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Original articles

Improvement of cardiac output estimation by the thermodilution method during mechanical ventilation

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Abstract. The reliability of cardiac output estimation by thermodilution during artificial ventilation was studied in anesthetized pigs at the right side of the heart. The estimates exhibited a cyclic modulation related to the ventilation. The amplitude of the modulation was independent of the level of positive end-expiratory pressure, ventilatory pattern and volemic loading of the animals. However, a non-constant phase relation existed between the ventilatory cycle and the modulation. Single observations at a fixed moment in the ventilatory cycle are therefore not appropriate for estimation of mean cardiac output nor for studying its relative changes. The averaging of estimates spread equally over the ventilatory cycle led to a much larger reduction in the deviation of the averages from the mean cardiac output than an averaging procedure of randomly selected estimates. The accuracy of estimation of mean cardiac output by two estimates equally spread in the ventilatory cycle was equal to the accuracy obtained by averaging five randomly selected estimates. Averaging four estimates, equally spread in the cycle, appeared to be the optimal procedure. For 89% of all averages an accuracy of 5% around the mean was obtained and for 99% an accuracy of ±10%.

Key words: Cardiac output – Flow modulation – Mechanical ventilation – Thermodilution method

The thermodilution technique for the estimation of cardiac output based on the classical Stewart-Hamilton equation has become widely accepted. Although this is valid only for constant blood flow, this method has been applied during artificial ventilation where a characteristic pattern of cyclic fluctuation i.e. modulation occurs in right ventricular output [1, 4, 5, 7, 8, 12, 13]. Few studies have been made of the errors which arise when the thermodilution technique is used during modulated flow as in artificial ventilation. Cropp and Burton [3] studied the errors in the estimation of cardiac output in a physical model using a constant injection rate of cold indicator. Bassingthwaighte et al. [2] simulated a bolus injection in their theoretical studies with a mathematical model. During experiments with pigs we found a cyclic modulation in cardiac output estimates by the thermodilution method [5]. The best moment of injection varied with the level of positive end-expiratory pressure. Snyder and Powner [11] confirmed our results and reported additionally the existence of variation in estimates in a patient.

The objectives of our present study were:

1. to investigate the errors in the estimation of mean cardiac output by single measurements during mechanical ventilation with changing conditions of PEEP, ventilatory pattern, ventilatory rate and blood volume, and
2. to search for an averaging technique which maximally reduces the errors with a minimum of measurements.

Methods

Experimental techniques

Surgical procedures, measurements, data acquisition and analyses were described in a previous paper [5]. The essentials and additional procedures will be mentioned here. Eighteen Yorkshire pigs, 5 – 7 weeks old, weighing 7 – 11 kg, were anesthetized with pentobarbital sodium, using a loading dose of 30 mg · kg^{-1} i.p. followed by a continuous infusion of 7.5 mg kg^{-1} h^{-1}. Muscle relaxation was induced with a loading

dose of d-tubocurarine hydrochloride (0.1 mg kg^{-1}) administered over a period of 3 min, followed by a continuous infusion of 0.2 mg $kg^{-1} h^{-1}$. Heparin (125 IU kg^{-1}) was given intermittently each hour.

The animals were ventilated with room air using a microprocessor controlled ventilator at rates of 10 and 20 cycles min^{-1}. Ventilation volume was adjusted to achieve an arterial carbon dioxide tension between 38 and 44 Torr and was subsequently kept constant for the applied pattern of ventilation. Body temperature was maintained at about 38 °C on a thermocontrolled operating table.

Catheters

Catheters were positioned under fluoroscopic control and pressure monitoring. A four-lumen catheter was inserted into the vena cava at the level of the right atrium for measuring central venous pressure and for drug infusions. A double-walled injection catheter (inner tube 0.86 mm ID, 1.27 mm OD, outer tube 1.40 mm ID, 1.90 mm OD) was inserted into the right atrium for injections of 0.5 ml of saline. The length of the intracorporeal part of this catheter was 12–15 cm. A Swan-Ganz 5 F catheter with a thermistor was positioned in the pulmonary artery. After the experiments the position of each catheter was confirmed at autopsy.

Fick method

Cardiac output (CO_{Fick}) was measured by the direct Fick method [5]. Inspiratory and mixed expiratory gases were sampled over 3 min with a mass spectrometer (Perkin-Elmer MGA1100) from a mixing box with a volume equal to 5 times tidal volume. Oxygen content of the arterial and venous blood was calculated from the directly measured oxygen saturation and hemoglobin values (Radiometer OSM2) and the oxygen pressure (PO_2) (Radiometer ABL3). Blood was continuously sampled over three ventilatory cycles. The OSM2 was recalibrated for pig blood by tonometry for the saturation and for hemoglobin (Hb) checked by the Hb cyanide method.

