

# Quantitation of left ventricular volumes and ejection fraction in post-infarction patients from biplane and single plane two-dimensional echocardiograms

## A prospective longitudinal study of 371 patients

M. St John Sutton\*, J.-E. Otterstat†, T. Plappert\*, A. Parker‡, D. Sekarski‡, M. G. Keane\*, P. Poole-Wilson§ and K. Lubsen‡

\*Cardiovascular Division, University of Pennsylvania Medical Center, Philadelphia, PA, U.S.A.; †Vestfold General Hospital, Division of Cardiology, Toensberg, Norway; ‡SOCAR SA, Givrins, Switzerland; §Department of Cardiac Medicine, National Heart and Lung Institute, London, U.K.

**Aims** To determine whether left ventricular volumes and ejection fractions calculated from single plane two-dimensional echocardiograms using the algorithm ( $0.85A^2L$ ) correlate with those calculated using the biplane Simpson's method, and whether small changes in volumes and ejection fraction occurring post-infarction could be detected from single-plane as well as from biplane two-dimensional echocardiograms.

**Methods and Results** Serial two-dimensional echocardiograms were obtained in 371 patients from the DEFIANT II trial a mean of 2 days, 1 week and 6 months post-infarction. Single plane volumes from the apical four chamber and apical long axis correlated closely with biplane Simpson's left ventricular volumes. Both single-plane left ventricular volumes significantly over-estimated biplane Simpson's

volumes. Biplane Simpson's ejection fractions were consistently slightly under-estimated from the single-plane images. Differences between biplane Simpson's and single-plane volumes increased independently with increasing left ventricular size and distortion. The small changes in left ventricular volumes and ejection fraction over time were as reliably detected from single plane as from biplane images.

**Conclusion** Single-plane left ventricular volumes over-estimate biplane Simpson's volumes and under-estimate ejection fraction, and these discrepancies are amplified in dilated hearts with abnormal shape.

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**Key Words:** Left ventricular volumes, ejection fraction, echocardiography.

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## Introduction

Quantitative two-dimensional echocardiography has frequently been used in multicentre clinical trials in the last decade to predict clinical outcome and to assess the efficacy of pharmacological interventions on left ventricular volumes and function in patients with heart failure and in survivors of acute myocardial infarction<sup>[1–11]</sup>. Most clinical trial protocols have required quantitation of left ventricular volumes and ejection fraction from biplane two-dimensional echocardiographic images using Simpson's method. However,

technically satisfactory trans-thoracic biplane two-dimensional echocardiographic images can only be obtained in about 75% of patients<sup>[4,6]</sup>, which substantially slows patient recruitment. Furthermore, when technical difficulties arise, obtaining biplane echocardiographic images at serial follow-up studies in patients already enrolled into clinical trials, single plane studies are often substituted.

Left ventricular volumes can be quantitated from single-plane echocardiograms which are obtainable in almost every patient, and if these volumes are representative, they would greatly facilitate patient enrollment and reduce trial duration and costs. No systematic prospective examination has been performed in a large cohort of patients to determine whether left ventricular volumes calculated from biplane two-dimensional echocardiographic images using Simpson's method correlate with volumes calculated from single-plane

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*Correspondence:* Martin St John Sutton, Division of Cardiology, University of Pennsylvania Medical Center, 3400 Spruce Street, Philadelphia, PA 19104, U.S.A.

echocardiographic images. In addition, no attempt has been made to determine whether the small changes in left ventricular volume that occur during post-infarction remodelling can be detected as well by single-plane as by biplane estimates of left ventricular volume.

The objectives of the present study were (1) to determine how closely left ventricular volumes and ejection fractions calculated from Simpson's biplane method correlated with those calculated from single-plane two-dimensional echocardiograms using the algorithm  $(0.85A^2/L)$  recommended by the American Society of Echocardiography<sup>[12]</sup>; (2) to establish whether biplane and single-plane left ventricular volumes were sufficiently similar as to be interchangeable; and (3) to assess whether the small changes in left ventricular volumes and ejection fraction during post-infarction remodelling could be detected as reliably by quantitative analysis of single-plane echocardiographic images as by biplane Simpson's method.

### Patient population

We studied the patient population of the DEFIANT II trial<sup>[13]</sup>, which consisted of 569 survivors of acute myocardial infarction who were enrolled in a multi-centre, double-blind, placebo-controlled trial in which the primary objective was to assess the effects of core-coated nisoldipine on exercise performance measured on a bicycle ergometer compared to placebo<sup>[13]</sup>. The criteria used to define myocardial infarction were described in the parent trial<sup>[13]</sup>. Five hundred and three of the 569 patient population survived 6 months post infarction. Three hundred and seventy one of the 503 6 months' survivors (74%) were selected for the present study population because they all had three sequential, biplane two-dimensional echocardiograms a mean of 2 days, 1 week and 6 months following acute myocardial infarction of sufficiently high quality for quantitative analysis. The remainder either had incomplete studies (missing one follow-up visit or had only single-plane and no biplane images at one or two of the follow-up visits), or were not of sufficiently high quality for quantitative analysis.

