Clinical validation of a radionuclide detector to measure ejection fraction in critically ill patients

A. C. Timmins, M. Giles, A. W. Nathan and C. J. Hinds

SUMMARY
The use of a new non-imaging nuclear probe (Cardioscint) capable of continuous online monitoring of left ventricular function is described in critically ill patients undergoing mechanical ventilation. Ejection fraction, measured by the Cardioscint, was compared with that measured by echocardiography. The mean difference was −1.1% (95% confidence interval −2.9 to +0.6%). Mean difference ± 2 SD was +10.6 to −12.8% (95% confidence intervals +7.5 to +13.6% and −15.8 to −9.0%, respectively). Examples of fluid loading and inotropic support showed comparable changes in stroke counts measured by the Cardioscint and stroke index measured by thermodilution. The Cardioscint is a practical bedside method for monitoring of left ventricular function in critically ill patients. (Br. J. Anaesth. 1994; 72: 523-528)

KEY WORDS

Cardiac performance and responsiveness to fluid resuscitation and inotropic support are important determinants of outcome in critically ill patients [1-3]. However, assessment of ventricular function may be difficult in the intensive care environment. Invasive haemodynamic monitoring allows determination of stroke volume, stroke work index and construction of ventricular function curves in response to fluid loading, but such monitoring has inherent risks and may be contraindicated in certain patients, for example those receiving thrombolytic therapy. Moreover, the use of pulmonary artery occlusion pressure to assess preload in the critically ill is complicated by alterations in ventricular compliance [4]. In sepsis, the situation is particularly complex; there is often marked vasodilatation associated with an increased cardiac index, despite myocardial depression, as evidenced by a diminished response of left ventricular stroke work index to volume loading [5].

Ejection fraction (EF) (stroke volume expressed as a percentage of ventricular end-diastolic volume) is a useful measure of cardiac performance in a wide range of clinical conditions [6-11]. Various techniques have been used to determine EF, including left-heart catheterization and angiography, first-pass and equilibrium multiple-gated radionuclide ventriculography and echocardiography. Although both echocardiography and radionuclide angiography may be used in critically ill patients [11], these methods are not suited for use in the intensive care unit. Gamma cameras are costly, relatively large and immobile, whilst echocardiography is dependent on finding an acoustic window through which cardiac structures can be imaged. As ultrasound waves are transmitted poorly through air, this poses particular difficulties when the lungs are relatively hyper-inflated as a result of mechanical ventilation with large tidal volumes or positive end-expiratory pressure [11]. In addition, neither method allows continuous monitoring and recording of rapid changes in ventricular volumes or EF. An alternative radionuclide approach is to use a non-imaging detector after blood pool labelling. Earlier non-imaging probes were not ideal for continuous use in the intensive care unit. The nuclear stethoscope (Bios Inc, Valhalla, NY), an early device, used a relatively heavy probe which made long-term positioning difficult. Another, the nuclear vest (Capintec Inc, Ramsey, NJ), can be fixed to the patient's chest and has been used for ambulatory monitoring for several hours [12]. However, it is relatively heavy and a gamma camera is required to position the detector over the left ventricle. Subsequently, a less bulky, lighter probe was developed and used to assess changes in EF related to exercise [13], although a gamma camera was still required for correct probe positioning.

Recently, a small, light-weight probe which uses a scintillation detector coupled optically to a photodiode has been developed (Cardioscint, Oakfield Instruments, Oxford, U.K.). This is portable, may be used at the bedside, provides continuous online monitoring and can be positioned without the use of a gamma camera. The device, which clearly has potential for use during anaesthesia and in the critically ill, has been validated in stable cardiology patients [14] and in patients after angioplasty [15, 16], but not in intensive care patients undergoing mechanical ventilation.

We describe the use of the Cardioscint in a...
FIG. 1. Correlation between ejection fraction (EF) measured by Cardioscint and echocardiography, \( r = 0.94 \).

heterogeneous group of critically ill patients and have compared ejection fraction measured by the probe with that determined by echocardiography.

**PATIENTS AND METHODS**

Approval of the hospital Ethics Committee and consent from next of kin were obtained.

We studied 32 patients (21 men) in the intensive care unit; all were undergoing mechanical ventilation. There were 15 patients with septic shock, five with complications after major non-cardiac surgery, four had low cardiac output after cardiac surgery and three had sustained multiple trauma; there were two neurosurgical patients, two medical patients with hypovolaemic shock and one patient with cardiogenic shock. Median age was 67 (range 19–80) yr and median APACHE II score was 15 (range 6–33).

