Single Injection Thermodilution

A Flow-corrected Method

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Background: Application of the Stewart-Hamilton equation in the thermodilution technique requires flow to be constant. In patients in whom ventilation of the lungs is controlled, flow modulations may occur leading to large errors in the estimation of mean cardiac output.

Methods: To eliminate these errors, a modified equation was developed. The resulting flow-corrected equation needs an additional measure of the relative changes of blood flow during the period of the dilution curve. Relative flow was computed from the pulmonary artery pressure with use of the pulse contour method. Measurements were obtained in 16 patients undergoing elective coronary artery bypass surgery. In 11 patients (group A), pulmonary artery pressure was measured with a catheter tip transducer, in a partially overlapping group of 11 patients (group B), it was measured with a fluid-filled system. For reference cardiac output we used the proven method of four uncorrected thermodilution estimates equally spread over the ventilatory cycle.

Results: A total of 208 cardiac output estimates was obtained in group A, and 228 in group B. In group B, 48 estimates could not be corrected because of insufficient pulmonary artery pressure waveform quality from the fluid-filled system. Individual uncorrected Stewart-Hamilton estimates showed a large variability with respect to their mean. In group A, mean cardiac output was 5.01 l/min with a standard deviation of 0.53 l/min, or 10.6%. After flow correction, this scatter decreased to 5.0% (P = 0.0001). With no bias, the corresponding limits of agreement decreased from ± 1.06 to ± 0.5 l/min after flow correction. In group B, the scatter decreased similarly and the limits of agreement also became ± 0.5 l/min after flow correction.

Conclusion: It was concluded that a single thermodilution cardiac output estimate using the flow-corrected equation is clinically feasible. This is obtained at the cost of a more complex computation and an extra pressure measurement, which often is already available. With this technique it is possible to reduce the fluid load to the patient considerably. (Key words: Blood; flow modulation; pulse contour. Heart: cardiac output. Lungs: mechanical ventilation. Measurement techniques, thermodilution: flow correction of dilution curve.)

SINCE the introduction of the pulmonary artery catheter (PAC) by Ganz and Swan,1 the measurement of cardiac output by the thermodilution technique has become routine in the assessment and management of critically ill patients. To compute cardiac output from the dilution curve, the Stewart-Hamilton equation is used.2 This equation is a simplification of the heat balance equation and is valid only when cardiac output is constant; otherwise, considerable errors may result.

Four types of blood flow variability have been reported:1:

1. In a beating heart the output is variable between zero in diastole and a peak value during systole.
2. Respiratory, and mechanical ventilation in particular, modulate stroke volume synchronously with respiration.
3. Various autonomic reflexes and reactions to stimuli as pain, blood loss, hemodilution, and psycholog-
cal, pharmacologic, and physical stress also change cardiac output, usually with slower variations than respiration.

4. Cardiac dysrhythmias may cause beat-to-beat changes of stroke volume.

Inaccuracies in the estimation of cardiac output by thermodilution are particularly large when variability in flow has a periodicity almost equal to the duration of the dilution curve. This is the case for the aforementioned second item of flow variability.

In addition to these changes in blood flow temperature, baseline fluctuations in blood temperature are present. These fluctuations can be subdivided into three types: (1) random fluctuations, (2) drift in body temperature as occurs after cardiopulmonary bypass, and (3) cyclic changes. Ignoring their presence also may lead to a considerable error in the estimation of cardiac output.

In this article, we present a solution to these problems by introducing a flow-corrected thermodilution method, under correction of baseline fluctuations of types 2 and 3. To test this new technique in patients, cardiac output values of single measurements with and without flow correction were compared with the averaged values of four estimates equally spread over the ventilatory cycle as the reference. We call this new flow-corrected technique the single injection thermodilution.