### Methods

Three serial trans-thoracic two-dimensional echocardiograms of high quality were obtained from each of the 371 patients, providing a total of 1113 echocardiograms. Each echocardiogram had to include an apical four-chamber image and an apical long-axis image of the left ventricle with simultaneous electrocardiograms of standard lead II recorded on half inch videotape. All two-dimensional echocardiograms were sent to the echocardiographic Core laboratory at SOCAR SA, Givrins, Switzerland, to assess their technical quality and suitability for quantitative analysis. Each

echocardiogram was transferred to the hard disc of an off-line Nova Microsonics computer analysis system with commercially available software. Left ventricular endocardial borders were digitized to obtain the following:

(1) Biplane left ventricular end-diastolic and end-systolic cavity volumes calculated using Simpson's rule<sup>[12]</sup> from paired apical four-chamber and apical long-axis echocardiographic images from a minimum of three cardiac cycles, and mean values for each variable were estimated. Biplane ejection fractions were calculated as:

$$\frac{(\text{End-diastolic volume} - \text{End-systolic volume})}{\text{End-diastolic volume}} \times (100\%)$$

Biplane Simpson's method was initially developed for quantitation of left ventricular volumes from contrast angiograms and was validated against volumes from anatomical casts and subsequently applied to echocardiograms. For the purpose of this study, we made the tacit assumption that biplane Simpson's left ventricular volumes more closely represented true volumes<sup>[14]</sup>, and for this reason we used them as our reference standard. (2) Single-plane left ventricular end-diastolic and end-systolic volumes and ejection fractions were calculated separately from the apical four-chamber view and from the apical long-axis view, each from a minimum of three cardiac cycles, and mean values were computed for each plane using the formulation:

$$\text{Volume} = 0.85 \times (\text{Cavity Area})^2 / (\text{Cavity Length})$$

recommended by the American Society of Echocardiography<sup>[12]</sup>.

(3) Left ventricular cavity lengths were measured from each of the two single-plane echocardiographic images of the left ventricular cavity at end-diastole and at end-systole as the distance from the apex to the centre of the mitral valve plane.

(4) Left ventricular shape was defined for each of the two single-plane echocardiographic views, (apical four chamber and long axis), as the ratio of the diameter of a circle with the same area as the left ventricular cavity area and the left ventricular cavity length, modified from a previous study<sup>[15]</sup>. We used this 'index' of cavity shape to assess left ventricular chamber distortion, and to determine whether differences between left ventricular volumes calculated from the individual single planes and biplane echocardiographic images using Simpson's method resulted primarily from distortion of left ventricular cavity shape.

### Statistical methods

Intra-observer reproducibility analysis was assessed from 100 consecutive two-dimensional echocardiograms, which were digitized to calculate left ventricular end-diastolic and end-systolic cavity volumes. These same 100 echocardiograms were re-digitized more than 3 weeks later, and left ventricular cavity volumes recalculated with no knowledge of the previous results.

**Table 1** Left ventricular volumes by biplane Simpson's, by single-plane four-chamber and single long-axis from baseline to 6 weeks post-infarction

	Baseline	1 week	6 weeks
LV end-diastolic volume (ml) (n=371)			
Biplane Simpson	189.5 ± 48.5	192.3 ± 49.11	202.3 ± 55.9†
Single plane four chamber	206.1 ± 52.1*	209.1 ± 53.2*	218.4 ± 59.7†
Single plane long axis	201.2 ± 52.2*	203.8 ± 51.9*	213.9 ± 58.9†
LV end-systolic volume (ml) (n=371)			
Biplane Simpson	118.1 ± 36.8	118.2 ± 37.4	123.0 ± 43.4†
Single plane four chamber	130.8 ± 39.9*	130.5 ± 40.8*	134.7 ± 47.6†
Single plane long axis	126.2 ± 40.4*	126.4 ± 40.7*	131.4 ± 45.9†

\* $P < 0.01$ , different from biplane; † $P < 0.01$ , different from baseline.

The two sets of left ventricular volume determinations were compared for their degree of concordance using linear regression analysis.

Reproducibility analysis to assess intra-observer variability demonstrated close agreement between the two repeated assessments of left ventricular end-diastolic volumes, with a correlation coefficient of  $r=0.949$  and regression equation  $y=1.00 \times -3.091$  with standard errors of the estimate of 13.2 ml; and for the two repeated measurements of end-systolic volume the correlation coefficient was  $r=0.938$  and the regression equation  $y=0.996 \times -0.162$  with a standard error of the estimate of 11.7 ml.