Thermodilution method

When hemodynamic stability was achieved, cardiac output measurements by thermodilution (CO_{TH}) were carried out by injection of 0.5 ml saline (0.9% NaCl) at room temperature. The cold fluid was injected through the double walled catheter within 300 ms by a pneumatically driven syringe.

After 12 s the syringe was automatically refilled. The temperature–time curve ($\Delta T_b(t)$) was derived from the thermistor of the Swan-Ganz catheter. The thermistor response was linear within the range of measurements (37–39 °C). The temperature–time curve was sampled on-line and analyzed with a sample frequency of 50 Hz by a PDP 11/23 computer.

The cardiac output (CO or Q′) was derived from a mass balance equation [15].

$$\rho_i S_i \int Q'_i(t)\,\Delta(T_b - T_i)(t)\,dt = \rho_b S_b \int \Delta T_b(t)\,Q'(t)\,dt \quad (1)$$

where Q′ (t) is the blood flow, $Q'_i(t)$ the injectate flow, T the temperature, ρ the density and S the specific heat of blood (b) and injectate (i) respectively.

For a bolus injection, assuming Q′ is constant, Eq. (1) can be written:

$$Q' = \frac{Q_i \rho_i S_i (T_b - T_i)}{\rho_b S_b \int \Delta T_b(t)\,dt} \quad (2)$$

where Q_i is the injected volume minus the volume of the intracorporeal part of the catheter.

For a reliable estimation of the area of $\int \Delta T_b(t)\,dt$ several corrections have to be made [5] (Fig. 1).

The recorded thermodilution curve (Fig. 1 a) has to be corrected for variations in base-line temperature concomitant with the ventilatory cycle (Fig. 1 b) [14], slow trends in body temperature (Fig. 1 c) and the leakage of cold from the intracorporeal part of the double walled injection catheter (Fig. 1 d).

No corrections for specific heat were made during hypervolemic and hypovolemic condition since calculations based on the equations of Rosen et al. [9] showed that the errors introduced were smaller than 1%.

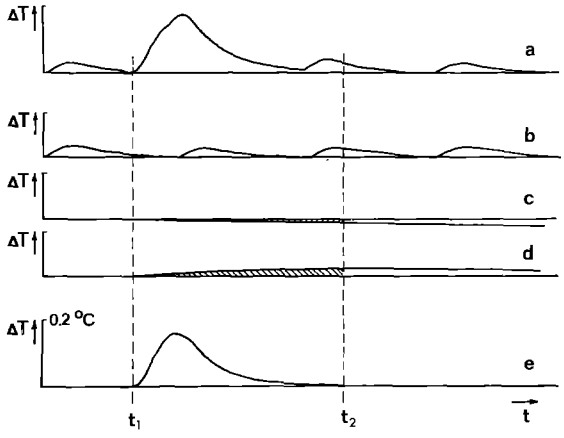

Fig. 1 a–e. Corrections to the thermodilution curve. **a** the curve as actually measured; **b** base-line fluctuations during each ventilatory cycle; **c** long-term baseline drift; **d** loss of cold from the catheter dead space and **e** the corrected dilution curve after subtraction of **b**, **c** and **d** from the original curve **a**

Series of observations and conditions

Series of 50 thermodilution measurements were carried out during hemodynamically stable conditions [5]. Five ventilatory cycles were inserted between two measurements, which implies that the series of 50 measurements was performed in 25 min. The ventilatory cycle was divided into 100 equal intervals. The beginning of insufflation was chosen as the start of the first interval (phase 0%). The injections of indicator for the thermodilution measurements were performed at the even numbered percentage phases of the cycle.

The sequence of injection moments in the ventilatory cycle was randomly chosen. The mean of all 50 measurements was taken as the 100% value. For the evaluation of the stationary state heart rate, aortic, central venous and pulmonary artery pressures were monitored throughout a series. Moreover, the random estimates were tested on their trend in time [5]. A negative or positive trend was assumed to indicate a nonstable condition. Two or three cardiac output estimates were made by Fick's method for oxygen just before and after each series. The interval between two series was about 30 min. Series without hemodynamically stationary conditions were rejected.

