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Measurement of extravascular lung water by thermal-dye dilution technique: mechanisms of cardiac output dependence*

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Abstract. The extent to which extravascular lung water (EVLW) is dependent on cardiac output was analysed in anaesthetized and mechanically ventilated pigs. EVLW was measured by thermal-dye dilution technique, by a fibreoptic thermistor catheter system (system 1), and by a thermistor catheter-external optical cuvette system (system 2). During baseline conditions, at which cardiac output was 3.65 l/min, EVLW was 11.7 and 7.7 ml/kg b.w. with systems 1 and 2 respectively. A reduction of cardiac output to a mean of 1.90 l/min by the addition of halothane to the inspired gas did not significantly affect EVLW with system 1 (−5%) but increased EVLW by 39% ($p<0.05$) with system 2. An increase of cardiac output to a mean of 4.78 l/min by intravenous infusion of isoproterenol caused a small increase in EVLW with system 1 (14%; $p<0.05$) and a decrease with system 2 (10%; $p<0.05$). The dependence on cardiac output was the same whether the catheters were positioned centrally (aortic root) or peripherally (abdominal aorta). With system 1 the CO dependence was due to different time constants in thermistor and optical systems, and with appropriate phasing the dependence could be eliminated. With system 2 a large overestimation of the mean transit time difference between the two indicators was seen when cardiac output was low, resulting in overestimation of EVLW. It is concluded that the dependence of EVLW volume on cardiac output is an artefact due to technical problems in the design of the recording equipment rather than a reflection of pulmonary or vascular effects.

Key words: Lung – Extravascular fluid – Measurement techniques – Indicator dilution – Thermal-dye

In a respiratory – compromised patient, the amount of extravascular lung water (EVLW) present is considered a potentially valuable indicator of lung damage and pulmonary function [1]. The double indicator dilution technique of assessing EVLW, with one indicator remaining in the blood vessel and the other diffusing into the extravascular space, is by now accepted. However, the access to the extravascular space depends on the kind of indicator being used, the most diffusible one being cold (thermal change) [2]. The intravascular marker most frequently used is indocyanine green which binds to albumin and thus remains intravascularly unless the capillaries allow leakage of larger molecules [3].

It has become apparent that EVLW assessed by the thermal-dye dilution technique is dependent on cardiac output. This was reported in 1982 by Goodwin et al. in burn patients with lung oedema [4]. These authors noted a decreasing amount of lung water with increasing cardiac output in sequential measurements over several days and considered the decreasing recorded levels to be inconsistent with clinical observations. They proposed the theory that there was a limitation of diffusion of the extravascular marker which became more apparent with increasing cardiac output. More recently, Fallon et al. noticed a similar dependence on cardiac output in non-oedematous anaesthetized dogs [5]. Since post-mortem gravimetric analysis showed that the lung water content was closer to values obtained at high cardiac output, they considered diffusion limitation to be rather unlikely and postulated instead a capacitive effect of extrapulmonary tissue, like the heart and extrapulmonary vessels, to cause a delay in the thermodilution curve, and that the effect was more apparent at low cardiac output. However, they did not test this hypothesis.

The described pattern of cardiac output dependence has been observed with a recording device that measures temperature intravascularly via a thermistor catheter and dye extravascularly in a conventional optical cuvette. This inevitably results in a phase shift of the dye curve in comparison with the temperature curve. The phase shift can be corrected for by superimposing one dilution curve above the other with a common starting point defined as the first appearance of the indicator. (This requires the

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assumption that both indicators appear at the very same time in the systemic circulation.) The technique will not allow true measurement of the mean transit time of the two indicators but only the difference between the mean transit times. This is, however, enough for the assessment of EVLW, which will be calculated as: $EVLW = CO \times (MTT_t - MTT_d)$, where CO is the cardiac output, and MTT_t and MTT_d are the mean transit times of temperature and dye, respectively. Whether this procedure by itself will have an effect on the calculated EVLW at different MTTs and shapes of the dilution curves (i.e. at different cardiac outputs) has not been analysed.