Differences in left ventricular end-diastolic, in end-systolic volumes and in ejection fractions calculated from biplane Simpson's method and from the two different single plane echocardiographic images, were compared by analysis of variance, and significance was established when  $P < 0.05$ . Changes in biplane Simpson's left ventricular and ejection fraction over time and changes in the two single plane left ventricular volumes and ejection fraction over time were compared by analysis of variance, and significant differences identified when  $P < 0.05$ . Differences between Simpson's biplane and the single-plane volumes and between the single-plane four-chamber and single-plane long axis views were tested by analysis of variance, and significance was established when  $P < 0.05$ . Discrepancies between single-plane and biplane Simpson's left ventricular volumes, and between the two single plane left ventricular volumes were examined as functions of increasing biplane volume (Simpson's method), and changing cavity shape index, as the left ventricular cavity became progressively more distorted by multivariate analysis.

## Results

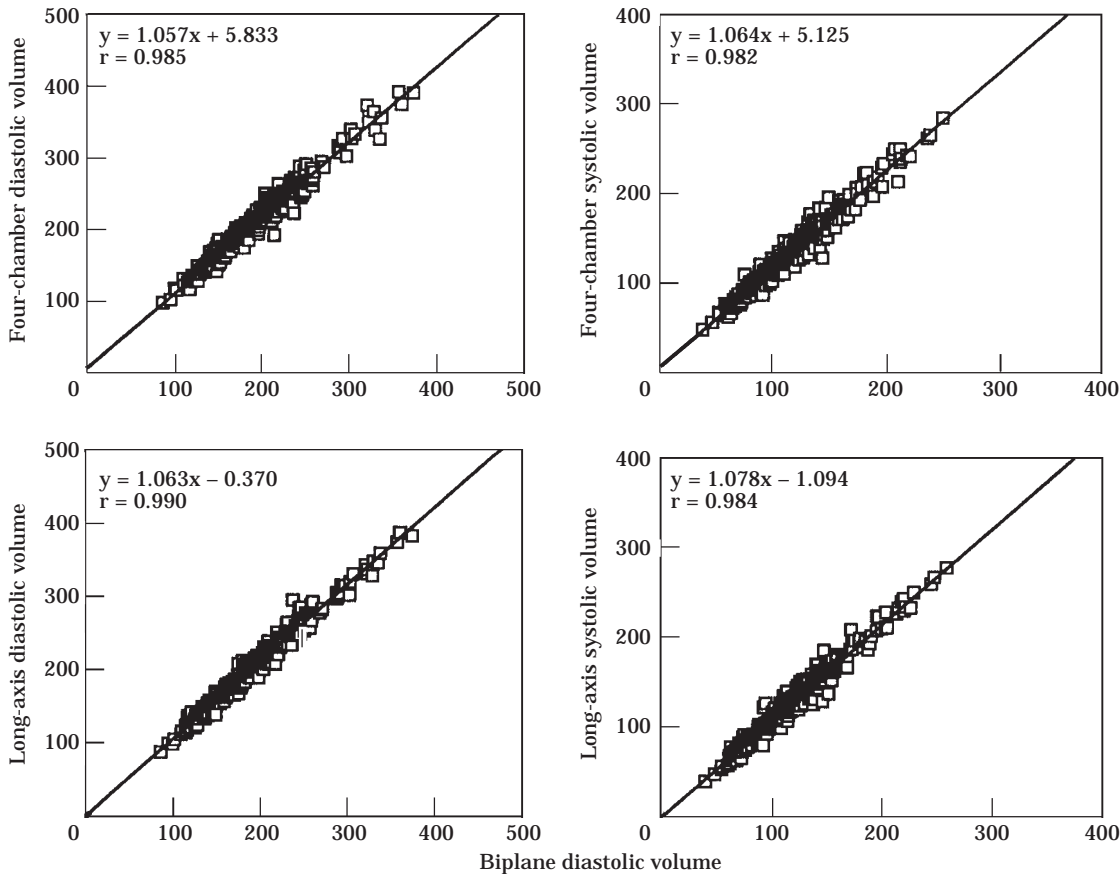
Biplane Simpson's mean and end-diastolic and end-systolic left ventricular cavity volumes within 48 h of acute infarction (baseline) did not change significantly by 1 week post-infarction (Table 1). At 6 months post-infarction, both mean end-diastolic and end-systolic left ventricular volumes had increased significantly (both  $P < 0.01$ ) (Table 1).

Baseline single-plane left ventricular end-diastolic and end-systolic cavity volumes from the apical four-chamber view and from the apical long-axis views did not change significantly from baseline to 1 week post-infarction (Table 1). By 6 months, mean end-diastolic and end-systolic volumes had increased significantly in the apical four-chamber view ( $P < 0.01$  and  $P < 0.05$ ) (Table 1); and in the apical long-axis view, respectively, (both  $P < 0.01$ ) (Table 1).