**Methods**

**Theory of the Thermodilution Method**

The thermodilution method is based on the law of conservation of thermal energy. A certain amount of cold fluid is injected into the blood upstream and detected, in diluted form, downstream. An accurate estimate of cardiac output is made if (1) there is no loss of cold between the sites of injection and detection, (2) mixing of indicator and blood is complete, and (3) the induced temperature change \( T_b(t) \) (by injecting of cold fluid) can be discriminated accurately from the predicted baseline temperature (without an injection of cold fluid) \( T_b(t) \), giving a temperature difference \( \Delta T_b(t) = T_b(t) - T_b(t) \). Then the equation for the thermodilution method can be formulated as:

\[
\rho_o S_o \int_{t_1}^{t_2} \frac{Q(t)T_b(t) - T_b(t)}{T_b(t)} dt = \rho_o S_o \int_{t_1}^{t_2} \Delta T_b(t)Q_b(t) dt
\]  

(1)

In this equation the injected amount of cold is on the left side, the detected amount on the right side. \( Q_b(t) \) is blood flow; \( \dot{Q}(t) \) is the input flow of indicator, \( T \) is the temperature, \( \rho \) is the density, and \( S \) is the specific heat of the indicator (t) and blood (b), respectively, \( t_1 \) is time, \( t_i \) is time of injection, and \( t_2 \) is the end of integration when all cold has passed the detector site.

If the injection of cold is fast (bolus injection) then \( T_b(t) \) and \( T(t) \) are constant, and the left side of the equation can be rewritten as:

\[
\rho_o S_o \int_{t_1}^{t_2} \Delta T_b(t)Q_b(t) dt = \rho_o S_o \int_{t_1}^{t_2} \Delta T_b(t)\dot{Q}_b(t) dt
\]  

(2)

where \( Q_b \) is the injected volume of cold fluid.

If blood flow, \( Q_b(t) \), is constant then the classical Stewart-Hamilton equation results:

\[
\dot{Q}_b = \frac{\rho_o S_o \int_{t_1}^{t_2} \Delta T_b(t)\dot{Q}_b(t) dt}{\rho_o S_o \int_{t_1}^{t_2} \Delta T_b(t) dt}
\]  

(3)

We will indicate \( \dot{Q}_b \) as \( \dot{Q}_b \) if the cardiac output is estimated by this classical thermodilution method.

**Correction for Nonconstant Flow.** For nonconstant blood flow, we modified the thermal energy equation (2) by multiplying and dividing the right side of the equation with mean blood flow, \( \dot{Q}_b \), as follows:

\[
\rho_o S_o \int_{t_1}^{t_2} \Delta T_b(t)\dot{Q}_b(t)\dot{Q}_b(t) dt = \rho_o S_o \int_{t_1}^{t_2} \Delta T_b(t)\dot{Q}_b(t)\dot{Q}_b(t) dt
\]  

(4)

The \( \dot{Q}_b(t)/\dot{Q}_b \) ratio represents the time course of the relative changes in blood flow. From equation (4) follows:

\[
\dot{Q}_b = \frac{\rho_o S_o \int_{t_1}^{t_2} \Delta T_b(t)\dot{Q}_b(t) dt}{\rho_o S_o \int_{t_1}^{t_2} \Delta T_b(t) dt}
\]  

(5)

To estimate \( \dot{Q}_b(t)/\dot{Q}_b \) we calculated beat-to-beat cardiac output from the pulse contour of the pulmonary artery pressure, measured near the site of the thermistor. Therefore, \( \dot{Q}_b(t)/\dot{Q}_b \) is inserted in equation (5) and \( \dot{Q}_b \) at the left side to \( \dot{Q}_b \), indicating corrected thermodilution cardiac output. Equation (5) can then be rewritten as:

\[
\dot{Q}_{reb} = \frac{\rho_o S_o \int_{t_1}^{t_2} \Delta T_b(t)\dot{Q}_b(t)/\dot{Q}_b dt}{\rho_o S_o \int_{t_1}^{t_2} \Delta T_b(t)\dot{Q}_b(t)/\dot{Q}_b dt}
\]  

(6)

Obviously, for \( \dot{Q}_b(t)/\dot{Q}_b \), no cardiac output is needed.

**Baseline Correction**

To apply the noninvasive cardiac output monitoring system (Card, Irvine, CA) \( T_b(t) \) and \( T(t) \) temperature signals were sampled by a computer every 0.05 s. An example of the measured temperature is given in figure 9. In figure 10 time is plotted between the two points describing the baseline curve. This period is called the period of passage, \( t_{pass} \), from the start to the end of the cardiac cycle. The resulting curve was caused by a change in body temperature, and \( t_{pass} \) was used as the time to calculate the cardiac output.