The aim of the present study was to analyse whether extrapulmonary lung tissue contributes to cardiac output-dependent EVLW. This was accomplished by measuring the dilution curves with centrally and peripherally placed catheters. We also aimed at analysing the possible effects on the calculated EVLW by the described technique of assessing the difference between MTT_t and MTT_d (Δ-MTT). This was done by comparing the described technique with direct measurement of the MTT of each indicator. This procedure was carried out with another device which measures the time from injection of the indicators to their appearance at the same place intravascularly by means of a fibreoptic thermistor catheter system. The study was conducted in apparently lung-healthy pigs under mechanical ventilation during anaesthesia with muscle paralysis.

Material and methods

Six pigs of weights ranging from 19 to 35 kg were studied. They were anaesthetized with thiopentone, intubated and ventilated with an Erica ventilator (Gambro Engström). Anaesthesia was maintained with intermittent doses of thiopentone. Halothane was added up to 3% for pigs with lower cardiac output during part of the study. Inspired oxygen concentration was kept at 30%. Tidal volume was set at 15–20 ml/kg b.w. and respiratory rate at 12–20/min to achieve an arterial carbon dioxide tension ($PaCO_2$) of approximately 5 kPa. Muscle paralysis was maintained by intermittent doses of pancuronium.

An ear vein was cannulated for induction and maintenance of anaesthesia. A triple lumen thermistor tipped catheter (Swan Ganz no. 7F, Edwards Laboratories) was advanced from a femoral vein to the pulmonary artery under pressure guidance. For the assessment of EVLW a fibreoptic thermistor catheter (no. 5F, Schwarzer) was introduced into the femoral artery. It was advanced either to the aortic root (central position) or left with the tip of the catheter in the distal aorta approximately 15 cm from the groin (peripheral position). The fibreoptic thermistor catheter was connected to a lung water computer which also recorded the time of the injection from an automatic injector (system COLD, Partig) [6]. This equipment is called system 1 in the following text.

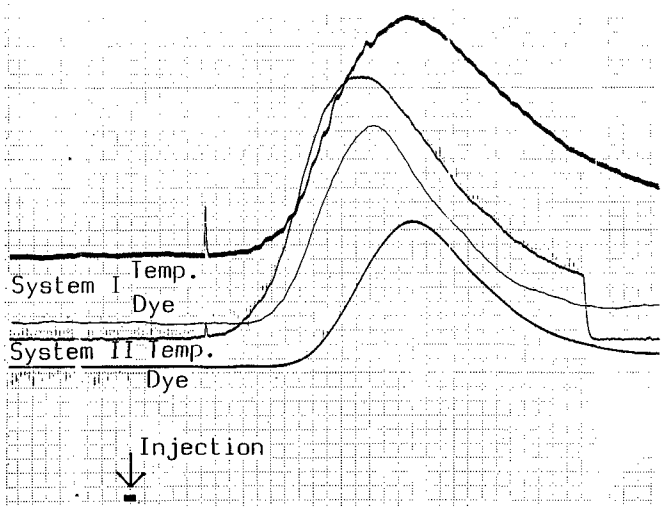

Fig. 1. Individual thermal and dye dilution curves obtained by system 1 and 2 after an injection of the indicators (ice-cold dye in glucose)

