The shape of indicator dilution curves used for cardiac output measurement in man

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1. In six patients arterial plasma lithium concentration–time curves were recorded following injection of lithium chloride into the right or left atrium.

2. Lognormal curve fitting was used to derive the areas under the first pass dilution curves.

3. Subjecting the curves produced by left atrial injection to a delay and sequential filtering produced curves that closely approximated those produced by right atrial injection.

4. We conclude that the transfer function of the right heart and lungs is equivalent to a delay and sequential filtering, that the primary indicator dilution curve is closely approximated by a lognormal curve and that loss of lithium in the lungs following right atrial injection is clinically insignificant.

Indicator dilution for the measurement of cardiac output has a long history. Originally, the indicator was infused at a constant rate intravenously, its dilution measured in arterial blood, and cardiac output derived (Stewart, 1897). Henriques (1913) used a bolus injection of indicator (sodium thiocyanate) in dogs and sampled at 1 s intervals from the femoral artery. Since then several different indicators have been used for bolus injection and the method of analysis of the indicator dilution curves has been refined (Hamilton, Moore, Kinsman & Spurling, 1932). One of the problems which the curve analysis has to overcome is that recirculation of the marker occurs before the first pass (or primary) curve is completed so that the secondary curve caused by recirculation overlaps the tail of the primary curve. Since it is the integral of the primary curve which is needed in the calculation of flow, some method of extrapolation is required to derive the tail of the primary curve. It is therefore important to know its shape.

We have been developing an indicator dilution technique for measuring cardiac output which uses lithium chloride as the indicator rather than the usual dye or thermal markers and has several advantages over the existing techniques (Linton, Band & Haire, 1993). In the course of this work we showed that the early part of human indicator dilution curves is very closely approximated by a lognormal curve (Linton, Linton & Band, 1995). A cascaded filter model, which consisted of a series of swirl chambers, was used to model the transfer function between the right atrium and systemic arterial system and this produced a transfer function which resulted in curves closely approximated by a lognormal. On theoretical grounds the whole of the primary indicator dilution curve would therefore be expected to be lognormal in shape:

$$y = [1/\{\sigma x\sqrt{(2\pi)}\}]e^{-(\ln(x)-\mu)^2/2\sigma^2},$$

where μ and σ are the mean and standard deviation, respectively, of the normal distribution from which the logarithmic transformation was obtained.

Given that the correct dose of LiCl is injected via the central venous catheter and that the sensor measures the resultant concentration–time curve correctly in the arterial blood, then the accuracy of the method depends on two assumptions: (1) the loss of lithium during its passage through the lungs is negligible; and (2) the curve fitting procedure accurately recovers the primary curve, despite its tail being obscured by recirculation, i.e. the filter model is a close representation of the circulation with respect to the shape of the primary curve.

It is difficult to test these assumptions in humans other than by simple comparison of the results of cardiac output measurements made using the lithium method with those made by other methods. Unfortunately the scatter of results achieved by thermodilution is considerable even though the overall correlation with the lithium method is good. Indocyanine Green or other dyes injected intravenously and detected in arterial blood give rise to the same problem of recirculation as does lithium. The Fick method gives an independent estimate but is an average over the collection time, so shorter term variations in cardiac output confuse the picture.

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In the present study we injected LiCl into the right or left atrium of patients and compared the curves produced. If the assumptions above are correct, then the derived cardiac outputs should be the same and passage of the left atrial injection curve through a delay and sequential filters (set up in Excel to be the mathematical equivalent of the filter model) should generate a curve similar to that produced by right atrial injection.