**Pulse Contour Analysis**

Relative changes in cardiac output are calculated from the pressure waveforms. The pressure changes are related to the change in blood volume. To eliminate the measured area of the pressure waveforms, the integral is divided by the baseline pressure waveforms, and the baseline area is removed. The baseline cycle thus shows the true time course of the cardiac output during the cardiac cycle. The change in blood volume is shown as a time-dependent increment in the mean area of the pulse waveform during a period of three cardiac cycles.

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Obviously, for the determination of the quotient \( \frac{Q_{pc}(t)}{Q_{nc}} \), no calibration of the pulse contour cardiac output is needed.

**Baseline Correction of the Temperature Signal**

To apply the new formula (6) we modified a commercial cardiac output computer (Baxter, Edwards Critical Care, Irvine, CA) to output continuously the unprocessed temperature signals of the blood and cold injectate that were sampled by a PC/AT computer at a rate of 10 Hz. An example of the recordings during a thermococulation measurement is presented in figure 1. In the period before the thermococulation curve, blood temperature fluctuated cyclically (type 2) with a periodicity equal to the ventilatory cycle. As described elsewhere,\(^6\) we used the temperature data over the ventilatory cycle immediately preceding the moment of injection as a point-by-point description of the blood temperature baseline curve. This periodic baseline was extrapolated to the period of passage of the dilution curve and subtracted from it. Slow temperature changes owing to gradual changes in body temperature and slow leakage of cold through the wall of the injection catheter were eliminated by further subtracting a linear gradient in temperature from the start to the end of the thermococulation curve.\(^6\) The resulting curve was regarded as the change in temperature caused by the injection of a cold indicator. These curves were used to compute the flow-corrected cardiac output and to estimate mean cardiac output by the average of a series of four measurements.

**Pulse Contour with Pressure Baseline Correction**

Relative changes in right ventricular output were obtained by processing the pulmonary artery pressure signal. The pressure baseline of this signal varied cyclically with the changes in intrathoracic pressure, owing to ventilation. To eliminate the effects of the pressure baseline on the area of the pressure pulse, we connected the points at the start of the systolic upstroke of each beat by straight line segments (fig. 1C). The area between this baseline and pulse contour was then computed. Stroke volume has shown to be proportional to this area.\(^1\) Beat-to-beat cardiac output was calculated as the quotient of stroke volume and cardiac interval. The irregularity in time-spaced values were next placed on the time grid of the dilution curve by cubic spline interpolation. The mean of the pulse contour values was calculated during a period of three ventilatory cycles.

\[ Q_{pc}(t) = \frac{Q_{nc}}{Q_{nc}} \]

**Fig. 1.** The single injection thermococulation method. In (A) \( T_b \) is blood temperature, \( v \) cycle is time for one ventilatory cycle, \( \Delta T_b \) change of blood temperature after correction for temperature baseline fluctuations, \( T(j) \) temperature at time sample \( j \). \( Q_{nc} \) cardiac output estimated by thermococulation without flow correction, \( T_{nc} \) temperature of the injectate, \( P_{pa} \) pulmonary artery pressure, \( Q_{pc} \) blood flow estimated beat-to-beat by pulse contour, \( Q_{pc,mean} \) mean blood flow estimated by pulse contour, min, max are minimal and maximal value in blood flow, respectively, \( T_{nc} \) flow-corrected response in blood temperature, \( T_{pc}(j) \) corrected temperature at time sample \( j \), \( Q_{pc,mean} \) cardiac output estimated by thermococulation after flow correction. See text for explanation.

**Patients Studied**

The single injection thermococulation technique was tested in patients undergoing elective coronary artery bypass graft surgery. After approval by the hospital ethical committee and obtaining written informed consent of
the patients, we studied 16 patients aged 44–70 years. All had multiple vessel disease without previous myocardial infarctions, stable angina pectoris with a normal ventricu-
lar function, and no signs of valvular dysfunction. None of the patients had acute or chronic pulmonary disease. Premedication consisted of 5 mg lorazepam. Anesthesia was induced with sufentanil (7.5 μg/kg body weight intravenous) administered over 5 min and maintained by a high-flow (7 μg/kg/min.) infusion. Complete muscle relaxation was achieved by administering 0.1 mg/kg pancuronium/brodil via a peripheral injection line. To control blood pressure after sternotomy and during dissection of the internal mammary artery, 0.5–1 μg/kg−1 min−1 nitroglycerin was administered. None of the patients required inotropic drugs. A Siemens (Solna, Sweden) model 900B servoventilator was used for mechanical ventilation. The lungs were ventilated at a rate of 10 per min and an inflation/pause/expiration ratio of 25/20/55%. The ventilatory volume was adjusted to maintain a PaCO2 between 32 and 42 mmHg. No positive end-expiratory pressure was applied.