Three patterns of ventilation were applied:

1. a sinusoidal like inspiratory flow (I) followed by a spontaneous expiration (E) with an I:E ratio of 44:56 (Fig. 4a);
2. a constant inspiratory flow followed by a spontaneous expiration after an inspiratory pause (IP) with an I:IP:E ratio of 25:5:70 (Fig. 4b);
3. the same pattern as 2. with an I:IP:E ratio of 15:5:80 (Fig. 4c).

Patterns (1 – 3) were applied at a ventilatory rate of 10 min^{-1}, pattern (2) was also applied at a rate of 20 min^{-1} (Fig. 4d).

Three volemic conditions were applied with ventilation pattern (2) and a ventilatory rate of 10 min^{-1}:

1. hypervolemia was obtained by infusion of 15 ml kg^{-1} 6% Macrodex solution in 5% glucose;
2. normovolemia by bleeding the animal 15 ml kg^{-1};
3. hypovolemia by a further bleeding of 15 ml kg^{-1}.

These changes were used to study the effects of changes in amplitude of the modulations in real output [13] on the amplitude of the thermodilution estimates.

Four levels of PEEP [0 (ZEEP), 5, 10, 15 cm H_2O] were studied at a ventilatory rate of 10 min^{-1} and with inflation pattern (1).

The averaging procedures

Averages were calculated according to a *systematic* and a *random* selection of single estimates. In both procedures the averages were derived from 2, 3, 4, 5 and 6 single measurements of each series of 50, and will be called two, three, four, five and six-point-averages respectively.

In the systematic procedure these averages were calculated from single values equally spread in the ventilatory cycle (Fig. 2). Thus, for each series 25 two-point-averages were attained from the phases 0 + 50%; 2 + 52%; etc. The total number for all 55 series is $n = 1375$. Sixteen three-point-averages per series were calculated from the phase 0 + 34 + 68%; 2 + 36 + 70%; etc. The phases 32% and 98% were left out ($n = 880$).

The 12 four-point-averages per series were taken from the phases 0 + 24 + 50 + 76%; etc., where the phases 48 and 74% were left out ($n = 660$). Ten five-point-averages per series were obtained from the phases 0 + 20 + 40 + 60 + 80%; etc. ($n = 600$) and 8 six-point-averages from the phases 0 + 34 + 50 + 66 + 82%; etc. without the phases 32 and 98% ($n = 440$). In the random procedure the same number of averages was calculated as for the corresponding averages of the systematic procedure, e.g. for the five-point averages within each series 10 times a random selection

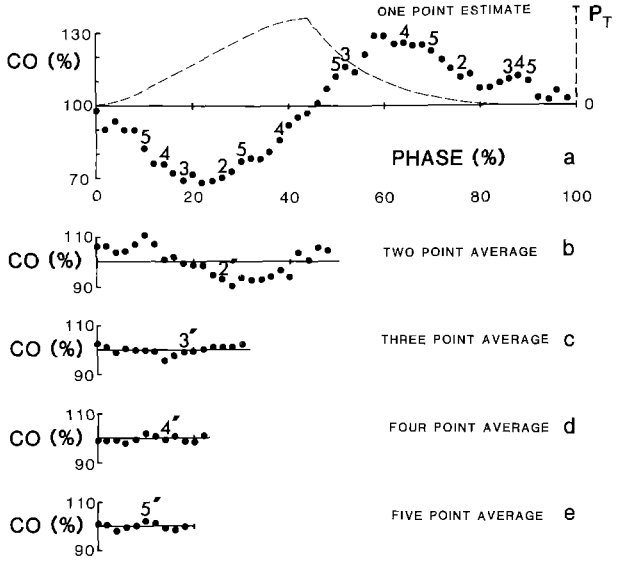

Fig. 2a – e. An example of averaging techniques. Values are given in % of the mean, which is 100% for all 50 single estimates. **a** 50 single estimates of cardiac output related to the moment of injection in the ventilatory cycle. **b** 25 two-point-averaged values. For example the dot marked with 2′ is the averaged value of two (equally spread) single estimates marked with sign 2. This average value is plotted on the phase axis at the same phase moment of the first dot 2, in Figure **a**. **c** 16 three-point-averaged values. The dot marked with 3′ is the averaged value of the three (equally spread) dots 3 in Figure **a**. Again the average value is plotted at the same phase of the first dot. **d** 12 four-point-averaged values. The dots marked with 4′ is the averaged value of the four equally spread points 4 in Figure **a**. **e** 10 five-point-averaged values