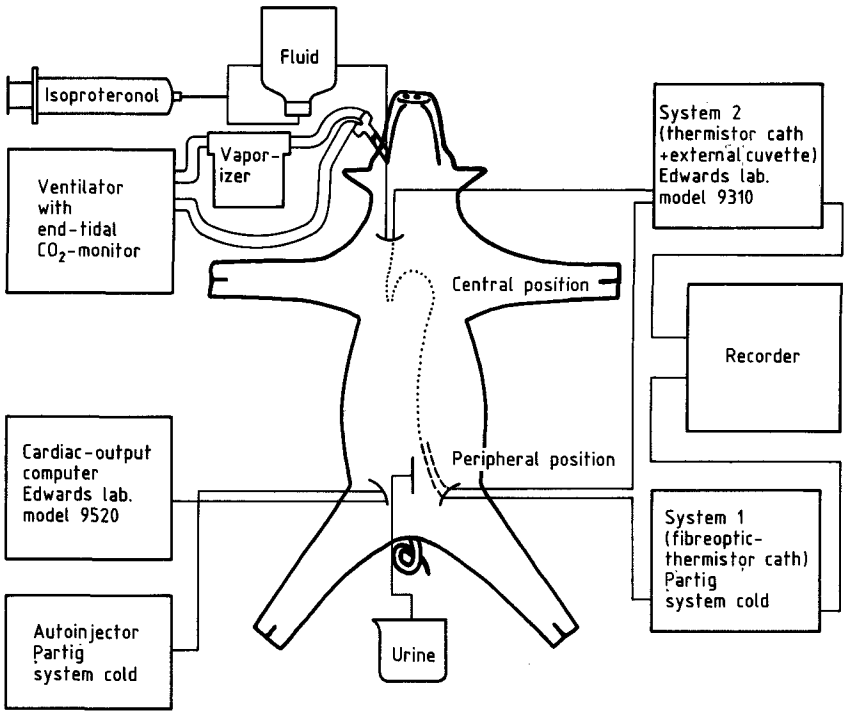

Fig. 2. Technical set-up of the study

A thermistor-tipped single lumen catheter (5F, Edwards Laboratories) was introduced into a carotid artery and advanced to the aortic root. Another similar catheter was introduced into the femoral artery (in the other leg than that used for the previously mentioned femoral artery catheter) and advanced 15 cm from the groin into the distal aorta. The catheter was too short to be moved to central and peripheral positions from one and the same introduction point. The catheter was connected to a Waters optical dye cuvette and the thermistor and dye signals were fed into a lung water computer (9310 Edwards Laboratories). This equipment constituted system 2.

The dilution curves from both systems were plotted on a recorder to make manual calculation of mean transit times possible. Four individual curves from one injection are shown in Fig. 1.

Both systems calculated cardiac output from the systemic artery thermodilution curve, and the value was used for the computation of EVLW. In addition, the thermodilution curve from the pulmonary artery was measured and cardiac output calculated by means of another computer (model 9520, Edwards Laboratories). This enabled a comparison of cardiac output obtained by the lung water system and by the cardiac output computer. The technical set-up is shown in Fig. 2.

For the assessment of cardiac output and EVLW 10 ml ice-cold glucose, 5.5% solution, containing 0.4 mg/ml indocyanine green, was injected into the right atrium via the side-hole of the pulmonary artery catheter by a pneumatic autoinjection. Measurements were made at different cardiac outputs, which were increased by intravenous administration of isoproterenol and reduced by the addition of halothane. An average of 44 individual recordings were made in each animal. Student's two-sided paired *t*-test was used to assess the significance of a difference. Linear regression analysis was used for correlation tests.

Results

Haemodynamic data

Central haemodynamic data and lung water values as measured by the two recording devices are shown in Table 1 at baseline conditions and during low and high cardiac output. "Baseline data" were the mean values of recordings before any deliberate change in cardiac output by cardiomimetic drugs or anaesthetic agents was made. "Low" and "high cardiac output" refer to the mean values obtained at the five lowest and the five highest cardiac outputs respectively. As can be seen, cardiac output varied on average between 1.9 and 4.8 l/min, i.e. at "low cardiac output" blood flow was reduced by 48% and at "high cardiac output" blood flow was increased by 31% from the baseline value. Pulmonary artery mean and wedge pressures varied only to a minor extent during the investigation, by at most 6–7 mmHg. Systemic artery mean pressure varied to a much greater extent, from a lowest value of 40 mmHg in pig no. 6 (low cardiac output) to a highest value of 148 mmHg in pig no. 5 (baseline cardiac output).