Single-plane left ventricular volumes from the four-chamber and from the apical long axis both correlated closely with biplane Simpson's volumes (Fig. 1). However, baseline biplane left ventricular end-diastolic and end-systolic volumes were significantly over-estimated from both the apical four-chamber view; (both  $P < 0.01$ ), and from the apical long-axis view, ( $P < 0.01$  and  $P < 0.001$ ) (Table 1). Biplane left ventricular end-diastolic and end-systolic volumes were consistently over-estimated by volume computations from single-plane echocardiographic images at 1 week and at 6 months post-infarction (Table 1). In addition, left ventricular end-diastolic and end-systolic volumes calculated from the apical four-chamber view were significantly greater than those calculated from the apical long-axis view at baseline, at 1 week and at 6 months post-infarction ( $P < 0.01$ ) (Table 1) (Fig. 2(a) and (b)).

The magnitude of the changes in mean left ventricular end-diastolic and end-systolic volumes over time from baseline to 6 months post-infarction assessed from biplane Simpson's and from each of the two single plane methods were similar (Table 1).

Ejection fractions calculated from biplane two-dimensional echocardiographic images at baseline, 1 week and 6 months are shown in Table 2. Biplane Simpson's ejection fractions were consistently slightly under-estimated by ejection fractions calculated from the single-plane four-chamber view and from the single-plane apical long-axis view, although this did not reach statistical significance (Table 2). Ejection fraction determinations from each of the single plane echocardiographic images correlated closely with the biplane values (Fig. 3). However, there was a much less close correlation between the single-plane ejection fractions from the apical four-chamber and from the apical long-axis



**Figure 1** Comparisons of end-diastolic and end-systolic left ventricular volumes calculated from the single-plane apical four-chamber view with left ventricular volumes from the biplane Simpson's method at baseline (left panels), and between left ventricular volumes determined from the single-plane apical long-axis view and biplane Simpson's method at baseline (right panels), showing the close correlations between the two individual single planes and the biplane Simpson's method.

view (Fig. 3). The small but progressive increases in ejection fraction that occurred post-infarction between baseline and 6 months were of similar magnitude whether calculated from either of the single-plane or from the biplane methods (Table 2).

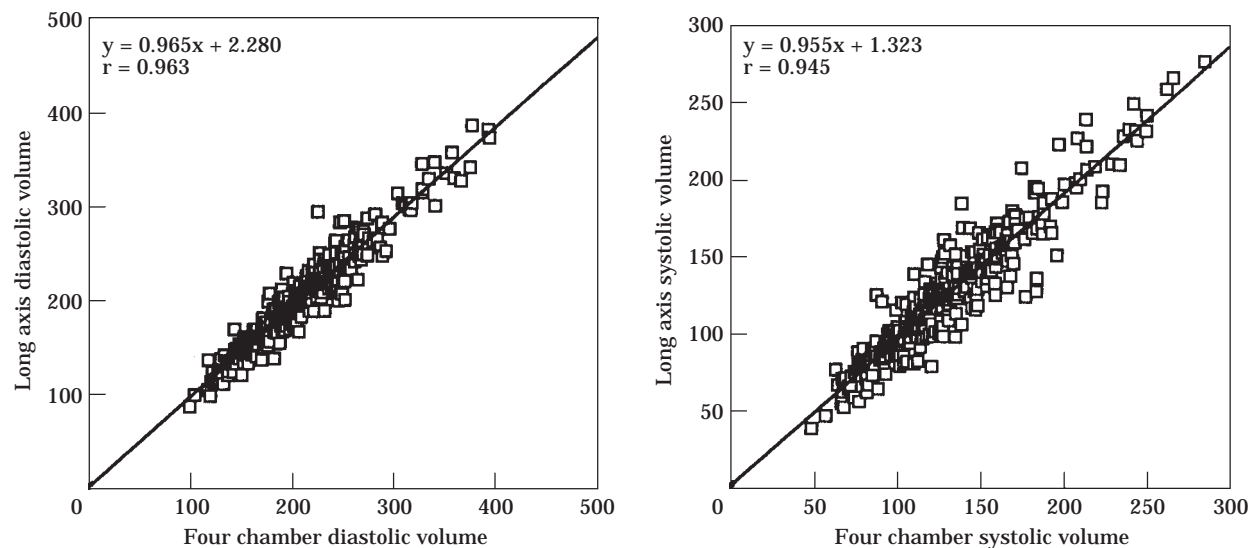
To identify potential explanations for the consistent differences between biplane Simpson's and single plane and between the two single plane left ventricular cavity volumes, we used biplane Simpson's volumes as our standard of reference. We investigated whether differences between the biplane and the two single-plane volume determinations were generated by systematic differences in measurement of cavity lengths, or resulted from abnormalities of cavity shape, or predominated in hearts with the largest biplane volumes. Specifically, we examined the interaction of the difference between each single plane and biplane Simpson's left ventricular volumes as the dependent variable, and sphericity index and biplane volumes as the independent variables, respectively, by multivariate analysis initially at one time point (baseline). At baseline, both sphericity index and biplane volume emerged as important and significant independent determinants of the differences between

end-diastolic and end-systolic volumes for biplane Simpson's and for each of the two single-plane volumes.

