CARDIAC IMAGING AND NON-INVASIVE TESTING

Left atrial Frank–Starling law assessed by real-time, three-dimensional echocardiographic left atrial volume changes

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Background: The Frank–Starling law describes the relation between left ventricular volume and function. However, only a few studies have described the relation between left atrial volume (LAV) and function.
Objective: To describe an LA Frank–Starling law by studying changes in LAV measured by real-time, three-dimensional echocardiography (RT3DE).
Methods: LAV was calculated by RT3DE in 70 patients at end-systole (LAV_{max}), end-diastole (LAV_{min}) and pre-atrial contraction ($LAV_{pre\text{-}A}$). According to LAV_{max}, patients were classified into three groups: LAV_{max} <50 ml (group I), LAV_{max} 50–70 ml (group II) and LAV_{max} >70 ml (group III). Calculated indices of LA pump function were active atrial stroke volume (SV), defined as $LAV_{pre\text{-}A} - LAV_{min}$, and active atrial emptying fraction (EF), defined as active atrial $SV/LAV_{pre\text{-}A} \times 100\%$
Results: Active atrial SV was significantly higher in group II than in group I (mean (SD) 19.0 (9.2) vs 8.2 (4.9) ml, $p<0.0001$), in group III it was non-significantly lower than in group II (16.7 (12.5) vs 19.0 (9.2) ml). Active atrial SV correlated well with $LAV_{pre\text{-}A}$ ($r=0.56$, $p<0.001$), but decreased with larger $LAV_{pre\text{-}A}$. Active atrial EF tended to be higher in group II than in group I (43.1 (18.2) vs 33.2 (17.5), $p<0.10$), in group III it was significantly lower than in group II (26.2 (18.5) vs 43.1 (18.2), $p<0.01$).
Conclusion: A Frank–Starling mechanism in the left atrium could be described by RT3DE, shown by an increase in LA contractility in response to an increase in LA preload up to a point, beyond which LA contractility decreased.

The Frank–Starling law, describing the relationship between increased length of myocardial fibres and its mechanical performance, is important for cardiac function.[1] The relation between myocardial preload and mechanical performance is described by a curve in which an upward position on the curve means increased performance, while a downward position means decreased myocardial performance.[2] Assessment of left atrial (LA) function has important therapeutic and prognostic value.[3] The instantaneous LA pressure–volume relation provides an accurate index of LA contractility.[4] However, measurement of this index is invasive and technically difficult and therefore not suitable for routine clinical application.[3] Non-invasive assessment of LA contractility has been studied by two-dimensional echocardiography, Doppler parameters, cine computed tomography, radionuclide methods and magnetic resonance imaging.[5–9] In previous studies it was suggested that a Frank–Starling mechanism also existed in the human left atrium.[10–12] The left atrium serves as a reservoir, conduit and booster pump for blood returning from the lungs to the heart. LA volume (LAV) is a better index of LA size,[13] and owing to complex LA anatomy it may echocardiographically be best assessed by three-dimensional echocardiography.[14 15] This study aimed at describing an LA Frank–Starling law by studying changes in LAV measured by real-time, three-dimensional echocardiography (RT3DE).

METHODS

The study comprised 70 clinically stable patients (mean age 45.6 (9.3) years, 66% men) in sinus rhythm without atrioventricular or intraventricular conduction abnormalities on a resting 12-lead electrocardiogram. Nineteen patients (27%) were not known with cardiovascular disease, 20 patients (29%) had essential hypertension, 16 patients (23%) had coronary heart disease, and 15 patients (21%) had non-compaction cardiomyopathy. None of these patients had mitral stenosis or significant (more than grade 1) mitral regurgitation. The patients were selected on good two-dimensional image quality.

RT3DE was performed with a Sonos 7500 ultrasound system (Philips Sonos 7500, Best, The Netherlands) attached to an X4 matrix array transducer capable of providing real-time B-mode images. Full volume three-dimensional images were collected within about 5–7 seconds of breath holding. Zoom function and gain adjustment were used to clarify the endocardial border. The probe position was modified to include the whole left atrium in the centre of the RT3DE image sector. The three-dimensional dataset was transferred to a Q-LAB system for offline analysis. Analysis of three-dimensional images was based on a two-dimensional approach relying on the images obtained from an apical four-chamber view and on semi-automated tracing of the LA endocardial border for calculation of LAV. Tracing was performed by marking five atrial points: the anterior, inferior, lateral and septal mitral annuli and the LA apex. Once this was completed, the endocardial surface was automatically delineated and the LA model could be visualised from different points of views and the LAV was obtained (fig 1). Manual modifications were made to correct automatic tracings in the majority of patients, and in particular in patients with a dilated left atrium to exclude the LA appendage and the pulmonary veins entrance from the LAV. Borders that manifested as lines were traced in the middle of the line. In addition, careful attention was given to neighbouring well-visualised pixels as guidance for the true LA wall.