METHODS

In six patients who were being ventilated postoperatively and in whom left atrial catheters had been inserted directly at the time of heart surgery, cardiac output was measured by giving a bolus injection of LiCl (0·45 mmol in one patient and 0·3 mmol in the others) into either the right or left atrium. In each patient the interval between the right and left atrial injections was kept as short as possible. The arterial plasma lithium concentration–time curve was recorded by withdrawing blood at 4 ml min^{-1} through a cell containing a lithium-selective electrode. The voltage across the membrane of the electrode was digitized on-line and recorded at 0·1 s intervals onto disk (Macintosh Powerbook). The voltages were converted into lithium concentrations using the span of the sensor and the Nernst equation. For each curve the least-squares lognormal was fitted iteratively to the data between a point just before the lithium concentration started to rise and the point which was 50% down from peak on the washout limb (KaleidaGraph, Synergy Software, Reading, PA, USA). The area under the primary curve (used in the calculation of cardiac output) was taken as the integral

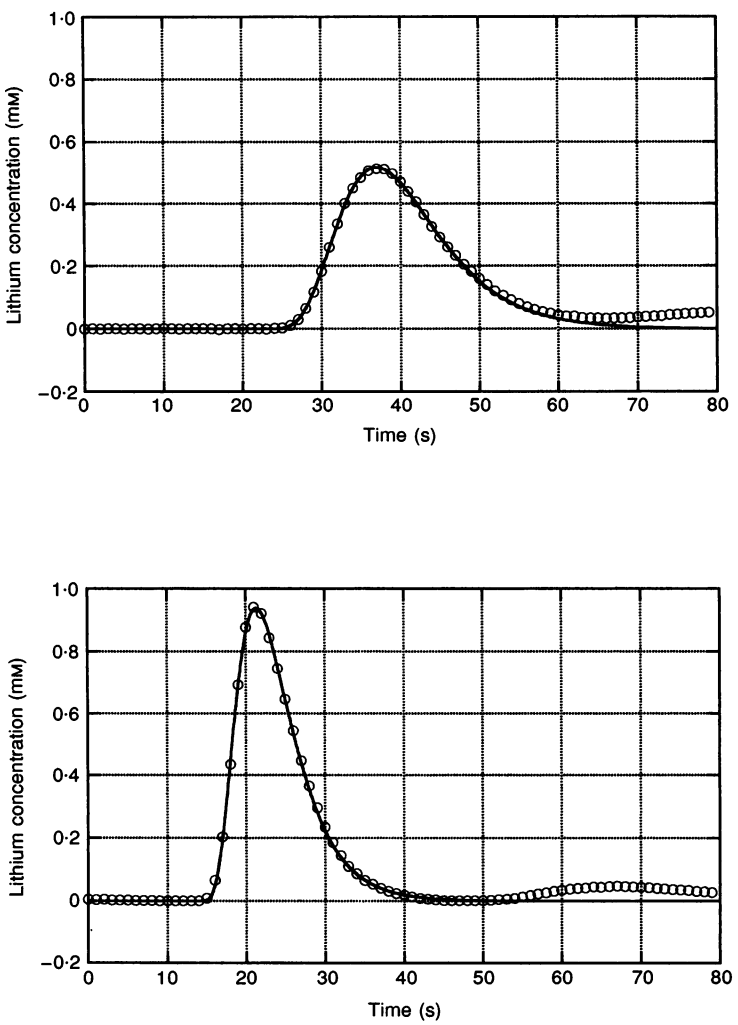

Figure 1. Results from one patient

Upper panel, LiCl (0·3 mmol) was injected into the right atrium via a central venous catheter at time = 0. The circles show every tenth data point recorded from the Li^+-selective electrode. The continuous line is the least-squares lognormal derived using the points from time 0 to 50% down from peak on the washout limb. The data points deviate from the lognormal as the Li^+ starts to recirculate. Parameters of the lognormal are: $\mu = 3{\cdot}737$, $\sigma = 0{\cdot}355$, and $\alpha = 8{\cdot}579$. The haemoglobin concentration was 10·4 g dl^{-1} and cardiac output 3·06 l min^{-1}. Lower panel, LiCl (0·3 mmol) was injected via a left atrial catheter at time = 0. The circles show every tenth data point recorded from the Li^+-selective electrode. The continuous line is the least-squares lognormal derived using the points from time 0 to 50% down from peak on the washout limb. The data points closely approximate the lognormal back to the baseline. Parameters of the lognormal are: $\mu = 3{\cdot}242$, $\sigma = 0{\cdot}428$, and $\alpha = 9{\cdot}017$. The haemoglobin concentration was 10·4 g dl^{-1} and cardiac output 2·91 l min^{-1}.