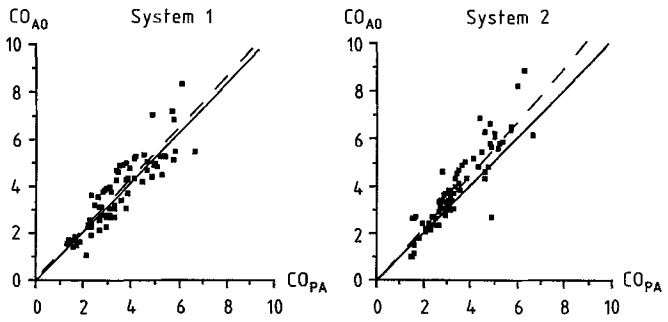

Fig. 3. A comparison of cardiac output measured by system 1 and 2 in the aortic root, and by a cardiac output computer measuring the dilution curve in the pulmonary artery. Good correlations were obtained according to the equations below, although the slope of the regression line was closer to 1 in the comparison with system 1. *System 1*: $CO_{ao} = 1.05 \cdot CO_{pa} + 0.11$ (l/min; n: 42; $p < 0.001$, $r = 0.90$); *System 2*: $CO_{ao} = 1.23 \cdot CO_{pa} - 0.24$ (l/min; n: 42; $p < 0.001$; $r = 0.93$)

EVLW volume was about 50% higher with system 1 (fibreoptic thermistor catheter system with individual measurement of MTT_t and MTT_d) than with system 2 (thermistor catheter, external dye cuvette) at baseline (Table 1). At high cardiac output, EVLW with system 1 was increased by an average of 14%, while with system 2 it was decreased by 10%. At low cardiac output, EVLW with system 1 was slightly reduced by 5%, whereas with system 2 it was increased by as much as 40%.

Since the cardiac output measurement is used in the calculation of EVLW volume, any error in its determination will also affect the calculated EVLW volume. We therefore made a comparison between cardiac output as measured by the lung water systems (thermal dilution measured in the aorta) and cardiac output as indicated by the system measuring the thermal dilution in the pulmonary artery. The results of the comparisons between the systems are shown in Fig. 3. A very close correlation between cardiac output obtained by lung water system 1 and the cardiac output computer was obtained, the slope of the regression line being close to 1 and the intercept as small as 0.11 l/min (Fig. 3, left panel). There was a good correlation between system 2 and the cardiac output computer as well, but the slope was further away from 1 than

Table 1. Central haemodynamics, venous admixture, and extravascular lung water volume during baseline conditions and at low and high cardiac output

	CO l/min	HR beats/min	P_{aom} mmHg	P_{pas} mmHg	P_{pad} mmHg	P_{pam} mmHg	P_{pcw} mmHg	Qs/Qt % QT	EVLW1 ml/kg	EVLW2 ml/kg
Baseline	3.65±0.45	133±10.6	119±7.8	33±2.7	23±2.2	27±1.9	10±0.7	4.2±0.8	11.7±1.8	7.7±1.6
Low CO	1.90±0.30[a]	103±6.6	51±5.8[a]	27±2.5	19±1.1	22±1.4	13±0.5[a]	1.9±0.6[a]	11.1±2.1[a]	10.7±1.4
High CO	4.78±0.55[a, b]	239±16.5[a, b]	74±9.1[a, b]	26±1.7	18±1.7[a]	21±1.1[a,b]	11±1.0[b]	5.7±1.4[b]	13.4±2.0[a,b]	6.9±1.6[b]

CO, cardiac output; HR, heart rate; P_{ao}, aortic pressure; P_{pa}, pulmonary artery pressure; P_{pcw}, pulmonary capillary wedge pressure; s, systolic; d, diastolic; m, mean; Qs/Qt, venous admixture; EVLW, extravascular lung water; 1, fibreoptic thermistor catheter system; 2, thermistor catheter-external optical cuvette system (mean ± s.d.; $n = 6$)