The Cardioscint system consists of a small (diameter 48 mm, height 39 mm), precordial probe interfaced to a Hewlett-Packard 286 computer. The probe contains a caesium iodide scintillation crystal coupled optically to a large area silicon photodiode, with integral low noise preamplifier. The field of view (1% maximum sensitivity) is an ellipse of width 110 mm and depth 110 mm in water using a technetium point source. Sensitivity is 30 000 counts per second for 100 µCi in 50 ml of water, with a maximum count rate of 80 000 counts per second. This high sensitivity allows ECG-gated or beat-to-beat high resolution (10 ms) time activity curves to be displayed continuously. The electrocardiogram is also displayed and analysed for ST segment depression.

All patients received *in vivo* blood pool labelling with Pyrolite (Dupont). This was followed 20 min later by sodium perchlorate 0.1 mg and \( ^{99} \text{technetium} \) 740 MBq i.v. The probe was positioned initially over the apex beat in a left anterior oblique plane with 10–15° caudal tilt. Then, maintaining the same angle, the probe was moved towards the patient’s head observing the time-activity curve until maximum stroke counts were achieved with minimum average counts. This process was aided by a computer-generated algorithm which displayed continuously the stroke count/average count ratio as a bar graph on the screen. The optimal left ventricular position was marked on the patient’s chest and the background value determined by moving the probe inferolaterally into the space between the apex and the spleen. The background count was taken when there was a sudden reduction in the amplitude of the time-activity curve, stroke counts being at a minimum. The average counts in this position were stored and the probe returned to the left ventricular position. The EF was calculated from (end-diastolic counts — end-systolic counts)/(end-diastolic counts — background counts). The instantaneous EF was displayed using the beat-to-beat mode before an ECG-gated recording was obtained. This uses the QRS complex to time-mark the concurrent count signal so that successive cycles of the time-activity curve are aligned to produce a cumulative result.
The probe monitored EF in the gated mode for 5 min using 15 acquisitions of 20 s. The mean EF over this period was recorded.

The EF was then determined immediately echocardiographically by a single blinded observer, expert in the technique, using the Acuson 128 system. Where possible, apical biplane images were used for calculating EF. When imaging proved difficult, a four-chamber view was utilized. Care was taken to obtain the optimal cavity dimensions by careful transducer positioning and angulation. Endocardial definition was improved by careful selection of correct transducer frequency, pre- and post-processing curves and grey scale-colour B-mode controls. The modified Simpson formula [17] was applied to five consecutive beats. End-diastole was identified as the onset of the QRS complex from the ECG and end-systole as either the frame immediately before mitral valve opening or the smallest cavity area.

Two patients are presented to demonstrate the effects of fluid loading and inotropic support. The former case was a 63-yr-old woman who was admitted to the ICU from theatre after a pelvic clearance; APACHE II score was 6. The haemodynamic effect of two rapid infusions of colloidal fluid 200 ml, 20 min apart are demonstrated. The latter case was a 75-yr-old woman who developed septic shock secondary to perforation of the sigmoid colon; APACHE II score was 25. The haemodynamic effects of changes in dobutamine infusion by 5 μg kg⁻¹ min⁻¹ are demonstrated, with readings obtained 20 min apart. Pulmonary artery catheterization was indicated clinically in both cases. All recordings were performed at least 20 min after any procedures, such as physiotherapy, and pressure measurements were obtained at end-expiration from a paper chart recorder. Cardiac output was measured in triplicate by thermodilution, the coefficient of variation being less than 10%. Stroke volume index was calculated from cardiac index/heart rate.

**Statistical analysis**

The correlation between EF measured by the Cardioscint and that measured echocardiographically was determined to allow comparison with previous work. As these techniques do not provide an absolutely accurate measure of EF, the extent of agreement between the two was assessed using the method described by Bland and Altman [18]. The mean difference (bias) and the mean difference ± 2 SD between the two methods (limits of agreement) were calculated: 95% confidence limits were used to describe the precision of these estimates of agreement.

**RESULTS**

The range of EF measured by the Cardioscint and echocardiography were 14–75% and 15–70%, respectively. The relationship between EF measured by the two methods is shown in figure 1. The correlation coefficient was $r = 0.94$. The bias between the Cardioscint and echocardiography was $-1.1\%$ with 95% confidence interval of $-2.9$ to $0.6\%$. The limits of agreement were $+10.6$ to $-12.8\%$ (fig. 2). The 95% confidence interval for the upper limit was 7.5 to 13.6% and for the lower limit $-15.8$ to $-9.0\%$.

Monitoring of EF after volume loading and inotropic support showed comparable changes in stroke volume measured by thermodilution and stroke counts measured by the Cardioscint (figs 3 and 4).