**Patient Instrumentation**
A radial artery cannula and a PAC were inserted. One of three types of pulmonary artery catheters was used: (1) a special 7.5-French PAC (Baxter, Edwards Critical Care, Irvine CA) with an extra lumen for a tip transducer, (2) a 7.5-French PAC equipped with a tip transducer (Sentron, Roden, The Netherlands), or (3) a normal PAC. They were inserted via the internal jugular vein. Through the extra lumen of the special PAC, ending 35 mm from the tip, a pressure tip transducer (Millar 2F, Model SPC-320, Houston, TX) was inserted. The standard lumen, ending at the tip, was still available for blood sampling and pulmonary artery pressure recording. This pressure signal was used to check for the presence of zero drift of the Millar tip transducer and to obtain a second pulse contour estimate.

**Experimental Protocol**
Radial arterial pressure, pulmonary arterial pressure via tip transducer and fluid channel, central venous pressure, ventilatory flow, and body temperature were monitored. Series of four thermomobilization measurements were carried out during hemodynamically stable conditions. During each measurement, data were collected for 32 s at a sample rate of 100 Hz. A period of 5–7 ventilatory cycles elapsed between two measurements in a series. Thus, each series of four measurements could be performed in approximately 5 min. Successive injections were done at the phases 25, 50, 75, and 100% of the ventilatory cycle. Zero phase was chosen as the start of inflation, obtained from a ventilator-supplied trigger signal. Based on previous studies, the mean of these four cardiac output estimates, calculated according to the Stewart-Hamilton equation, yields an accurate and precise reference, provided that the hemodynamic condition is stable during this period. To verify stability, averages of blood pressures and heart rate were computed for each of the single measurements. Hemodynamic stability of the patient was accepted if during each series of four measurements none of the individual averages deviated by more than 5% of the mean of the four measurements (fig. 2).

**System Description**
Data collection and the automatic execution of the observations were performed with use of a personal computer. Blood pressure signals, a respiratory signal from the ventilator, and temperature signals from the modified thermodilution cardiac output computer were recorded digitally on a PC/AT computer hard disk for off-line analysis. The respiratory cycle time was derived from the ventilator. For respiratory phase-controlled injections of cold fluid, percentage phases of the respiration were computed in real time. At times decided by the anesthesiologist, the series of four phase-controlled thermodilution estimates were performed automatically. The injectate was delivered through the pulmonary artery catheter in approximately 1.5 s by a pneumatic power injector. After three ventilatory cycles, the syringe was refilled automatically using a three-way valve. To obtain a maximal signal-to-noise ratio, 10-ml injections of iced 5% glucose were used. The three-way valve and cooling unit were parts of a closed injection system (CO-set, Baxter). All signals to and from the computer were routed via an interface box providing full patient isolation. A red "break-key" on the front panel of the interface box could interrupt the computer-controlled injections in case of emergency.

**Statistics**
To apply one-way analysis of covariances, single cardiac output estimates were made the dependent variable, and the means of four estimates together with the patient the independent variables. The patient was treated as a categorical factor using dummy variables.
FLOW-CORRECTED THERMODILUTION METHOD

Fig. 2. Cardiac output and stability throughout a series of four measurements. In (A) $Q_{\text{id}}$ th of cardiac output (t) uncorrected and □ flow-corrected, respectively; (100% = 4.53 L/min); (B) $P_{\text{pa}}$, pulmonary artery pressure; (100% = 17.7 mmHg); systolic pressure $\nabla$ (100% = 22.4 mmHg); and diastolic pressure $\times$ (100% = 14.2 mmHg), respectively; (C) $P_{\text{rad}}$, mean radial artery pressure $\Delta$ (100% = 78.7 mmHg); and (D) estimated mean cardiac output by pulse contour $Q_{\text{pc}}$. $n_r$ is number in series of four. For all panels values are expressed in percentage of the mean of the series of four measurements.