Table 1. Details of the six patients

Patient	Sex	Age (years)	Weight (kg)	Time (h)	Systolic (mmHg)	Diastolic (mmHg)	Heart rate (beats min^{-1})	Site	CO (l min^{-1})	Δ (l min^{-1})	Δ%	τ (s)	Operation
T	M	61	81	17.27	92	47	90	RA	6·247				CABG
				17.32	99	55	92	LA	6·08	0·167	2·747	2·05	
R	M	58	95	17.29	118	49	89	RA	7·269				CABG (IABP)
				17.35	114	53	82	LA	6·85	0·419	6·117	2·4	
K	M	78	65	16.53	102	44	107	RA	3·438				MVR, AVR, CABG
				17.04	87	36	107	LA	3·13	0·308	9·84	3·12	
H	F	68	84	19.28	105	54	126	RA	5·688				CABG
				19.34	103	56	126	LA	5·532	0·156	2·82	1·52	
B	M	75	59	16.23	113	46	91	RA	5·316				AVR, CABG
				16.17	109	47	91	LA	5·58	−0·26	−4·73	1·49	
W	M	68	58	16.06	75	23	100	RA	3·06				CABG (IABP)
				16.01	80	26	100	LA	2·914	0·146	5·003	4·5	
									Mean	0·155	3·633		
									S.D.	0·232	4·857		

Time refers to the time of injection. Systolic pressure, diastolic pressure and heart rate were recorded just before the injection was given into the right atrium (RA) or left atrium (LA). CO, cardiac output; Δ refers to the difference between the two cardiac output estimations; Δ% is the difference expressed as a percentage of the left atrial injection value; τ is the time constant of the two filters; CABG, coronary artery bypass grafts; IABP, intra-aortic balloon pump (which was in use in 2 patients); MVR, mitral valve replacement; AVR, aortic valve replacement.

of the fitted lognormal extrapolated to baseline. Following an injection of lithium chloride its dilution curve was recorded in arterial blood with a lithium-selective electrode (Linton *et al.* 1993). Cardiac output was then calculated as:

$$\text{Cardiac output} = (\text{LiCl dose} \times 60)/(\text{area}(1 - \text{PCV})),$$

(in l min^{-1}, where LiCl dose is in millimoles; area is the integral of the primary curve (mM s); PCV is packed cell volume which may be calculated as haemoglobin concentration (g dl^{-1}) divided by 33: this correction is needed because lithium is distributed in the plasma; a correction for plasma sodium is also included in the calculation).

The procedures adopted in this study were approved by the Ethics Committee of the West Lambeth Health Authority.

RESULTS

Details of the six patients and results are summarized in Table 1. All curves closely approximated to a lognormal as far as 50% down from peak ($R > 0{\cdot}999$). For each patient the cardiac output derived from the curve produced by left atrial injection was subtracted from that produced by right atrial injection. This difference was expressed as a percentage of the cardiac output measured following left atrial injection. The mean of these differences was $3{\cdot}6 \pm 4{\cdot}9$% (mean ± S.D.). In one patient the primary dilution curve returned to baseline before the secondary (recirculation) curve appeared. In the lower panel of Fig. 1 every tenth data point of the curve produced by left atrial injection in this patient has been plotted together with the least-squares lognormal curve. The upper panel shows a similar presentation of the data for the curve produced by right atrial injection, with recirculation causing the data points to deviate from the lognormal before the baseline was reached.

