A NEW METHOD OF MEASURING CARDIAC OUTPUT IN MAN USING LITHIUM DILUTION

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SUMMARY
We describe a new indicator dilution method of measuring cardiac output in man. A bolus injection of lithium chloride 0.6 mmol was given via a central venous catheter and arterial plasma [Li+] recorded using a specially developed sensor incorporating an Li+-selective electrode. Cardiac output was derived from the lithium dilution curve, with a correction for packed cell volume. Lithium dilution cardiac output (LiDCO) was compared with thermodilution cardiac output (TD) using 22 lithium sensors in nine patients. For each sensor, one LiDCO was measured immediately before and one immediately after three TD estimations and mean values of LiDCO and TD derived. The correlation coefficient, r, was 0.89; slope of the regression 0.84; y intercept 0.72; bias 0.3 (0.5) litre min⁻¹ (mean (TD-LiDCO) (1 SD). LiDCO appeared to be a safe, simple and accurate technique which does not require insertion of a pulmonary artery catheter.

KEY WORDS
Heart: cardiac output. Measurement techniques: cardiac output, thermodilution.

Existing methods of cardiac output measurement have several disadvantages. Both the indicator dilution method using indocyanine green and the Fick method can be accurate but they are difficult and impractical. Non-invasive methods such as Doppler and thoracic bioimpedance are inaccurate [1-4] and the most commonly used thermodilution [5] requires a pulmonary artery catheter with its attendant risks. In the words of a Lancet editorial “...development of a simple, safe, reliable and cheap method remains a worthwhile objective” [6].

We have developed a new indicator dilution method which is minimally invasive, requiring only central venous and arterial catheters which would probably already have been inserted in patients whose management would be helped by cardiac output measurement. The indicator is lithium (Li⁺) which is rapidly injected into a central vein (as lithium chloride (LiCl) 0.6 mmol in 2 ml) and detected using a lithium-selective electrode in arterial blood.

PATIENTS AND METHODS
We studied nine patients during the immediate postoperative period after either coronary artery bypass grafting (seven patients) or aortic valve replacement (two patients). The study was approved by the Ethics Committee and written, informed consent was obtained from all patients. The patients' ages and weights were in the ranges 38-73 yr and 64-90 kg and none was receiving oral lithium.

After induction of anaesthesia, a thermodilution pulmonary artery catheter (Baxter Edwards Swan-Ganz) was inserted via the right internal jugular vein. The catheter was advanced until the pressure recorded from the injectate port showed this to be in the right ventricle. The catheter was then withdrawn 2 cm further than the point at which the pressure changed from ventricular to atrial. An arterial cannula (22-, 20- or 18-gauge, depending on the normal practice of the anaesthetist) was inserted into a radial or brachial artery. During the study, which took less than 1 h, the patients were sedated with morphine and propofol infusions and their lungs ventilated using a Servo ventilator.

Thermomilution cardiac output
TD measurements were carried out using a Baxter (Edwards COM-2) thermodilution computer. Injections of ice-cold 5% glucose 10 ml were made into the right atrium and a minimum of four readings was made as rapidly as possible. The first was rejected, as were any which differed by more than 0.5 litre min⁻¹ from the mean of the others. In this case, further readings were taken until three acceptable values were obtained. TD was taken as the mean of these values. No individual value differed from the mean of that set by more than 10.9%.

Lithium dilution cardiac output
The lithium sensor (fig. 1) consisted of a 2–3 cm length of 18-gauge Teflon tubing containing an internal reference material and with a PVC membrane dip-cast over one end. The membrane contained the crown ether lithium ionophore VI (6,6-Dibenzyl-14-crown-4; 6,6-Dibenzyl-1,4,8,11-tetra-
oxacyclotetradecane) (Fluka) which made it selectively permeable to Li\(^+\) [7]. The sensor was mounted in a Y-connector (VYGON, 889). The voltage across the membrane was recorded between two chloridized silver wires, one in the reference material and the other in the lumen of the Y-connector. This second wire was coated with polyurethane (Tecoflex) to protect the silver chloride from plasma proteins. The voltage was recorded via an optically isolated preamplifier [8]; displayed on a chart recorded (PAR 1000) and recorded on magnetic tape for later analysis.

Before the sensors were mounted in the Y-connectors, they were tested in vitro to ensure that the voltages recorded in saline and [Li\(^+\)] \(1\) mmol litre\(^{-1}\) in saline were correct: change from one solution to the other should produce a 10-mV change in membrane potential. The sensor was then sealed into one limb of the Y-connector and sterilized by immersion in glutaraldehyde. The gluteraldehyde was washed out with saline and the calibration repeated. The Y-connector with three-way tap was connected via a second three-way tap to the hub of the arterial cannula. A 10-cm length of tubing and 20-ml syringe were connected to the open limb of the Y-connector so that blood could flow past the sensor into the syringe. The flow varied depending on the size of the arterial cannula, packed cell volume (PCV) and arterial pressure, but was in the range 15–30 ml min\(^{-1}\); at no stage did blood or flushing fluid pass back over the sensor into the arterial catheter.