These analyses were done with the statistical package BMDP v7, program IV (BMDP, Los Angeles, CA). If no statistical differences were observed between the regressions found for each patient the weighted regression was used. The correlation coefficient was computed after removal of the variation owing to patient differences.\textsuperscript{15}

To allow the computation of the limits of agreement for the difference between two methods\textsuperscript{16} for the whole data set, we first need to provide evidence that the variances among patients are small, and that the variances among the individual patients of one group do not differ significantly. Because we computed the difference between single estimates of a series of four and the mean of this series, the variance between patients is zero. The variance and Levene's test for equality of variances within each patient as well as the group standard deviation and bias for the differences were derived from program BMDP-7D. If Levene's test provided no evidence against equality of variances for the different patients, it is appropriate to pool the data of all sets. Then it is allowed to calculate the limits of agreement. If the test of equality is rejected then we present two times the averaged value of the standard deviations of all patients as an indication of the error range. Furthermore, the distributions of the differences were tested for normality by the Kolmogorov-Smirnov one-sample test. The limits of agreements are given by $\text{bias} \pm 2 \text{SD}$. The coefficient of variation (CV) is defined as $\text{CV} = (\text{SD/mean}) \times 100\%$.

To test whether the flow-corrected thermodilution method has a better precision (i.e., lower standard deviation) than the uncorrected thermodilution method, we used the BMDP-5V program, unbalanced repeated-measures models with structured covariance matrices. As input data for this model we used the calculated standard deviation (SD) for each series of four thermodilution measurements, both for the uncorrected and corrected thermodilution estimates. We defined a dummy variable to quantify the two different methods, that is, uncorrected and corrected. Furthermore, the sequence of the repeated measurements and the interaction terms were included in the model.

Results

In sixteen patients, 388 thermodilution measurements (i.e., 97 series of quadruple determinations), were performed during periods when the criteria of 5% stability in pressures and heart rate were fulfilled. Hemodynamic stability was not present in 22 series and these data were rejected. These unstable series were primarily found in the period directly after the cardiopulmonary bypass period.\textsuperscript{9,10} This period is usu-
Table 1. Patient Characteristics and Hemodynamic Status

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<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
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<th>$P_{\text{a}CO_2}$ (mmHg)</th>
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$P_{\text{a}O_2}$ = pulmonary arterial pressure (Ppa) measured by either a tip transducer (T) or by a fluid-filled manometer (F), gender male (M) or female (F), radial arterial pressure ($P_{\text{a}O_2}$) mean cardiac output ($CO_{\text{a}}$).

ally characterized by cardiac dysrhythmias, rapid temperature changes, and reperfusion of the lungs.

Table 1 lists patients' gender, age, height, and weight, with the hemodynamic variables obtained just after induction of anesthesia. We indicated whether the pulse contour analysis was applied on the pulmonary pressure derived from a PAC with a tip transducer or via the fluid-filled lumen of the PAC.

An individual measurement and analysis is presented in figure 1. In figure 1A, the blood temperature change in the pulmonary artery after a bolus injection of 10 ml cold injectate is given. In figure 1B, the cyclic baseline fluctuations and slow baseline drift have been eliminated and the temperature signal is inverted. In figure 1C, the pressure in the pulmonary artery, as measured by the Millar tip transducer, is shown. Straight lines connect the pressures at the beginning of the upstroke of each beat. In figure 1D, the beat-to-beat cardiac output values of the pulse contour computation are given as dots. They show a cyclic pattern of change with a periodicity equal to the ventilatory cycle of 6 s. During inflation of the lungs, a decrease in cardiac output occurred and during exhalation an increase was seen. The dashed line is the computed mean cardiac output over the three ventilatory cycles corresponding with the period of the dilution curve. In figure 1E, the result of the flow-corrected change in blood temperature is given. The shape of this curve is considerably different from the one in figure 1B. The corresponding cardiac output estimate is 4.34 l/min for the uncorrected and 4.93 l/min for the corrected thermodilution curve, a difference of 14%.