LAV was measured at three phases of the cardiac cycle: (*a*) maximum volume (LAV_{max}) obtained from an end-systolic frame just before mitral valve opening; (*b*) minimum volume (LAV_{min}) obtained from an end-diastolic frame just before

Abbreviations: EF, emptying fraction; LA, left atrial; LAV, left atrial volume; RT3DE, real-time, three-dimensional echocardiography; SV, stroke volume

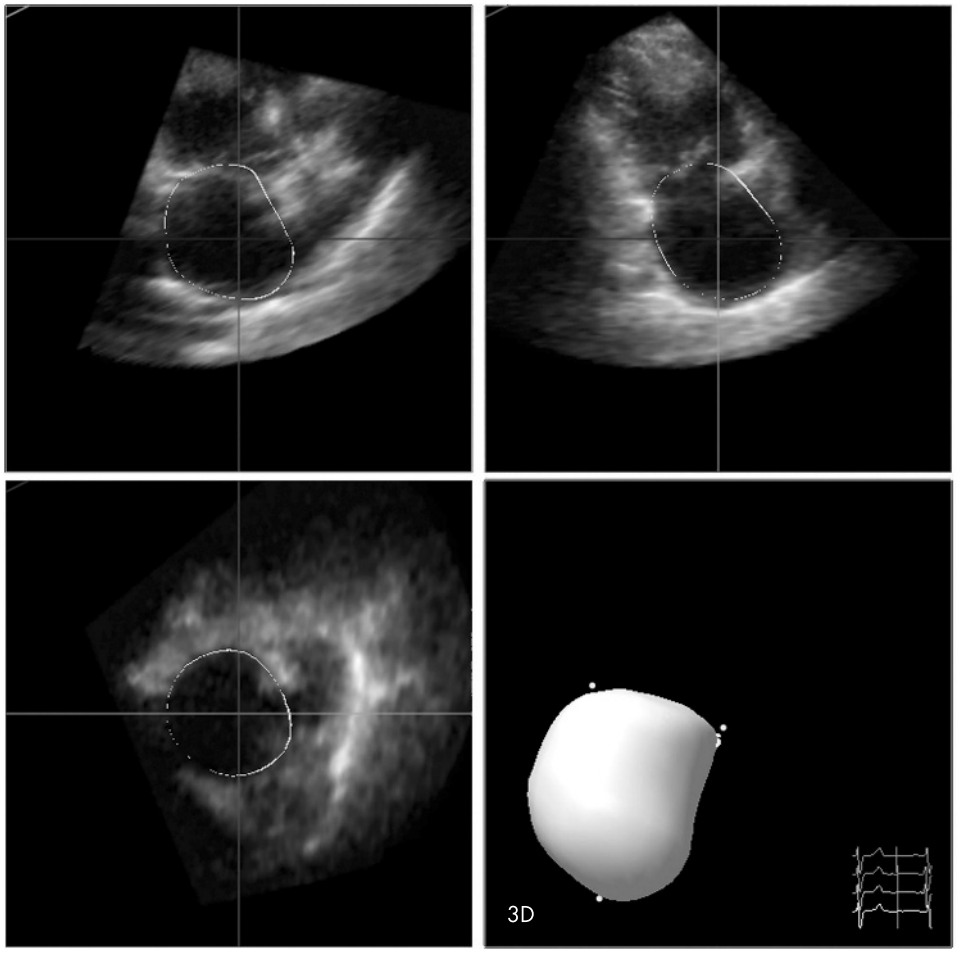

Figure 1 Quad screen display of the Q-LAB analysis software showing methodology for left atrial volume calculation by marking the five left atrial points.

mitral valve closure; and (*c*) volume before atrial contraction ($LAV_{pre\text{-}A}$) obtained from the last frame just before mitral valve reopening.