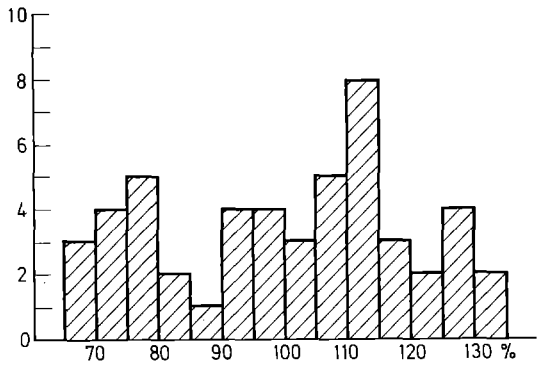

Fig. 3. Frequency distribution of the cardiac output estimates of Figure 2a. f is the frequency of estimates for the given %-interval

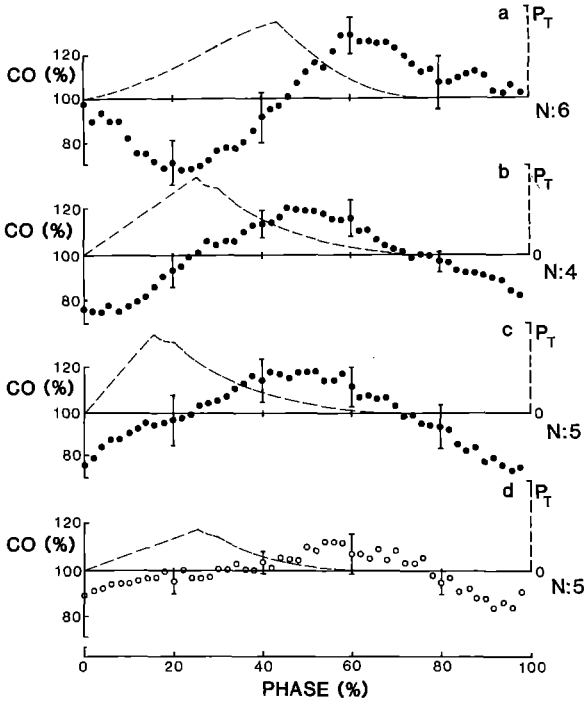

Fig. 4a–d. Estimation of cardiac output (CO) as a function of the injection phase during different ventilatory conditions. Vertical bars represent standard deviations from the mean. The ventilatory mode is given in broken lines as airway pressure (P_T). N is the number of animals

of five estimates was made. Each selection of a single estimate was done with replacement, implying that the same estimate could be selected more than once for one averaged value. This was done in order to simulate random estimations of cardiac output, where the same moment (or phase) in the ventilatory cycle can be taken.

Statistical analyses

The figures 2, 4 and 5 demonstrate that the series of 50 single estimates have a sinusoidal-like pattern within the timeperiode of the whole ventilatory cycle. In the systematically obtained two-point-averages (Fig. 2) a second sinusoidal-like pattern with a lower amplitude can be observed. Thus, the pattern of single estimates seems to be composed of two harmonic waves.

In a sinusoidal pattern the values, positioned on the curve at equally spaced places on the horizontal phase axis, are concentrated around the maximal and minimal values, i.e. the largest amplitudes. When a second harmonic is present a third concentration around the mean will be present, which can be verified from a composed wave of two harmonics with a frequency ratio of 2. In such a pattern the distribution of values will not be normal either, which is demonstrated in Figure 3 for the single data of Figure 2. In this single series the range of ± 1 SD around the mean contains 55% of the 50 data, which is far below the theoretical value of 68% for a normal distribution.

However, the aim of our study was to analyze the accuracy of estimation of mean cardiac output under a diversity of ventilatory and hemodynamic conditions. For that reason we lumped the data of all series and studied the distribution patterns of the single estimates and those of the different averages. Moreover, mean values, standard deviations, number of values within the range of ± 1 SD around the mean and the number of data within the accuracy limits of 5 and 10% around the mean were calculated. p-levels for differences between measurements within the same animals were calculated according to a paired Student t-test for small samples.

Results

Pattern of blood flow estimation

In 6 animals cardiac output was estimated during four different modes of ventilation. The averaged estimates at all 50 phases are shown in Figure 4. Series without stationary conditions were excluded. The mean value of cardiac output over the whole ventilatory cycle was calculated from all 50 estimates and taken as the 100% value. In all series there was a cyclic variation of cardiac output estimates with a periodicity equal to that of the ventilatory cycle. In each ventilatory mode the pattern of estimates was approximately sinusoidal.