[a] Significantly different from baseline, $p < 0.05$

[b] Significantly different from "low" cardiac output, $p < 0.05$

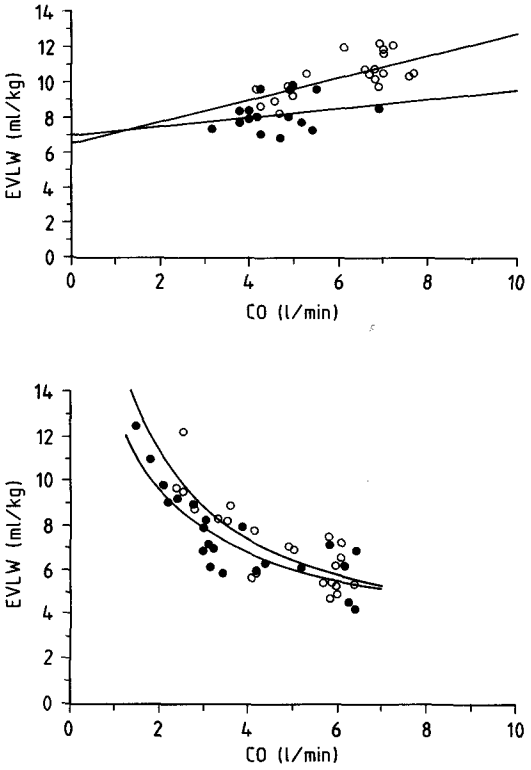

Fig. 4. Dependence of EVLW volume on cardiac output (CO) and catheter position (central position: ●; peripheral position: ○) with system 1 (*upper panel*) and system 2 (*lower panel*). Note the slight increase in EVLW with increase in cardiac output with system 1, and rapid decrease with system 2. (Results varied with system 1.) Observe also the slightly lower EVLW with the centrally positioned catheter in both systems

in the previous comparison, and the intercept was higher (*Fig. 3, right panel*).

The dependence of EVLW volume on cardiac output remained unchanged whether the catheter position was central or peripheral, and whether the measurements were made with system 1 or system 2. However, in both systems EVLW volume tended to be recorded as lower with the catheter in the central position than with the one in the peripheral position (Fig. 4).

Dependence on cardiac output

System 1 displayed a varying dependence on cardiac output; in some pigs EVLW volume increased with rising cardiac output, while in others no dependence on cardiac output was observed at all. The quantitatively different dependence on cardiac output appeared to be due to the use of different catheters, some fibreoptic thermistor catheters showing more dependence on cardiac output than others. An example is given in Fig. 4 (upper panel).

With system 2, a dependence of EVLW on cardiac output was noted in all animals. Thus, EVLW volume fell as cardiac output increased, with a highly significant negative logarithmic correlation between EVLW volume and cardiac output. Accordingly, EVLW volume varied markedly with blood flow changes at low cardiac output levels whereas the dependence was reduced at higher cardiac output levels. This closely agrees with what has been reported earlier by Fallon [5]. An example is given in Fig. 4 (lower panel).

Thus, different responses to a change in cardiac output were noted with the two systems.

Discussion

Effect of catheter position

Since the two recording systems displayed completely opposite dependencies on cardiac output, it was considered highly unlikely that the change in EVLW volume accompanying a change in cardiac output was due to a capacitive effect of extrapulmonary tissue like heart and extrapulmonary vessels. An initial plan of measuring EVLW volume with the catheter positioned in the left atrium, in order to eliminate or reduce any capacitive effect of the left heart, was therefore cancelled.

Cardiac output dependence with system 1

The linear dependence of EVLW volume on cardiac output as measured with the fibreoptic thermistor catheter system (system 1) was analysed by testing the response time of the thermistor and optic sensors, and a graphic analysis with calculation of individual mean transit times was made from the indicator dilution recordings. It emerged that the response time of the two sensor systems varied: in animals in which no dependence on cardiac output had been observed, the response time to a sudden change in temperature was the same for the thermistor as for a sudden change in dye concentration with the fibreoptic system, whereas those in which EVLW volume had been dependent on cardiac output there was a visible difference in response times, the thermistor catheter lagging behind that of the fibreoptic system. This suggested that the cardiac output dependence might be attributable to inconsistencies within the recording device rather than to physiological events within the lungs or the body of the animal.