In addition, the study echocardiograms from all three time points, baseline, 1 week and 6 months, were pooled and divided into quartiles on the basis of biplane Simpson's left ventricular end-diastolic and end-systolic cavity volumes, (three echocardiograms from a single patient might fall in a single quartile or be dispersed among two or three quartiles). Differences between biplane and each of the single-plane volumes (apical four chamber or the apical long axis) increased progressively and independently as biplane volume increased from quartile I through quartile IV (Fig. 4).

Further, when the study echocardiograms were divided into quartiles with respect to end-diastolic and end-systolic cavity shape index, the differences between biplane Simpson's and both of the single plane left ventricular end-diastolic and end-systolic cavity volumes increased independently as the left ventricle became more spherical from quartile I through quartile IV (Fig. 5).

There were minor but significant differences (<2 mm) in left ventricular lengths measured from the



**Figure 2** Comparison between the left ventricular volumes from the apical four-chamber and the apical long-axis views at end-diastole and end-systole at baseline, demonstrating that the apical four-chamber volumes consistently over-estimated apical long-axis volumes.

**Table 2** Ejection fraction by biplane Simpson's, single-plane four-chamber and single-plane long-axis from baseline to six months post-infarction

Ejection fraction (n=371)	Baseline	1 week	6 months
Biplane Simpson's	38.3 ± 5.8	39.2 ± 6.3	40.1 ± 7.2
Single plane four chamber	37.1 ± 6.1	38.1 ± 6.2	39.2 ± 7.5
Single plane long axis	38.0 ± 6.1	38.7 ± 6.8	39.5 ± 7.3

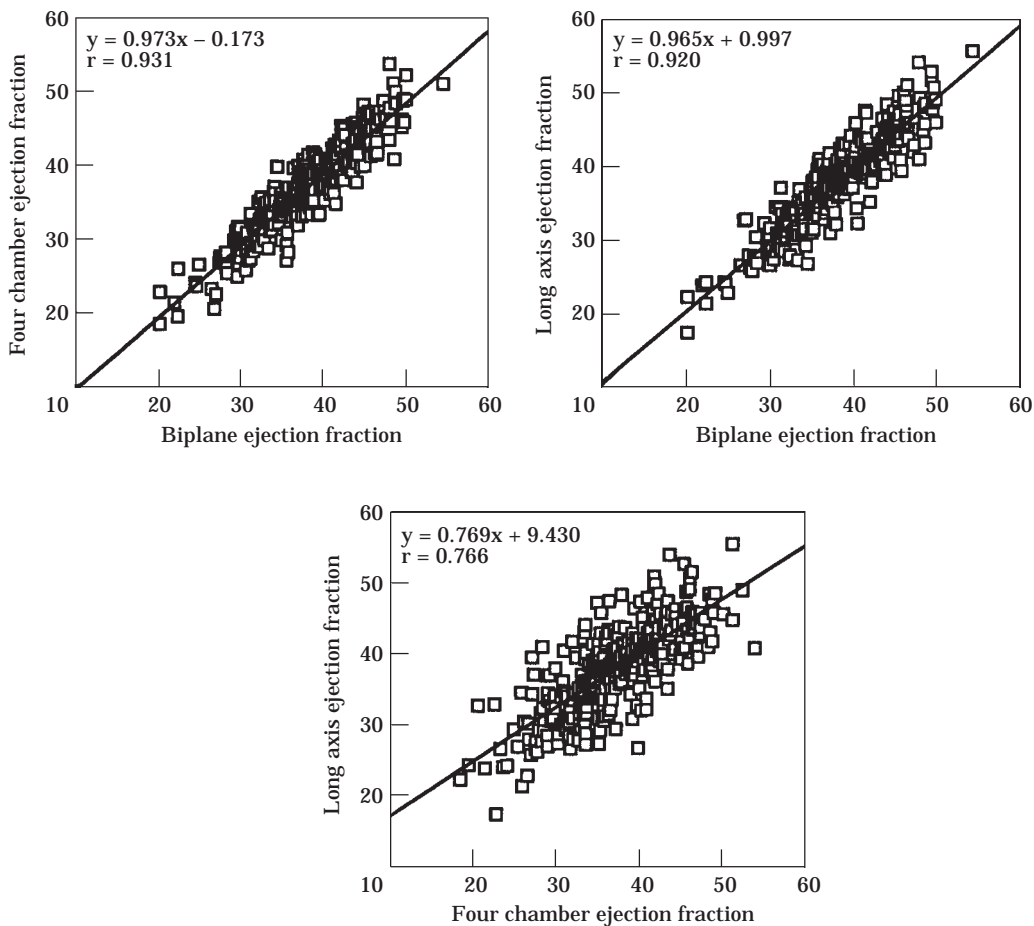
single-plane apical four-chamber and apical long-axis two-dimensional echocardiographic images. Left ventricular lengths were greater in the apical four chamber than the apical long axis,  $9.42 \pm 0.76$  vs  $9.60 \pm 0.78$  cm at end-diastole ( $P < 0.01$ ), and  $8.40 \pm 0.77$  vs  $8.64 \pm 0.79$  cm at end-systole ( $P < 0.01$ ), but these could not account for the systematic differences in left ventricular volumes because the volumes were larger in the apical four chamber than in the apical long axis.