An individual example of a series of four thermodilution measurements is given in figure 2. The stability of the patient's condition is reflected in the small changes in pressure observed in the radial and pulmonary arteries (figs. 2B and 2C). Also, the mean for pulse contour over the periods of 18 s is stable, within a CV of 2% (fig. 2D). The first single thermodilution cardiac output estimate for the uncorrected dilution curve (fig. 2A) is about 1 l/min less than the value of the other three estimates. However, after correction of the thermodilution curves, the four estimates are close to the mean value, i.e., 100%. In this example, the spread of cardiac output estimates decreased from a CV of 15% for the uncorrected to a CV of 1% for the flow-corrected estimates.

**Tip Transducer**

For the whole data set, using the tip transducer, none of the 208 analyses had to be rejected because of insufficient pressure quality. The correlation of all single uncorrected thermodilution measurements versus the mean of their corresponding single estimates is shown in figure 3A. Individual correlation coefficients range from 2 to 9.5 l/min. The one-way analysis of variance indicates a correlation coefficient of 0.99 for each patient (weight: $R^2 = 0.99$, correlation: $0.99$, SE = 0.06, correlation: $0.99$, SE = 0.06).

The error diagram method is given in figure 3B. The mean of the difference between each patient's cardiac output measurements is close to zero, as indicated by the absence of a trend or a cycle. The 95% confidence interval is 5.1 l/min. The results at flow-corrected by the pulmonary artery were 3.5 and 3.6. In the left line of the ventricle, the correlation coefficients showed a good correlation: for each patient, $R^2 = 0.98$, SE = 0.06.

The correlation method shows a better agreement with the pulmonary artery.
FLOW-CORRECTED THERMODYLATION METHOD

Fig. 3. Series with tip transducer. (A) The correlation diagram of single measurements $Q'_m$ and the averaged value of four measurements performed at four instants equally distributed over the ventilatory cycle $Q'_m_{total}$. Line of identity is given. (B) Scatter diagram plotting the difference between single estimates and the mean of the four phase controlled estimates versus their mean. The level of ±2 SD is also indicated in the figure. (C) Correlation diagram of thermodilution estimates corrected by pulse contour $Q'_m$ and the averaged value of four measurements $Q'_m_{total}$. Line of identity is given. (D) Scatter diagram plotting the difference between estimates corrected by pulse contour and the mean of the four phase controlled estimates versus their mean. The level of ±2 SD also is indicated in the figure.

The mean of their corresponding series of four is given in figure 3A. Individual cardiac output estimates ranged from 2 to 9.5 l/min, with a mean value of 5.01 l/min. The one-way analysis of covariances showed no statistical difference between the regression obtained for each patient (weighted regression coefficient = 0.97, SE = 0.06, correlation coefficient = 0.77).

The error diagram for the difference between the methods is given in figure 3B. The one-way analysis of variance showed that the variance between patients is close to zero, as expected, and Levene’s test provided no evidence against equality of variances for the patients ($P > 0.05$). Therefore, we used all data sets to analyze the differences between the two methods according to Bland and Altman.16 There is no bias and the standard deviation is 0.53 l/min (CV = 10.6%), the 95% confidence interval (i.e., the limits of agreement) is ±1.06 l/min.

The results after flow correction of the thermodilution curve by the pulmonary pulse contour are shown in figures 3C and 3D. In the correlation diagram, the results are close to the line of identity. The one-way analysis of covariances showed no statistical difference between the regression for each patient (weighted regression coefficient = 0.98, SE = 0.03, correlation coefficient = 0.92).

The error diagram for the difference between the methods shows a better agreement between the methods and a substantially decreased error compared to the uncorrected thermodilution estimates. The individual data points for the differences are independent and unrelated (one-way analysis of variance, Levene’s test provided no evidence against equality of variances for each patient ($P > 0.05$)). There is no bias and the standard deviation is 0.25 l/min (CV = 5.0%) resulting in a 95% confidence interval of ±0.50 l/min. The distributions of errors in the Bland-Altman diagrams (figs. 3B and 3D) were not significantly different from normal ($P < 0.05$).

The standard deviation of all series of four measurements was significantly lower (program 5V, $P > 0.001$) for the flow-corrected method compared to the uncorrected method. Thus, the flow-corrected method estimates cardiac output more precisely. Neither an influence on the sequence of the measurements within the patient ($P > 0.7$) nor an influence of the cross term between method and repetition of the measurements ($P > 0.7$) could be found.