The data points produced by left atrial injection were passed through a two-stage filter. The time constants of the two filters were the same (see Table 1) and were chosen so that the peak of the filtered curve was the same as that of the curve produced by right atrial injection. A time offset was added to align the peaks on the time axis. Figure 2 shows this filtered curve together with the curves produced by right and left atrial injection for each patient. The close agreement between the filtered left atrial injection curve and the corresponding right atrial injection curve for each patient indicates (1) that the transfer function of the right heart and lungs can be approximated by two sequential filters and a delay, and (2) that there is minimal loss of lithium from the pulmonary circulation.

DISCUSSION

The cardiac output measurements were made during periods of relative cardiovascular stability, but some variation in cardiac output would have occurred between the two determinations in each patient. It is therefore not possible to be precise about the loss of lithium in the lungs, although it seems to be clinically insignificant from the point of view of measuring cardiac output with this method. The extent of diffusion of lithium into pulmonary extracellular fluid may be small or diffusion back into capillary blood may be very

rapid once the diffusion gradient reverses. Chinard and co-workers (Chinard, Enns & Nolan, 1962) injected $^{22}Na^{+}$ into the right atrium of anaesthetized dogs and showed that its recovery in the arterial blood was similar to that of T1824 (Evans Blue, which is protein bound) demonstrating that there was minimal loss in the lungs. It is likely that lithium behaves in the same way. The pulmonary capillary permeability of these dogs was presumably normal, so there might be significant loss if it was increased. In some, if not all, of our patients pulmonary extracellular water and capillary permeability would have been greater than normal due to raised left atrial pressure and residual effects of recent cardiopulmonary bypass.

Separation of the primary and secondary curves was greatest in the patient with the lowest cardiac output. The curve produced by left atrial injection returned to baseline before the appearance of recirculating lithium and so provided evidence that the whole of the primary curve is lognormal, as predicted on an empirical basis by Stow & Hetzel (1954). This patient had had coronary artery bypass grafts the previous day and was noted at the time of operation to have severe distal coronary disease. Due to continued myocardial ischaemia his cardiac output post-operatively was low and his circulation was assisted with an intra-aortic balloon pump. Since the first blood to recirculate comes from the coronary circulation, which has the shortest path from aorta to right atrium, a greater than normal delay would have been expected. Others have observed that distortion of the washout of the primary curve by recirculation is more of a problem at low cardiac outputs. Hillis, Firth & Winniford (1985) studied patients with a range of cardiac outputs and found that when it was less than 2 l min^{-1} m^{-2}, estimates made by indicator dilution were lower than those made by Fick. Using data obtained in man by several authors, Rahimtoola & Swan (1965) calculated that cardiac output derived from indicator dilution curves (injection into the pulmonary artery) is 4–9% lower than that obtained by the Fick method. They suggested that this difference might be due to overestimation of the area of the primary curve. It has been shown in anaesthetized dogs