## Discussion

The DEFIANT II trial provided an opportunity to investigate the correlations between left ventricular volumes and ejection fractions calculated from biplane echocardiographic images and from single-plane trans-thoracic two-dimensional echocardiograms in post-infarction patients using the volume algorithms recommended by the American Society of Echocardiography<sup>[12]</sup>. The major findings in this study which involved a large cohort of 371 patients with abnormal left ventricular shape, studied serially from within 48 h of infarction to 6 months post-infarction, were the close correlations between biplane Simpson's and single-plane left ventricular volume computations. In spite of the close correlations, there were significant systematic

differences in end-diastolic and end-systolic left ventricular volumes calculated using biplane Simpson's and the single-plane volume computational algorithm ( $0.85A^2L$ ) recommended by the American Society of Echocardiography<sup>[12]</sup>. Biplane left ventricular volumes were consistently over-estimated by single-plane volume determinations from the apical four-chamber and from the apical long-axis planes, indicating that single-plane and biplane left ventricular volumes are not interchangeable.

We made the pre-test assumption that the biplane Simpson's volumes were more representative of true left ventricular volumes<sup>[14]</sup> than left ventricular volumes calculated from either the single-plane apical four-chamber or from the apical long-axis, and we used them in this study as the standard of reference. The three data sets for volumes and ejection fraction, including baseline, 1 week and 6 months post-infarction, for biplane Simpson's and for single-plane left ventricular end-diastolic and end-systolic volumes by each method were available for statistical comparison. Single-plane end-diastolic and end-systolic volumes calculated from the apical four-chamber and apical long-axis views individually correlated closely with biplane volumes at each time point. Although the two single plane volumes were calculated using the same computational algorithm, end-diastolic and end-systolic volumes from the apical



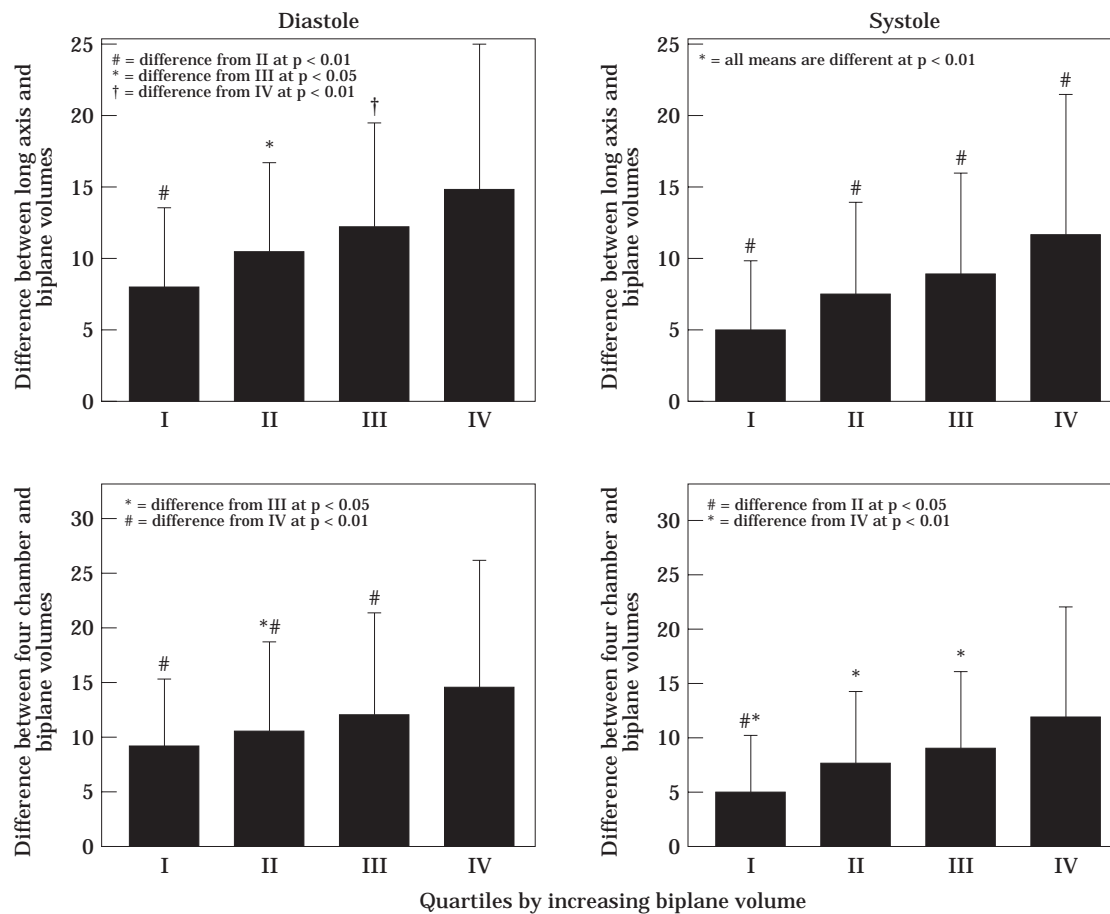
**Figure 3** Comparison between left ventricular ejection fraction calculated from the single-plane apical four-chamber view and biplane Simpson's ejection fraction, between the single-plane apical long-axis and biplane Simpson's, and between the two individual single-plane ejection fractions at baseline, demonstrating that single-plane ejection fractions under-estimate biplane ejection fraction.