**Fluid-filled Manometer System**

For the whole data set, 12 of 57 series of four measurements were rejected in this group of patients, because of insufficient signal quality of the pulmonary artery pressure for pulse contour analysis. The remaining results confirmed those found in patients with
a tip transducer. The correlation of all single uncorrected thermodilution measurements versus the mean of their corresponding series of four is given in figure 4A. The individual cardiac output estimates ranged from 2 to 9.5 l/min, with a mean value of 4.95 l/min. The one-way analysis of covariances showed no statistical difference between the regression obtained for each patient (weighted regression coefficient = 0.99, SE = 0.048, correlation coefficient = 0.84).

The error diagram for the difference between the methods is given in figure 4B. The one-way analysis of variance indicates that the individual data points for the differences are dependent (Levene’s test provided evidence against equality of variances for each patient (P < 0.05)). Therefore, we may not analyze the differences between the two methods according to Bland and Altman. Instead, we calculated the averaged standard deviation to give an indication of the errors for the differences. There is no bias, the standard deviation is about 0.5 l/min (CV about 10%).

The regression data for all single corrected thermodilution measurements and the mean of their corresponding series of four is given in figure 4C. The one-way analysis of covariances showed no statistical difference between the regression for each patient (weighted regression coefficient = 1.00, SE = 0.03, correlation coefficient = 0.95).

The error diagram for the difference (fig. 4D) between the methods shows a better agreement between the methods and a substantially decreased error compared to the uncorrected thermodilution estimates. The individual data points for the differences are independent and unrelated (one-way analysis of variance, Levene’s test provided no evidence against equality of variances for each patient (P > 0.05)). There is no bias and the standard deviation is 0.25 l/min (CV = 5%) resulting in a 95% confidence interval of ±0.50 l/min. The distributions of errors in the Bland-Altman diagrams (figs. 4B and 4D) were not significantly different from normal (P < 0.05).

The standard deviation of all series of four measurements for the flow-corrected method was significant lower (P > 0.005) compared to the uncorrected method. Neither an influence of the sequence of the measurements within the patient (P > 0.1) nor an influence of the cross term between method and repetition of the measurements (P > 0.5) could be found.

Cyclic Changes of Flow Estimates
We found a cyclic modulation of blood flow according to the estimates of the pulse contour method. For the individual example of figure 1D, the modulation was 100° (Q’max/Q’min)/Q’mean = 59%. For all 388 measurements, the modulation ranged from 10% to 95%, with a mean of 49%.

Discussion
Since Fegler14 in 1954 it became clear that output measurements regarding accuracy of the method.2,9,10,11,12 toward the adaptation to the situation of the commercial market the classical Stewart-Hamilton standard deviation of output estimates requires accurate estimates of sequential estimates. Because respiratory changes and practicality of three or four methods are equally spread over the monitored period in pigs,14,16,17 in this study, we showed that a variation decrease standard deviation whereas it decreases for measurements with bolus injections of constant temperature was supposed to be precisely timed injection sequence is clinically relevant. A highly precise respiratory steady state is maintained by this technique as the computer control unit.

To limit the number of other methods, the standard deviation, which also contributes to flow modulation, as has already been known for patients participating in cyclical modulation in the peak-to-peak range could be more than

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FLOW-CORRECTED THERMODILUTION METHOD

Discussion

Since Fegler\textsuperscript{17} introduced the thermodilution method in 1954 it became the most often used clinical cardiac output measurement. Nevertheless, concern exists regarding accuracy and reproducibility of the thermodilution method.\textsuperscript{1,18,19} Yet, little effort has been directed toward the adaptation of the Steward-Hamilton equation to the situation of nonconstant blood flow. Most of the commercial cardiac output computers still apply the classical Steward-Hamilton equation. Clinically, a standard deviation of approximately 15% for single cardiac output estimates has been accepted.\textsuperscript{18,19} If more accurate estimates were needed, averaging of many sequential estimates became the standard procedure. Because respiration alters flow periodically, an adequate and practical solution appeared to be an average of three or four measurements performed at moments equally spread over the ventilatory cycle. This has been verified in pigs,\textsuperscript{6,11} dogs,\textsuperscript{2} and humans.\textsuperscript{12,20,21} In a previous study, we showed that in patients the coefficients of variation decreased from 14% to 3.2% if four equally spread thermodilution measurements were averaged, whereas it decreased to 7% if four randomly performed measurements were averaged.\textsuperscript{12} A procedure of four bolus injections of 5 ml 5% glucose solution at room temperature was sufficient, but a power injector under computer control was needed to obtain identically and precisely timed injections. Application of this procedure is clinically reliable in many situations.\textsuperscript{21} It yields highly precise results if circulatory and respiratory steady state is maintained during the series. We used this technique as the reference cardiac output method.