In accordance with previous studies,[12 16] the following indices of LA function were assessed: (*a*) total atrial stroke volume (SV), defined as $LAV_{max} - LAV_{min}$; (*b*) total atrial emptying fraction (EF), defined as total atrial $SV/LAV_{max} \times 100\%$; (*c*) active atrial SV, defined as $LAV_{pre\text{-}A} - LAV_{min}$; (*d*) active atrial EF, defined as active atrial $SV/LAV_{pre\text{-}A} \times 100\%$; (*e*) passive atrial SV, defined as $LAV_{max} - LAV_{pre\text{-}A}$; (*f*) passive atrial EF as an index for LA conduit function, defined as passive atrial $SV/LAV_{max} \times 100\%$; and (*g*) atrial expansion index as an index for LA reservoir function, defined as $(LAV_{max} - LAV_{min})/LAV_{min} \times 100\%$. To characterise the three phases of LA activity, passive atrial SV and EF were defined as indices for LA conduit function, active atrial SV and EF for LA pump function, and atrial expansion index for LA reservoir function.

Depending on the LAV_{max} values, the patients were arbitrarily classified into three groups: group I included 29 patients with $LAV_{max}<50$ ml, group II included 15 patients with LAV_{max} 50–70 ml and group III included 26 patients with $LAV_{max} >70$ ml.

Table 1 Baseline criteria of the studied left atrial volume groups

Baseline criteria	Group I: V_{max} <50 ml (n = 29)	Group II: V_{max} 50–70 ml (n = 15)	Group III: V_{max} >70 ml (n = 26)
Age (years), mean (SD)	40.2 (7.5)	44.8 (8.5)	46.2 (9.5)
Male gender (%)	17 (59)	10 (67)	19 (73)
Clinical diagnosis (%)			
Normal	19 (66)	0 (0)	0 (0)
Hypertension	7 (24)	10 (67)	3 (12)
Coronary disease	3 (10)	5 (33)	8 (31)
Non-compaction CM	0 (0)	0 (0)	15 (58)
Mitral regurgitation (%)			
None	25 (86)	10 (67)	16 (62)
Mild (grade 1)	4 (14)	5 (33)	10 (38)

CM, cardiomyopathy.

Statistical analysis

The statistical package used was SPSS version 12.1. All LAV values and its functions were expressed as mean (SD). An independent sample *t* test was performed to determine whether the difference in the values was significant, with a level of significance set to $p<0.05$. Interobserver agreements for LAVs, were expressed according to the Bland and Altman method.[17]

RESULTS

Table 1 lists the baseline criteria of the different LAV groups. There were no significant differences in age and sex distribution between the groups. Mild mitral regurgitation was present in 19 patients: 4 patients (14%) in group I, 5 patients (33%) in group II, and 10 patients (38%) in group III. All patients in groups II and III had cardiac abnormalities (hypertension, coronary artery disease, or cardiomyopathy), whereas in group I only 10 patients (34%) had cardiac abnormalities.

Calculation of LAV was obtained within 5–7 minutes for each patient. Absolute interobserver agreement for RT3DE was