four-chamber view were consistently significantly greater than volumes calculated from the apical long axis.

The differences between the biplane Simpson's and single-plane left ventricular volumes were partly explained by the different algorithms used in the modified Simpson's rule and the single-plane volume calculations. This did not explain the consistent differences between the end-diastolic and end-systolic volumes for the single-plane apical four-chamber and the single-plane apical long-axis, for which the same volume algorithm was used. We demonstrated that, in addition to the different volume algorithms employed, at least two other factors also contributed to the systematic differences between biplane and single-plane volumes. First, when the study echocardiograms were divided into quartiles in terms of biplane Simpson's left ventricular volumes, the differences between biplane and single-plane volumes (apical four-chamber vs apical long axis) escalated progressively and independently as biplane volume increased (Fig. 3). Second, the differences between biplane and single-plane volumes increased

independently and significantly as left ventricular shape became more spherical with progressive left ventricular cavity distortion post-infarction (Fig. 4). The discrepancies between left ventricular volumes calculated from the two individual single planes were more difficult to explain. Left ventricular cavity lengths both at end-diastole and end-systole were smaller in the apical four-chamber view than the apical long-axis, probably due to transducer placement, but these differences did not account for the differences in left ventricular volumes, which were consistently larger in the apical four-chamber than in the apical long-axis. Systematic differences between the single-plane left ventricular volume estimates may have been generated by difficulties in defining the plane of the mitral valve in the four-chamber view and the limits of the left ventricular outflow tract in the apical long-axis plane during digitization of the endocardial borders.

The changes in left ventricular volumes with time showed that there was little or no change in cavity volumes between 2 days and 1 week post-infarction, by that there was progressive left ventricular dilatation