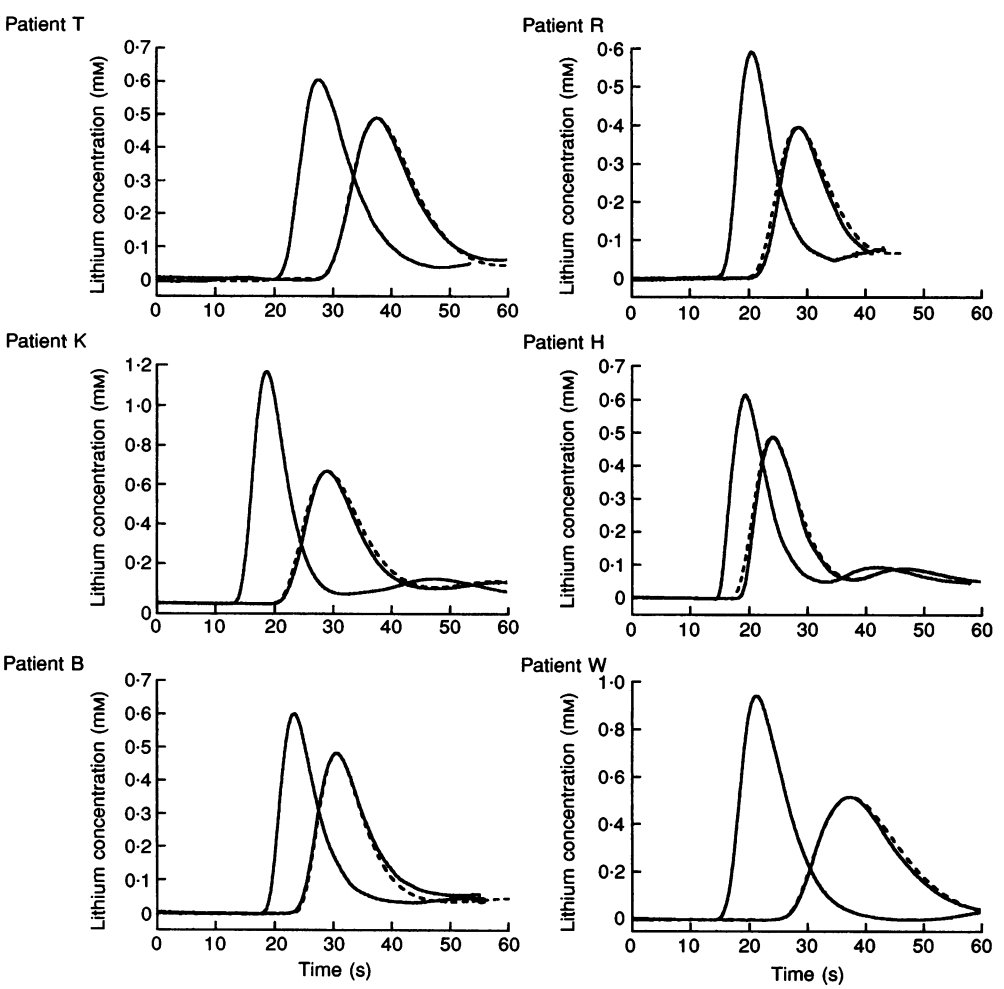

Figure 2. Results from six patients

In each panel the continuous lines show the curves produced by right and left atrial injection and the dashed line shows the left atrial injection curve data after passage through 2 sequential filters and a delay (using Excel). The time constants of the filters are shown in Table 1.

that low cardiac output secondary to haemorrhage may result in falsely high estimates of the primary indicator dilution curve (and therefore underestimate of cardiac output) as a result of recirculation affecting the Hamilton extrapolation (Oriol, Sekelj & McGregor, 1967; Blackburn & Leigh, 1972). In anaesthetized dogs, estimates of cardiac output from Indocyanine Green curves produced by injection into the left side of the heart were higher than when it was injected into the right side (Homer, Moss & Herman, 1969; Weaver, Bailey & Redding, 1970). This must have been a result of inappropriate curve analysis since extra indicator could not have been produced in the lungs to generate larger curves following right-sided injection.

We have previously shown, using Laplace transforms, that sequential filtering of a step signal produces a χ^2 distribution curve, which in turn is closely approximated by a lognormal curve over the range of skewnesses found for indicator dilution curves. Use of the lognormal has been criticized on the basis of the agreement being 'purely fortuitous' (Zierler, 1962) and 'without any physiological background' (Jansen, Bogaard & Versprille, 1987). For the purposes of modelling indicator dilution curves, a simplified description of the circulatory system is necessary in order for the extrapolation of the primary curve to be solvable. The present results provide the 'physiological background' to justify treating the transfer function of the heart and lungs as a delay plus sequential filtering. The resulting lognormal primary arterial dilution curve allows simple and accurate derivation of the integral so that cardiac output can be calculated (Linton *et al.* 1995); the overestimate inherent in treating the washout as monoexponential (Hamilton method) is avoided and the problem of inaccuracy due to distortion of the washout by recirculation is overcome.

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