The observations under different volemic conditions are presented in Figure 5. The only result was a forward shift of the estimated flow pattern during

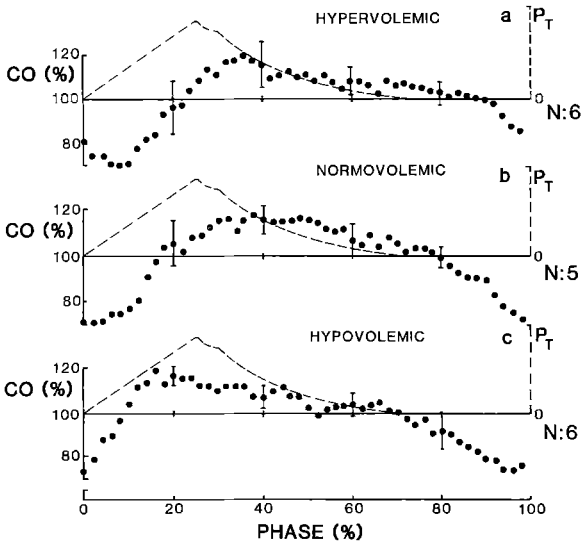

Fig. 5a – c. Estimation of cardiac output (CO) as a function of the injection phase during **a** hypervolemic, **b** normovolemic and **c** hypovolemic conditions. Vertical bars represent standard deviations from the mean. The ventilatory mode is given in broken lines as airway pressure (P_T). N is the number of animals

bleeding from hypervolemia via normovolemia to hypovolemia, which is a shift to earlier phases in the ventilatory cycle. The occurrence of a shift was tested by comparing the points at the same phases. In Figure 5c 29 points were significantly different ($p<0.05$) from those in Figure 5a. These points were mainly in the slopes of the modulation. Between the phases 0 – 20% the points of 5c were higher than those of 5a and between 70 and 100 they were lower.

Amplitude of the estimated flow

In Table 1 the averaged amplitude of the single estimates is given for the different ventilatory modes and hemodynamic conditions.

For all PEEP levels in the series with a sinusoidal like inspiratory flow a similar value was found for the positive and negative amplitudes with respect to the mean, $\bar{Q}_{TH,\,max}/\bar{Q}'_{TH,\,50}$ and $\bar{Q}'_{TH,\,min}/\bar{Q}'_{TH,\,50}$ respectively. Differences in amplitude were not observed for the two constant flow patterns (square wave) at rates of 10 min^{-1} or for the three volemic conditions at a level of $p<0.05$.

However, under all these conditions mean cardiac output changed substantially, implying that the relative fluctuations in estimated flow are independent of mean flow.

At a higher ventilatory rate (20 min^{-1}), however, the amplitudes of fluctuations were smaller than the corresponding values during ventilation at a rate of 10 min^{-1}.

Comparison of thermodilution and Fick method

The ratios of the mean of all 50 thermodilution estimates to the corresponding mean of the Fick estimates ($\bar{Q}'_{TH,\,50}/\bar{Q}'_{Fick}$), are shown in Table 1. Comparing all circumstances for all animals $\bar{Q}'_{Fick}$ and $\bar{Q}'_{TH,\,50}$ were not different at a p-level equal to 0.05. However, the mean of all 50 thermodilution measurements underestimated mean cardiac output during ventilation at a rate of 20 min^{-1} and overestimated it during hypovolemia.

Table 1. Cardiac output data for ventilatory and hemodynamic conditions. Sinus is sinusoidal air flow pattern, Square is constant air flow pattern