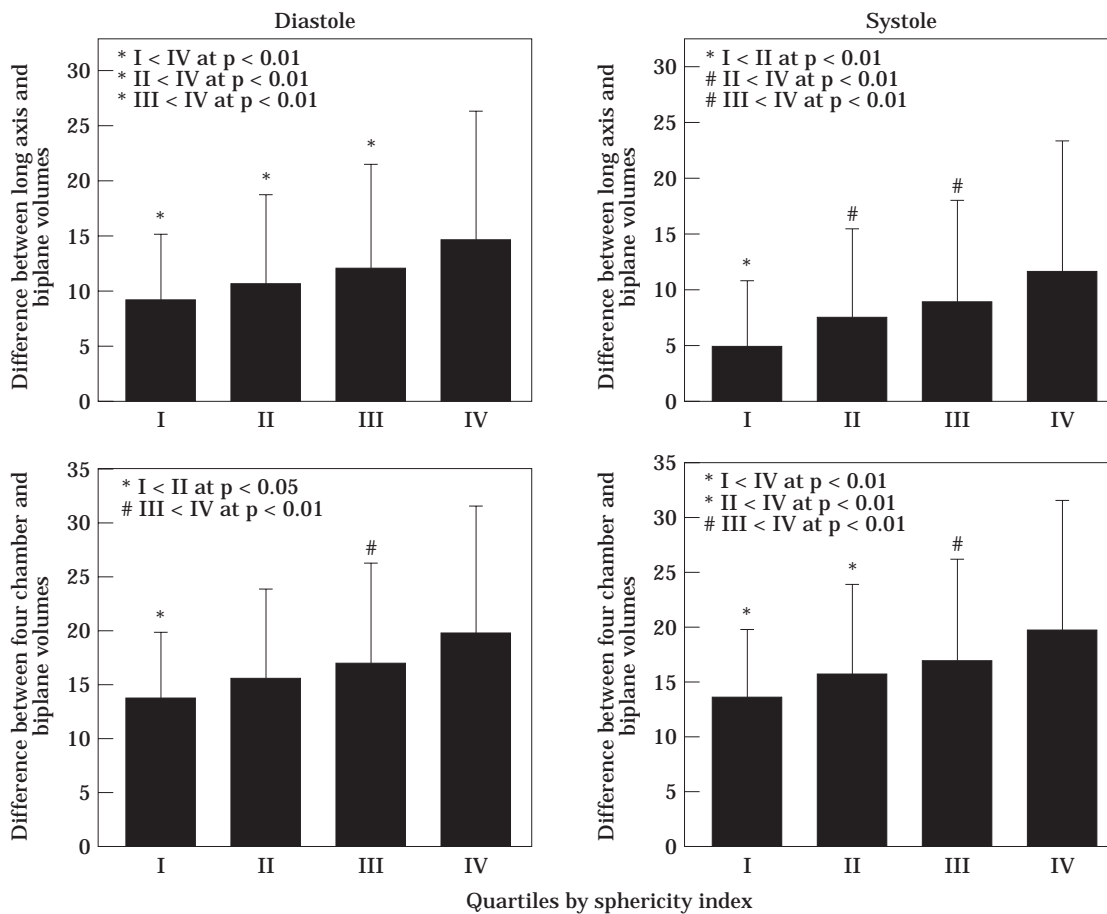
**Figure 4** The study population echocardiograms were divided into quartiles by biplane Simpson's volumes at end-diastole and end-systole. They demonstrate that the differences between single-plane apical four-chamber and biplane Simpson's volumes increase progressively as biplane volume increases, and the differences between single-plane apical long-axis and biplane Simpson's volumes increase as biplane volume increases at end-diastole and at end-systole.

between 1 week and 6 months as the left ventricle remodelled post-infarction. Biplane Simpson's and both of the single-plane left ventricular volume computations detected the small changes in volume over time from baseline to 6 months. Importantly, the small differences in left ventricular volume over time following infarction that we have demonstrated between serial biplane Simpson's and single-plane assessment of left ventricular volume in this study, are of the same order of magnitude as the changes in left ventricular volumes that have been reported to demonstrate efficacy or pharmacological interventions and improved survival<sup>[4,5,7,8]</sup>. Caution must therefore be exercised in interpreting small changes in left ventricular volumes determined echocardiographically following pharmacological interventional therapies without the certain knowledge that the same single or biplane images have been used in consecutive studies.

Ejection fractions calculated from the single-plane apical four-chamber and from the apical long-axis correlated well with biplane ejection fractions, although less closely than the correlations between respective

measurements of either end-diastolic or end-systolic volumes. The poorer correlations between single-plane and biplane ejection fractions are most likely related to compounding the differences in end-diastolic volume and end-systolic volume from the two methods by summing the discordant volumes from which ejection fraction is derived. Mean values for ejection fraction calculated from biplane were systematically slightly under-estimated by ejection fractions derived from single-plane echocardiograms. Although changes in ejection fraction with time post-infarction were small, they were similarly detected by single and biplane methods. All methods revealed that ejection fraction was depressed at baseline but improved significantly by 6 months.

We conclude that using the two conventional algorithms recommended by the American Society of Echocardiography, left ventricular volume determinations from single-plane echocardiographic images correlate closely with biplane Simpson's volumes. However, single-plane volumes systematically and significantly over-estimate biplane left ventricular volumes and



**Figure 5** The study population echocardiograms were divided into quartiles with respect to left ventricular shape index. The graphs show that the differences between left ventricular volumes from the single-plane apical four-chamber view and biplane Simpson's method increase progressively with increasing left ventricular distortion, and the same was true regarding the differences between single-plane apical long axis and biplane Simpson's volumes, which also increased as the left ventricular shape index became more spherical.

slightly under-estimate biplane ejection fraction. The differences between biplane and single-plane volumes predominate the dilated left ventricles, and in those with more spherical cavities due to left ventricular chamber distortion. Left ventricular volumes and ejection fractions calculated from single-plane echocardiographic images should not be interchanged for biplane values in clinical trials in which the efficacy of drug interventions is established upon small changes in left ventricular volume or function, because they are of the same order of magnitude as differences derived from the individual methods themselves. Thus, a strong case can be made for using single-plane volume and ejection fraction determinations because the small changes in left ventricular volumes and ejection fraction over time during post-infarction remodelling are equally well detected by single plane as by biplane. Moreover, single-plane echocardiograms, in contrast to biplane can be obtained in more than 95% of all patients in the apical four-chamber view, which would dramatically reduce the duration of patient recruitment and trial costs.

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