As a second step, MTTs were calculated from the recorded dilution curves and compared with those calculated by the computer. A very close correspondence was observed, indicating that the calculation by the computer was correct. In a third step, a constant time of 1 or 2 s was added or subtracted from the MTT of the thermistor system. When time was added to the measured MTT of the thermistor catheter, the dependence on cardiac output increased, whereas subtraction from the mean transit time reduced the dependence on cardiac output and even reversed it, so that EVLW volume decreased on an increase in cardiac output. In all cases a linear relationship between EVLW volume and cardiac output remained. For each catheter system a certain constant time could be subtracted that resulted in an independence of EVLW volume on blood flow; this time varied from 0.47 to 0.98 s. An example is shown in Fig. 5. It was realised that the thermistor at the tip of the catheter was embedded in plastic in order to reduce the likelihood of leaking electric currents, and this safety precaution prolonged the response time of the thermistor. To compensate for this a similar prolongation of the dye signal via the fibreoptic

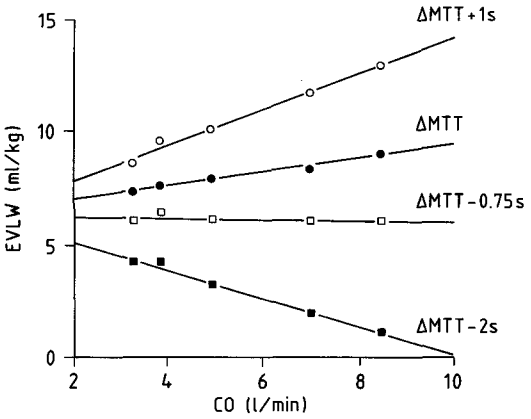

Fig. 5. The effect of changing ΔMTT (difference in mean transit time between the thermal and dye indicators) on the cardiac output dependence of measured EVLW volume (system 1). The line denoted ΔMTT has been fitted onto EVLW values measured in pig no. 4 and shows a slight increase in EVLW with increase in cardiac output (CO). Addition of 1 s to each ΔMTT increased the dependence on cardiac output, whereas subtraction of 0.75 s more or less eliminated it, and subtraction of 2 s reversed the dependence

system is necessary. The lung water equipment has a built-in variable filter, and a constant filter position prolonging the response time by approximately 2 s is recommended for this purpose, but variations between catheter systems make a fixed filter position inappropriate for some catheters.

In the theoretical analysis the lag time was varied with no simultaneous distortion of the dilution curve. In practice the built-in filter will delay the dye signal by distorting the dilution curve, and with the filter right positioned to give the right time constant the distortion should be the same as that created by the plastic insulation of the thermistor. An additional final test of the effect of a phase shift between thermistor and optic sensors was therefore undertaken by varying the time constant of the filter in the fibreoptic system during recording of EVLW volume at different cardiac outputs. The results for an experiment in a pig is shown in Fig. 6. It can be seen that

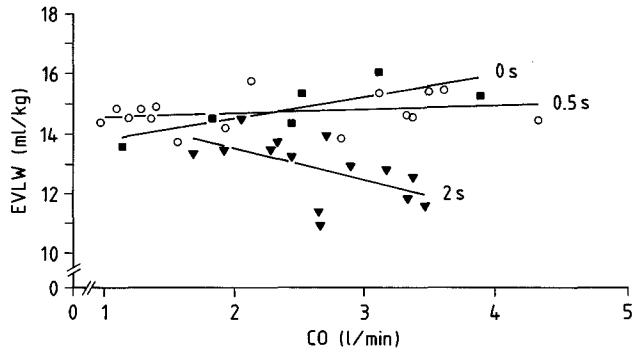

Fig. 6. Effect of changing the filter time constant of the dye dilution recording (system 1) in order to match the thermistor signal (pig no. 6). Note the increase in EVLW volume with increase in cardiac output when no filter delayed the dye signal, the reverse cardiac output dependence with a long time constant (2 s), and the elimination of dependence with a filter time constant of 0.5 s

with a filter time constant of 1 s recorded EVLW volume was more or less independent of changes in cardiac output, whereas a shorter time constant caused an increase in EVLW volume with cardiac output and a longer time constant reversed the cardiac output dependence. Thus, the cardiac output dependence can be eliminated with proper matching of the thermistor and dye recording systems.

Still, this does not necessarily mean that the measured EVLW volume is a true value, inclusion of extrapulmonary tissue still being a possible source of overestimation of EVLW. It has also been reported that system 1 leads to overestimation of EVLW volume compared to postmortem gravimetric results, but there is a linear correlation with a slope close to 1 [7]. The resulting intercept would thus indicate the amount of tissue that is non-pulmonary but included in the indicator dilution measurement [8].