	Conditions						$\bar{Q}_{Fick}$			$\bar{Q}_{TH,\,50}$			$\bar{Q}_{TH,50}/\bar{Q}_{Fick}$		$\bar{Q}_{TH,\,max}/\bar{Q}_{TH,\,50}$		$\bar{Q}_{TH,\,min}/\bar{Q}_{TH,\,50}$	
	I %	P %	E %	RR /min	PEEP cm H_2O	Vol. ml/kg	ml/s per kg	SD	*n*	ml/s per kg	SD	*n*		SD		SD		SD
Sinus	44	0	56	10	0	0	2.08	0.34	6	2.12	0.23	6	1.03	0.12	1.30	0.15	0.69	0.09
	44	0	56	10	5	0	1.78	0.34	6	1.85	0.44	6	1.04	0.08	1.23	0.13	0.72	0.06
	44	0	56	10	10	0	1.33	0.14	6	1.46	0.20	6	1.09	0.11	1.24	0.11	0.75	0.05
	44	0	56	10	15	0	1.05	0.13	6	1.12	0.07	6	1.07	0.11	1.22	0.10	0.74	0.05
Square	15	5	70	10	0	0	2.31	0.58	5	2.38	0.41	5	1.05	0.11	1.19	0.13	0.75	0.05
	25	5	70	10	0	0	2.71	0.51	4	2.61	0.50	4	0.96	0.08	1.22	0.05	0.75	0.05
	25	5	70	20	0	0	2.87	0.43	5	2.44	0.49	5	0.86	0.11	1.13	0.06	0.85	0.05
	25	5	70	10	0	+15	3.86	0.41	6	3.62	0.32	6	0.95	0.06	1.18	0.10	0.71	0.08
	25	5	70	10	0	0	2.66	0.39	5	2.66	0.31	5	1.00	0.07	1.19	0.08	0.71	0.11
	25	5	70	10	0	−15	1.92	0.27	6	2.16	0.29	6	1.13	0.09	1.20	0.14	0.74	0.03
												55	1.02	0.09				

Values are means. SD is standard deviation; *n*, the number of animals; I, P, E, the duration of inspiration, inspiratory pause and expiration as a percentage of the ventilatory cycle; PEEP, positive end-expiratory pressure; R. R., respiration rate; Vol., volemic state of the animals; Q'_{Fick}, mean cardiac output estimated by the Fick method from the measurements before and after each series; $Q'_{TH,\,50}$, mean cardiac output estimated from 50 thermodilution measurements; $Q'_{TH,\,max}$ and $Q'_{TH,\,min}$, the mean highest value and the mean lowest value of the series respectively

Table 2. Averaging procedures

	Systematic procedure							Random procedure					
	n	Mean %	SD	Number of data within ±1 SD		% of data within		Mean %	SD	Number of data within ±1 SD		% of data within	
				n	%	±5%	±10%			*n*	%	±5%	±10%
Single data	2750	100	17.5	1865	68	23	43	100.8	17.0	1876	68	23	43
2-p-a	1375	100	8.6	983	71	47	79	100.8	11.9	982	71	31	58
3-p-a	880	99.9	4.2	620	70	79	98	100.3	10.1	614	70	40	69
4-p-a	660	100.0	3.3	486	72	89	99	100.3	8.9	449	68	45	75
5-p-a	550	100	2.6	378	69	93	100	100.8	8.1	385	70	46	79
6-p-a	440	99.9	2.4	318	74	95	100	100.3	7.5	307	70	48	84

2-p-a is two-point-averages, 3-p-a is three-point-averages, etc. *n* is the total number of measurements. Procedures are explained in text

Average procedure

The derived data of all single estimates are presented under "systematic procedure" in Table 2, where the data of randomly selected single estimates are given under "random procedure". This selection was done 50 times from each complete series. In the systematic procedure the mean value is by definition 100%. In the randomly selected population of 2750 single estimates the mean value shows a slight difference due to the fact that some data are selected more than once and others not at all.

The distribution of the single estimates was symmetrical in both procedures and much more concentrated around the mean than those of Figure 3. The random selection of single estimates gave approximately similar data for the mean, for SD, for the number of estimates within ±1 SD around the mean and for the number of estimates within the accuracy limits of ±5 and ±10% respectively.

The distributions of averages were also symmetrical in both procedures and became increasingly concentrated around the mean when more single points were used for calculation of the averages. The SD-values decreased when the number of points for the averages increased. This decrease in SD was much more pronounced in the averages of the systematic procedure than that in the random procedure.

In all populations of single estimates and averaged values the percentage of estimates around the mean ±1 SD were close to 68%, the theoretical value for a normal distribution. Another indication of the increasing concentration of data around the mean was the percentage of estimates within the accuracy limits of ±5 and ±10% around the mean.

The decrease of SD and the increase in percentage numbers within the accuracy limits were much larger in the systematic averaging procedures than those in the random procedure.

Discussion

The mean values in ml s^{-1} of the series of 50 thermodilution estimates represent reliable values for mean cardiac output [5], which was again demonstrated by comparing them with the Fick values (Table 1). For each series the mean of the 50 thermodilution estimates was normalized to 100% in order to lump all series for the study, independent of the absolute level of cardiac output.

