertainty about non-invasively obtained arterial pressure pulsations. Even though mean arterial pressure was measured well, non-invasively, in a similar setting in similar patients,[32] this does not automatic guarantee that non-invasive pressure pulsations as input to the model are also correct. In view of the similarity in results between the present and Hirschl and colleagues' study, however, we support their comment that differences between model and thermodilution cardiac output *before calibration* (our emphasis) are substantially caused by the uncertainty in the model calibration for each patient.

In a non-invasive study in young adult healthy volunteers who underwent a laboratory tilt table procedure, model stroke volume with non-invasive finger arterial pressure as input tracked changes in thermodilution to within 10% error during head-up tilt. Head-up tilt and standing induce blood volume shifts in the body with 50 and 30% reductions in stroke volume on average.[16] Although not obtained in critically ill patients we interpret these results as confirmation that non-invasive tracking of changes in cardiac output may be valuable in the future.

The model simulation method could be tested for cardiac output tracking in other categories of patients, including children for which little information is yet available, and more extensively than is already done,[15 16] with non-invasive finger pressure as input.

Conclusions

In patients without aortic abnormalities, undergoing coronary artery bypass surgery, the continuous monitoring of *changes* in cardiac output by simulation of a non-linear,

self-adapting model of arterial input impedance is reliable and response to changes in cardiac output is almost immediate. After an initial thermodilution calibration for each individual patient, it has near zero bias and, a 7% error, and a precision sufficient to replace subsequent conventional triplicate thermodilution. Close control of the quality of peripheral artery pressure measurement is necessary. In our automated set-up this is facilitated by computer detection of damped waveforms. Vasoactive drugs and cardiac stimulants in the usual doses do not appear to affect the ability to track the changes in cardiac output thus induced.

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