Cardiac output dependence in system 2

The small inaccuracy of cardiac output calculation using system 2 (compared to the standard pulmonary artery thermal dilution curve) hardly explains at all the cardiac output dependence of EVLW volume as measured with system 2. According to the manufacturer the thermistor catheter-external cuvette system should position the two dilution curves on each other with a common starting point; thus, no systematic phase shift can occur between the starting points of the curves. Also, the non-linear dependence on cardiac output that was seen in this and in earlier studies does not fit with a simple constant phase shift. This suggested that there was an additional or other factor causing the cardiac output dependence. We therefore proceeded with recording and analysing the temperature and dye dilution signals before they were fed into the computer in order to obtain a manually calculated ΔMTT. The results was then compared with the ΔMTT calculated by the computer.

The manual analysis required determination of the onset of the dilution curves. This was in general easy to determine in recordings at higher cardiac output levels where the onset was sharp. The time lag between the thermistor and dye signals caused by the recording device should be the same irrespective of cardiac output (dye being withdrawn through the catheter and cuvette by means of a pump at a constant rate). We therefore measured the time lag at high cardiac output (1.7 s) and used the same time for analysis of dilution curves obtained at lower cardiac outputs with less clear onset of the dilution curves. Our manually calculated ΔMTT showed a good correspondence with computer-derived ΔMTT values at high cardiac outputs, but increasing difference at lower cardiac output. Thus, for example, in pig no. 3, at a cardiac output of 1.5 l/min the computer calculated a ΔMTT of 11.0 s, whereas manual calculation gave 3.3 s. This resulted in a computer-calculated EVLW volume of 12.5 ml/kg whereas it had been 6.2 ml/kg at a cardiac output of 6.1 l/min. The manually calculated EVLW volume at a cardiac output of 1.5 l/min was 3.8 ml/kg compared to 3.7 ml/kg at the higher cardiac output of 6.1 l/min. Simi-

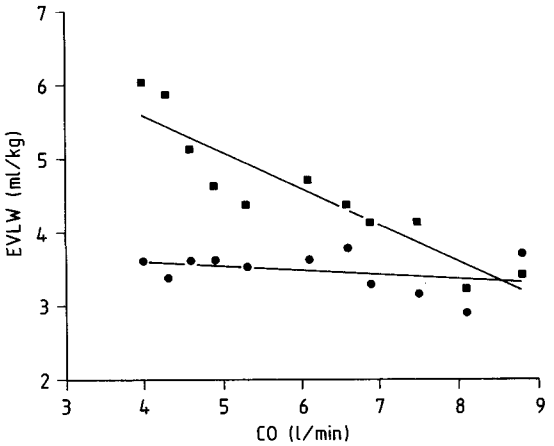

Fig. 7. Plot of manually calculated EVLW (by planimetry, ●) and computer-calculated EVLW (system 2; ■) on cardiac output (CO). Note the higher computer-calculated EVLW at low cardiac output compared to manually calculated values. (Data from pig 5)

lar results were obtained with recordings from the other pig experiments (see Fig. 7).

Obviously, the system 2 computer also receives dye dilution and temperature signals that potentially can give EVLW volume measurements which are not cardiac output dependent. Lacking information on signal processing in the system 2 computer, however, we are at present unable to identify exactly why the computer-calculated EVLW volume is cardiac output dependent. Possible causes are difficulties in identifying the starting point of dilution curves and/or in the extrapolation of these curves.

Conclusions

The finding of completely opposite cardiac output dependencies of two lung water measurement systems suggests that the cardiac output dependence is not due to phenomena within the lungs (diffusion equilibrium impairment) or extrapulmonary phase shift caused by capacity phenomena in heart and extrapulmonary vessels, but rather to difficulties in the processing of the indicator signals. It should also be stressed that this study has been limited to an analysis of possible causes of the cardiac output dependence of recorded EVLW volume. The study has not dealt with the accuracy of the determined EVLW volume and thus no comparison has been made with other techniques for the assessment of EVLW volume.

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