To limit the number of estimates we evaluated another method, the single injection thermodilution technique, which also corrects for cyclic flow modulation. Flow modulation, as a result of mechanical ventilation, has already been known for a long time.\textsuperscript{22,23} In all patients participating in the current study, we found a cyclic modulation in relation to mechanical ventilation. The peak-to-peak ratio for these fluctuations of flow could be more than two.

Pulse Contour Analysis

Pulse contour analysis of a pulmonary artery pressure signal has been done before\textsuperscript{3,4,24-26} to obtain beat-to-beat estimates of cardiac output. This method requires a pressure signal of reasonable quality, otherwise errors will be made in the detection of pressure upstroke and incisura. To avoid such problems, we first used a Millar or Sentron tip transducer providing high-fidelity pressure signals of a good quality and no problems were encountered in the pulse contour method. To test whether a normal pulmonary artery catheter is feasible we also analyzed the results of 11 patients equipped with a fluid-filled pressure transducer. We had to reject 12 of the 57 series of four measurements because of insufficient signal quality, although we paid much attention to this problem. In the remaining series, the results were not different from those with the pressure tip transducer (compare figs. 3D and 4D). Clearly, the highest reliability is achieved with a PAC equipped with a pressure tip transducer. Such catheters are already commercially available, easy to use, reliable, and have a low zero drift. The current cost of these catheters is twice that of a normal PAC but is expected to decrease.

For our correction technique, we assumed a constant calibration factor within a heartbeat for the pulse contour method. The reasonableness of this assumption is reflected in the low coefficient of variance (5%) in single thermodilution cardiac output estimates after flow-correction of the dilution curve. Also, several authors\textsuperscript{27-29} described a linear behavior of cross-sectional area versus pressure of the pulmonary arterial system. However, a pressure dependency of the parameters (i.e., compliance, impedance, and pulmonary vascular resistance) of a windkessel model describing the pulmonary circulation also have been reported.\textsuperscript{30-32}

Error Analysis

In this study, the coefficient of variation for repeated measurements decreased from 10% for the uncorrected estimates to 5% for the flow-corrected estimates. This error of 5% combines two types of errors: (1) errors in the reference mean cardiac output by the series of four uncorrected thermodilution measurements, and (2) errors of the flow-correction method. In a previous study,\textsuperscript{12} the error in a repeated series of four measurements equally spread over the ventilatory cycle under stable circumstances was 3.2%. If we subtract this variance, (3.2%) from the variance of the flow-corrected thermodilution measurements (i.e., 5%) the remaining coefficient of variation for the flow-corrected thermodilution method is 3.8%. From this we can compute the standard deviation, \( SD = CV \times CO \, \text{mean}/100 = 3.8 \times 5.0/100 = 0.19 \, \text{l/min} \). Accepting a change of two SD (\( \pm 5\%\) uncertainty) as significant, the limits of agreement between successive flow-corrected thermodilution measurements range from \(-0.38 \, \text{l/min}\) to \(+0.38 \, \text{l/min} \). Thus, a change of 0.4 l/min already is significant.

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A proper thermodilution baseline correction reduces scatter from the usual 15% to about 10%. Averaging four such estimates obtained under phase-controlled injections reduce scatter to a maximum of 5%. Flow correction of the thermodilution curves reduces scatter to 5% for single estimates, a factor twofold in precision compared to single uncorrected estimates. Using our technique, changes in cardiac output of 0.4 l/min can be considered significant. The reduction of four injections to one to obtain an estimate of mean cardiac output greatly reduces fluid load to the patient.

References

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