Studying the effects of modulation on the estimation of cardiac output by thermodilution using the Stewart-Hamilton equation, which is common clinical practice, we conclude that this method is too inaccurate for the estimation of mean cardiac output, even when systematic errors are accepted. The reason is that the errors are not constant when mean cardiac output is changed. The pattern of flow estimates will shift forward in the ventilatory cycle when cardiac output decreases. This is shown for changes in ventilatory pattern (Fig. 4) and volemic conditions (Fig. 5). Similar findings have been reported for changes in PEEP [5].

The shift in the volemic group does not seem to be related to the dilution of blood nor to the order of observations. We did not observe any difference between the results presented in Figure 4b and those in Figure 5b, where the differences between both series is another order of circumstances. In another study [10] we demonstrated similar hemodynamic state and responses on PEEP in animals before and after hemodilution, even when a period of hypervolemia was inserted. When the conditions are changing also the momoments in the cycle will change for estimation of mean cardiac output by one single measurement.

Cyclic modulation

The ventilatory pattern hardly influences the amplitude of the modulation in the cardiac output esti-

mates. The constant amplitude of modulation in the thermodilution estimates might be due to the same basic frequency of all three ventilatory patterns. Probably these patterns differ only in their effect on real flow fluctuations in the range of the higher harmonics. The influence of higher harmonics in the real flow on the modulation of thermodilution estimates will decrease progressively [2].

The amount of modulation is also similar for the three different volemic conditions (Fig. 5, Table 1) and, hence, for different values of mean flow. This is shown by the ratios of maximum to mean estimates ($\bar{Q}'_{TH,\,max}/\bar{Q}'_{TH,\,50}$) and of minimum to mean estimates ($\bar{Q}'_{TH,\,min}/\bar{Q}'_{TH,\,50}$). It could be due to two counteracting phenomena. First, electromagnetic recordings showed that the amplitude of the modulation during mechanical ventilation was reversely proportional to mean flow [13]. Second, according to Knopp and Bassingthwaighte [6] the dispersion of indicator is also reversely proportional to flow over a wide range of values. Consequently, during hypervolemia, when flow is high, the dilution curves are peaked, resulting in an estimation of flow over a shorter period of the ventilation than during hypovolemia, when indicator is spread out. In that case a flow is estimated which is a weighted mean over a longer period of the ventilatory cycle, causing a larger smoothing effect on real modulation than during hypervolemia. Apparently this leads to the coincidence of an almost equal modulation in the thermodilution estimates. We expect that the larger dispersion of indicator in low flow conditions causes the forward shift of the modulation of estimates during PEEP and bleeding. As suggested by us in a previous study [5], a low cardiac output during insufflation will contribute relatively more to the area of a dilution curve corresponding to an injection phase in the end-expiratory period of the preceding cycle because the curve is more spread out.

During shorter insufflation we also observed a forward shift of the modulation (Fig. 4a – c). In these three patterns of ventilation, however, mean flow was the same. The more pronounced fall in actual flow during a faster insufflation will contribute more to the area of a dilution curve after injection in the preceding end-expiratory period than a more gradual fall in actual flow during a slower insufflation.

Increasing ventilatory rate decreases the amplitude of the cyclic variation of the estimates (Fig. 4). This reduction will be caused by two mechanisms. Firstly, tidal volume and therefore intrathoracic pressure rise is smaller leading to a reduction in real amplitude of modulation. Secondly, the duration of a dilution curve is constant, when cardiac output is constant, and independent of the duration of a ventilatory cycle. This implies an estimation of cardiac output by the thermodilution over a larger part of ventilatory cycle when this cycle is shortened. Therefore, the estimated value will deviate less from the mean cardiac output over the whole ventilatory cycle [2].

Accuracy of estimates

In this study a series of different conditions, usually found in intensive care medicine, were applied to different groups of animals in order to evaluate the accuracy of the thermodilution method for estimation of mean cardiac output.

A normal distribution of data around a mean value is characterized by an SD-value containing 68% of all data. A single series of 50 thermodilution measurements did not show a normal distribution (Fig. 3). The SD-value of 55% is much lower than the theoretical value. We conclude that also other series of the total of 55 will not be characterized by a normal distribution.