**DISCUSSION**

Non-invasive techniques such as echocardiography and radionuclide imaging are used widely to determine EF because, being a ratio, absolute values for ventricular volumes are not required for calculation. These techniques have been used to assess left ventricular performance [7, 8, 10, 19] and some have suggested that, despite being dependent on both preload and afterload, EF is particularly sensitive to changes in myocardial contractility when ventricular function is impaired [6]. In addition,
simultaneous determination of stroke volume by thermodilution allows derivation of ventricular volumes, a method which has been used to demonstrate that in septic shock the reduction in EF is associated with ventricular dilatation which maintains stroke volume [7]. This is probably related to increased ventricular compliance and is more obvious in survivors than in non-survivors [7]. Survival from septic shock has been shown to be associated with return of EF towards normal [7]. EF also influences the prognosis of patients with ischaemic heart disease [8] and those undergoing abdominal aortic aneurysm surgery [10].

Although measurement of EF clearly provides valuable additional information concerning alterations in myocardial function in the critically ill, there are practical difficulties associated with the use of echocardiography and gamma cameras in the intensive care unit. Non-imaging nuclear detectors are cheaper and less cumbersome than a gamma camera and, unlike echocardiography, they do not depend on an acoustic window for imaging, which usually requires the patient to be placed in the left semi-recumbent position. In addition, whereas echocardiography measures dimensions and uses these to calculate volumes, radionuclide techniques estimate EF independently of dimensions. Non-imaging systems rely on the principle that after blood pool labelling the left ventricular region can be isolated from other structures and that alterations in externally detected counts will then reflect relative changes in ventricular volumes [2]. The resulting time–activity curve can be used to track rapid changes in EF which may be displayed either as beat-to-beat changes or the counts from synchronous phases of the cardiac cycle can be gated with the ECG signal and summed to produce a cumulative result. This technique was described first in 1976 using the nuclear stethoscope [21] and has been used to assess the response to nitroglycerin infusion in patients with stable angina [22] and to demonstrate significant decreases in EF after laryngoscopy and tracheal intubation in patients undergoing coronary artery surgery [23]. The Cardioscint relies on the same principles but by using a caesium iodide crystal coupled optically to a photodiode and interfaced with a personal computer, it has been possible to develop a compact, portable probe for continuous monitoring which can be positioned without the aid of a gamma camera. Clinically, the Cardioscint has been used to monitor patients after percutaneous transluminal coronary angioplasty (PTCA). One study showed a significant decrease in ejection fraction (and peak ejection and filling rate) during balloon inflation that subsequently returned to normal [16] and another described clinically important changes in EF in four of 12 patients monitored over a 4–6-h period after PTCA [15].

The use of non-imaging detectors has not been validated previously in critically ill patients. We have evaluated the performance of the Cardioscint in intensive care patients undergoing mechanical ventilation and have assessed the degree of agreement between EF determined by echocardiography and that obtained using the radionuclide detector. Echocardiography has been shown to be a useful technique in critically ill patients [11, 19] and EF measured by echocardiography correlates sufficiently closely with that measured by first-pass radionuclide or cine angiography techniques [24] and gated equilibrium radionuclide angiography [25] for clinical purposes.

Our results are comparable with those obtained in spontaneously breathing patients and suggest that agreement over a wide range of EF values is sufficiently close for most clinical and research applications in the intensive care unit. The correlation between EF measured by the Cardioscint and echocardiography in our study \( r = 0.94 \) is similar to that found between the Cardioscint and the gamma camera \( r = 0.8 \) [14], \( r = 0.94 \) [15] and \( r = 0.87 \) [16]. The mean difference between the two techniques used in this study \(-1.1(\text{SD} 5.85)\%\) also compares favourably with that found previously between the Cardioscint and gamma camera \(-2(9.5)\%\) [14]. Measurement with one technique was followed immediately by the second to avoid differences caused by the inherent instability of critically ill patients. Because of this instability, studies of the variability of EF measured by the Cardioscint have been performed only in healthy volunteers, who remained relatively still in the semi-supine position. This has shown an acceptable coefficient of variation for comparison between the Cardioscint and the gamma camera [26]. It has also been shown that the accuracy of the device is maintained satisfactorily for up to 6 h [27].

To assess the value of the Cardioscint as a means of continuously monitoring the response to interventions, we compared changes in stroke counts with alterations in stroke volume measured by thermodilution. Fluid loading and inotropic support produced similar changes in stroke counts and stroke volume (figs 3 and 4 are examples). Previous work in six cardiac patients during atrial pacing has also shown satisfactory correlation between percentage changes in stroke index measured by thermodilution and percentage change in stroke counts measured by the Cardioscint [14].