Blood was allowed to flow past the sensor until a stable baseline voltage was recorded and then LiCl 0.6 mmol (2 ml of a 0.3-mol litre\(^{-1}\) solution) was injected into the superior vena cava via one of the catheters in the right internal jugular vein. The deadspace of this catheter had previously been cleared with the LiCl solution and care was taken to inject exactly 2 ml. Ampoules containing 10 ml of LiCl 0.3 mol litre\(^{-1}\) had been prepared by St Thomas’s Hospital pharmacy. When the second LiDCO curve had been obtained, another sensor was attached and the same procedure repeated. Each lithium sensor was used to make two cardiac output measurements. Between these two measurements, three TD measurements were made. The LiDCO and TD estimates were therefore not simultaneous, but the intervals between them were as short as possible, usually less than 1 min. The mean of the LiDCO values was compared with the mean of the TD values. Up to three sensors were tested in this way in each patient; results were obtained from 22 electrodes in the nine patients.

The plasma flow was derived from the dilution curve by dividing the injected dose of LiCl by the area which would have been inscribed by the curve if there had been no recirculation of the Li\(^+\). Using an iterative model based on a two-compartment filter, a simple algorithm was developed to allow calculation of this area (fig. 2): it is equal to \(A + B + B/2\), where \(A\) = the area enclosed between the start of the increase in [Li\(^+\)] and the peak concentration and \(B\) = the area enclosed between the peak concentration and a point on the curve when [Li\(^+\)] had decreased to 50% of its peak. This procedure is similar to that used for thermodilution, except that the cut-off is slightly earlier, to avoid recirculation. On the basis of this model, the calculated total area was correct to within 2%. The areas were measured by amplifying the curves during playback on to standard paper, cutting out the areas \(A\) and \(B\), weighing them and multiplying these weights by the area per unit weight of the paper. Weighing was accurate to ±0.5 mg using a Sartorius balance, which is equivalent (in terms of cardiac output) to an accuracy of ±0.5%. The area is in units of mmol litre\(^{-1}\) s. Cardiac output was then derived:

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\text{Cardiac output (litre min}^{-1}\text{)} = \frac{\text{dose of LiCl (mmol) } \times 60}{\text{area of curve (mmol litre}^{-1}\text{ s}) \times (1-\text{PCV})}
\]

where the factor 60 converts flow from litre s\(^{-1}\) to litre min\(^{-1}\) and division by (1-PCV) converts plasma flow to blood flow, since Li\(^+\) is distributed only in the plasma fraction of blood. PCV was calculated as haemoglobin concentration (g dl\(^{-1}\)) divided by 33 (Radiometer OSM3 Hemoximeter).

The sensor gave a constant reading in blood in the absence of any Li\(^+\), as a result of the cross-sensitivity of the ligand with Na\(^+\), so that it read the background plasma [Na\(^+\)] (140 mmol litre\(^{-1}\)) as approximately [Li\(^+\)] 2.4 mmol litre\(^{-1}\). The injections of LiCl...
0.6 mmol produced small increments on top of this background voltage and, over this narrow range, the voltage change of the sensor approximated closely to a linear response to [Li⁺]. The linearity of the response over this range was confirmed by adding aliquots of Li⁺ to blood in vitro. LiDCO values could therefore be calculated without transformation of the curves before determining their areas.

**RESULTS**

Figure 3 shows three LiDCO curves obtained in different patients at different cardiac outputs. Peak plasma [Li⁺] reached in the third curve was about 1.3 mmol litre⁻¹. Results were obtained from 22 of 27 electrodes in the nine patients. Results from five electrodes were rejected either because of excessive drift or because they had a reduced span when calibrated after use. The correlation between the LiDCO and TD measurements is shown in figure 4. The average of all the LiDCO readings was 6.1 litre min⁻¹ and that of the TD readings 6.4 litre min⁻¹; the average TD estimate was 295 ml min⁻¹ greater than the LiDCO. This is also shown in figure 5, in which bias (TD − LiDCO) is plotted against (LiDCO + TD)/2, as recommended by Bland and Altman [9]. The sd of the bias was 498 ml min⁻¹.

**DISCUSSION**

It is not possible to conclude from our data that LiDCO is more accurate than TD, although this may prove to be the case. Stetz and colleagues [10] analysed 14 reports of the reliability of TD and concluded that, for commercially available systems, there should be a minimum difference of 13% between triplicate (or 22%, between single) measurements for it to be considered to be clinically significant. If this magnitude of error existed in the TD estimations in the present study, this could have accounted for a significant proportion of the discrepancy between the two methods. There are circumstances, such as tricuspid regurgitation or peripheral migration of the Swan−Ganz catheter, in which TD has been shown to give unreliable measurements [11, 12].