The total population of single estimates over all 55 series was characterized by a symmetrical distribution and an SD value of 68% (Table 2). Testing the number of estimates for ± 2 SD revealed 96% of all data within these limits. Therefore, we considered this total population as a normal distribution of data around the mean. The number of data within SD-values of the populations of averages were all but two close to 68%. The exceptions were the systematic four-point- and six-point-averages with SD values containing 72 and 74% data within ± 1 SD respectively. In such populations the SD-value underestimates the concentration of data around the mean. To avoid such underestimation of the reliability of a measurement accuracy limits were used and the percentages estimates within these limits were calculated.

The reliability of a single measurement for estimation of mean cardiac output was low, because 57% of all measurements deviated more than 10% from the mean. Only 68% was within ± 17.5% from the mean implying that in 5% of all measurements a deviation larger than 35% from the mean can be predicted. A random sampling of the single data gave the same results as the original population of estimates. Such a random sampling imitates the random performance of a series of single estimates, independent of the phases of a ventilatory cycle.

An improvement of the accuracy in estimating mean cardiac output was obtained when randomly selected estimates from the series were averaged. Within the accuracy range of 10% around the mean the percentage of all estimates gradually increased from 43 to 84% going from single estimates to the six-point-averages (Table 2, "random procedures"). But more than 50% of all random six-point-averages were beyond the accuracy limits of 5%.

Table 3 (see text)

	Q_i ml	ti s	$T_b - T_i$ °C	Bodyweight kg	Blood flow $ml \cdot s^{-1} kg^{-1}$	Indicator flow $ml \cdot °C \cdot s^{-1} kg^{-1}$	ΔTinj site °C
Patient	10 (5)	3 (1.5)	37	70	1.19	1.76	1.5
Pig	0.5	0.3	17	10	2.0	2.83	1.4

Q_i: volume of injection fluid; t_i: duration of injection; $T_b - T_i$: difference between blood and injectate temperature; indicator flow: $[Q_i \cdot (T_b - T_i)]/(t_i \cdot \text{bodyweight})$; ΔTinj site: the change in blood temperature at the injection site; (indicator flow/blood flow)

A much better result was found by the systematic averaging procedure. Two estimates differing half a ventilatory cycle in phase gave averages with an accuracy which was similar to that of the random five-point-averages. However, 21% of the systematic two-point-averages and the random five-point-averages deviate more than 10% from the mean. The largest improvement in the accuracy of mean cardiac output estimation was found in the systematic averaging procedure up to the four-point-averages. Above this number progress in accuracy was much smaller.

The averages of four cardiac output estimates equally spread in the ventilatory cycle will give almost 100% of all measurements within the accuracy limits of 10% and will have a chance of 9 to 1 to be within the 5% limits.

When 10% limits are sufficient a systematic averaging procedure of three single estimations is satisfactory, because that probability is 98%. From Table 2 we concluded that the systematic averaging procedure is far superior to the random averaging procedure. The reliability of the random averages is insufficient even when six single estimates are used.

Clinical application

The amplitude of an indicator dilution curve depends on the amount of indicator entering the bloodstream within a certain time and the level of blood flow [15]. As an example we have calculated the ratio between the amount of cold (°C · ml) entering the blood stream per second and per kg body weight, and the blood flow in ml per second and per kg body weight (Table 3). For both patients and pigs these calculated ratios approximate the temperature change of blood at the injection site. The values are in the same order of magnitude. Thus, injection of a relatively low amount of indicator will give only an acceptable amplitude of the dilution curve when injection time is short.

The shorter injection time leads to a shorter dilution curve which approximates mean flow over a shorter period. In a flow with cyclic variations a procedure with short injection time will approximate real variation better than a procedure of longer injection time. Studying the differences between single estimates and mean cardiac output during cyclic variation of blood flow, and, searching for reduction of these errors by averaging techniques, we used a short injection time to accentuate the errors. Using a longer injection time will certainly reduce but not eliminate the errors. However, the differences in the reduction of errors of both averaging techniques will also count for longer injection times.

Phase-controlled injection of indicator needs an equipment, which is not (yet) available for clinical purposes. For those ventilators which deliver a constant number of pulses during each ventilatory cycle, development of a phase selecting system is satisfactory. Such as system can be used in combination with an injector system, which discharges automatically on a signal from the phase selector. As a power supply for the discharge of the syringe airpressure routinely available in the hospital can be used.

We conclude in general that during mechanical ventilation the average of four estimates spread equally over the ventilatory cycle, is preferable to single estimates or to averages of single estimates obtained randomly in the ventilatory cycle. For patients with contra-indications to volume loading a regime of three or two estimates could be adopted, reducing correspondingly the accuracy of the estimation of mean cardiac output.

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