Certain limitations are common to all non-imaging probe systems; as only global left ventricular function is analysed, specific valvular and wall motion abnormalities cannot be defined, hence the cause of left ventricular dysfunction and possibly early signs of myocardial ischaemia may not be detected. Nevertheless, EF measured by the Cardioscint has been shown to correlate well with that determined using a gamma camera, even in the presence of wall motion abnormalities [14] and the Cardioscint has been able to detect changes in EF related to episodes of myocardial ischaemia [15, 16].

Non-imaging probe systems also have a fixed field of view and therefore the left ventricle must be isolated from other structures. Before undertaking this study the operator (ACT) initially gained experience in identifying the optimal left ventricular position by studying eight stable cardiac patients who required radionuclide investigation. In a previous study it was impossible to distinguish an adequate time–activity curve in three of 77 cardiac
patients and in five a gamma camera was required to aid positioning [14]. In other studies a gamma camera was never required [15, 26], and despite a wide variety of physique and diagnoses, as well as the presence of lung pathology and the use of mechanical ventilation with or without positive end-expiratory pressure, an adequate time–activity curve could be obtained in all our patients. In two patients not analysed here, the left ventricle could not be seen by echocardiography and yet good time–activity curves were displayed by the Cardioscint, allowing calculation of EF.

Separation of the left ventricle from background is dependent on the quality of red blood cell labelling. In this study initial labelling problems were resolved by changing the brand of stannous pyrophosphate. Subsequently, it was found that 85–90% of the radioactivity was bound to red cells as opposed to plasma. After completion of this study, however, we were unable to achieve satisfactory labelling in one patient; the cause was unclear but in vitro labelling on the following day proved successful and good identification of the ventricular time–activity curve and background was then achieved. In patients where in vitro labelling is unsatisfactory we would recommend in vitro labelling as described in the Appendix.

In a previous study, EF, determined using an automatically derived background, calculated as a fixed percentage (74%) of end-diastolic counts, was compared with that determined from a manual background, as determined in this study [14]. These authors found that although reliable results were obtained using automatic background, values were slightly too high and EF was therefore overestimated. Another study, using a different probe system, compared background calculated as 75%, 70%, 65% and 60% of end-diastolic counts and found that agreement between EF measured by the probe and a gamma camera was closest when 70% of end-diastolic counts was used in the calculation [13]. In our experience, although the automatic and manual backgrounds were often comparable, occasionally they differed considerably, possibly because of the larger tidal volumes during mechanical ventilation or the variations in pulmonary vascularity associated with critical illness. We therefore recommend using manual background determination.

When using radionuclide techniques the exposure of patients and staff to radiation must be minimized, particularly if repeated studies are being performed with staff in close proximity to the patient for prolonged periods. In our study the effective dose equivalent to the patient was estimated to be 6.3 mSv [28] which is about the same as a chest CT scan [29]. Staff, positioned 1 m from a patient given 750 MBq 99technetium, are exposed to an initial dose rate of 5.6 μSv h⁻¹ [30], which is below the maximum permissible dose rate in a controlled area recommended by U.K. ionizing radiation regulations [31]. Nevertheless, staff should use disposable gloves and aprons when in contact with the patient and body fluids should be disposed of as soon as possible.

Our experience suggests that the Cardioscint is a practical, relatively low cost, bedside tool that may be used reliably to estimate EF in critically ill patients undergoing mechanical ventilation and to monitor continuously changes in left ventricular function in response to therapeutic interventions. The technique depends on adequate red cell labelling and accurate identification of left ventricular and background positions.

APPENDIX

IN VITRO RED BLOOD CELL LABELLING

1. Reconstitute Pyrolate vial with normal saline 4 ml and mix thoroughly.
2. Add 1 ml to normal saline 500 ml and mix well.
3. Withdraw 1 ml of the above and add to 10 ml of heparinized whole blood.
4. Centrifuge at 1000 rpm for 5 min.
5. Withdraw plasma from the top of the sample leaving the red blood cells.
6. Add technetium approximately 100 MBq to the red blood cells.
7. Incubate for 10 min.
8. Add normal saline 5 ml to sample, mix well and spin at 1000 rpm for 5 min.
9. Remove supernatant.
10. Add normal saline 5 ml, mix well and draw into syringe for injection.

ACKNOWLEDGEMENTS

We thank Dr Paul Broadhurst, Ravin Sobnack and Kishor Solanki for advice and Lilly Industries for financial support.

REFERENCES