Lithium was the obvious choice of cation as the indicator in this technique as various ligands are available for the construction of Li⁺-selective electrodes and Li⁺ is not normally present in the blood, except in trace quantities, nor is it bound by protein. The electrodes have a fast frequency response and, as they respond to proportional changes in concentration, large signals are produced for small changes close to zero, in accordance with the Nernst equation. The main shortcomings of ion-selective electrodes, namely long-term drift and the difficulty of absolute calibration, are of no significance because, in the computation, it is the area under each curve which is used and this is inscribed within 15 s.

There were several possible problems with this technique. One was that lithium might be taken up by the blood cells or lungs during its transit from the right atrium to peripheral arterial blood; either of these effects would result in a falsely increased estimate of the cardiac output. The present study indicates that such uptake is unlikely to be significant. The addition of aliquots of lithium chloride to whole blood in vitro showed that there was no measurable reduction in plasma [Li⁺] during at least the first 30 min after the additions. The TD estimate of cardiac output was, on average, 295 ml min⁻¹ greater than the LiDCO estimate. Although this difference is not significant, had there been a
significant loss of Li\(^+\) there would have been an obvious difference in the opposite direction.

Another possible problem was that the sudden transition from room temperature saline to warm blood may have caused an unacceptable drift in electrode potential, or the non-heparinized blood may have caused a rapid deterioration in electrode span. In practice, five of the 27 sensors used in this investigation were rejected because of either drift or failure to calibrate; it is likely that these failures were caused by errors in the construction of the sensors, rather than a fault in the fundamental design.

Another problem could have been that the frequency response of the system, with its deadspace of taps and associated tubing, might have been inadequate for the purpose. The dilution curves themselves contain internal evidence that this is not a limiting feature. The cardiac oscillations in [Li\(^+\)] shown in figure 2 and the first and third curves in figure 3 are genuine rather than pressure or flow artefacts, as they do not appear on the trace before the increase in [Li\(^+\)] or during the recirculation peaks. They are caused when [Li\(^+\)] is increasing or decreasing rapidly and occur because the first fraction of blood to fill the left ventricle is the last to be ejected. Whether or not cardiac oscillations are seen depends on the response time of the sensing system, the rate at which [Li\(^+\)] is changing in pulmonary venous blood, left ventricular ejection fraction and heart rate. The present flow-through cells were relatively crude and based upon available components. A considerable reduction in deadspace is possible and a total blood sample of less than 5 ml per measurement is our objective.

Measurement of cardiac output by lithium dilution has potential advantages over other methods. It is accurate, quick, simple and avoids the hazards of pulmonary artery catheterization. Non-invasive methods of measuring cardiac output, such as thoracic bioimpedance and Doppler ultrasound, have the advantage of continuous monitoring but are both difficult and inaccurate, especially in patients who have recently undergone heart or aortic surgery.

Lithium is distributed initially into plasma and then extracellular fluid and later into a volume equal to that of total body water (40 litre in a 70-kg subject). It is not metabolized and is excreted almost entirely in the urine, with a renal clearance of approximately 25% of glomerular filtration rate or about 30 ml min\(^{-1}\) [13]. The therapeutic range is 0.4–0.8 mmol litre\(^{-1}\), with the blood being taken 12 h after the last dose [14]; peak concentrations may be considerably greater than those at 12 h [15]. The acute lethal dose of lithium varies, but is generally associated with a plasma concentration greater than 3.5 mmol litre\(^{-1}\) 12 h after ingestion. The greatest concentration in our patients was about 1.3 mmol litre\(^{-1}\), but this was only for a few seconds and would not have been transmitted to the extracellular fluid. We have found that awake subjects experience no sensation of any sort when given doses of LiCl up to 1 mmol, rapidly i.v. A recommendation would need to be made concerning the total number of LiDCO measurements which could be made safely within any period. We are not yet in a position to do so, but the number would be large before the therapeutic concentration of lithium in extracellular fluid was reached, even in the absence of excretion. The dose used (0.6 mmol) was chosen to give an adequate signal over a range of cardiac outputs. It may be possible to develop a membrane which has a greater selectivity ratio for Li\(^+\) over Na\(^+\) and this would allow a corresponding reduction in the dose of lithium. LiDCO would probably not be a suitable method for patients receiving oral lithium.

Improved quality control in manufacture of the electrodes should avoid any failures and they will be disposable, sterilized by gamma irradiation and stored dry. The signal from the lithium sensor would, of course, be analysed by computer at the bedside, with immediate display of the curve and calculated cardiac output. It is possible that a scaled-down version of the sensing system would allow cardiac output measurements in babies and small children, with correspondingly smaller doses of LiCl.

With further development, we hope that lithium dilution may prove to be an accurate method of measuring cardiac output, while avoiding the hazards associated with pulmonary artery catheters. It would allow measurements to be made within a few minutes in patients in whom central venous and arterial catheters are in place, without exposing them to any further risk. (The sensor is the subject of patent applications held by Monitoring Technology Ltd, United Medical and Dental School, St Thomas's Hospital, London SE1 7EH.)

REFERENCES

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