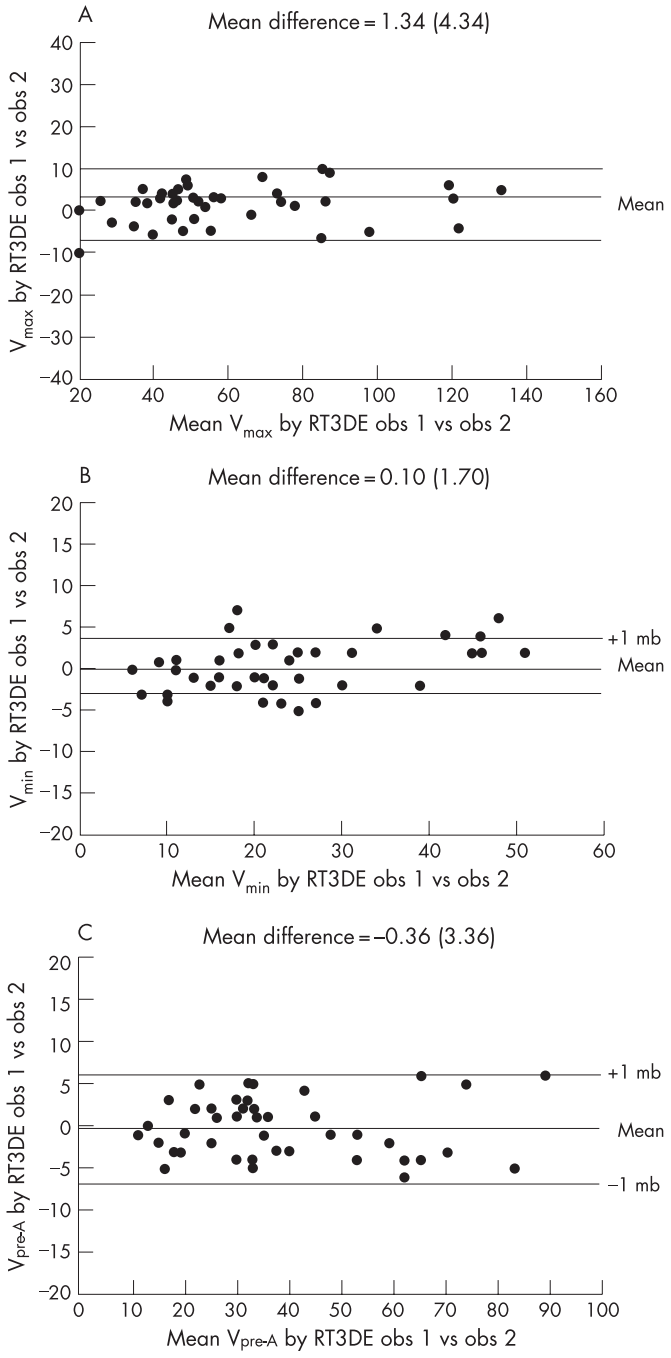

Figure 2 Interobserver agreement for real-time, three-dimensional echocardiography (RT3DE) measurement of the different left atrial volumes (LAV): (A) maximum; (B) minimum and (C) pre-atrial contraction according to the Bland and Altman principle.

(mean difference 1.3 (4.3) ml, agreement −7.3, 10.0 ml) for LAV_{max}, (mean difference −0.36 (3.36) ml, agreement −7.1, 6.6 ml) for LAV_{pre-A}, and (mean difference −0.1 (1.7) ml, agreement −3.2, 3.6 ml) for LAV_{min} (fig 2).

LA volumes in the different patient groups

Figure 3 shows significant differences (higher values for patients with larger LAV) for LAV_{max} in group I compared with II (36.3 (10.7) vs 55.2 (5.7) ml, $p<0.001$) and in group II compared with III (55.2 (5.7) vs 92.0 (19.9) ml, $p<0.001$), for LAV_{min} in group I compared with II (15.4 (5.5) vs 23.1 (7.0) ml, $p<0.001$) and in group II compared with III (23.1 (7.0) vs 45.7 (15.9) ml, $p<0.001$), and for LAV_{pre-A} in group I compared with II (23.6 (7.7) vs 42.1 (9.6) ml, $p<0.001$) and in group II compared with III (42.1 (9.6) vs 62.4 (16.5) ml, $p<0.001$).

LA pump function

Active atrial SV was significantly higher in group II than in group I (19.0 (9.2) vs 8.2 (4.9) ml, $p<0.001$), in group III it was non-significantly lower than in group II (16.7 (12.5) vs 19.0 (9.2) ml). Figure 4A shows that active atrial SV correlated well with LAV_{pre-A} ($r = 0.56$, $p<0.001$), but decreased with larger LAV_{pre-A}. Active atrial EF tended to be higher in group II than in group I (43.1 (18.2) vs 33.2 (17.5), $p<0.10$), in group III it was significantly lower than in group II (26.2 (18.5) vs 43.1 (18.2), $p<0.01$).

LA conduit function

Passive atrial SV was comparable in groups I and II (12.8 (7.4) vs 13.2 (8.5) ml), but more than twofold greater in group III than in group II (29.6 (24.4) vs 13.2 (8.5) ml, $p<0.005$). Passive atrial EF tended to be lower in group II than in group I (23.8 (16.1) vs 34.0 (14.7)%, $p<0.10$), but tended to be higher in group III than in group II (30.0 (19.3) vs 23.8 (16.1)%, $p<0.10$).

LA reservoir function

The atrial expansion index was nearly identical in groups I and II (156.1 (97.7)% and 158.8 (78.7)%, respectively), and non-significantly lower in group III (128.2 (107.3)%).

Total LA function

Total atrial SV was significantly larger in group II than in group I patients (32.2 (5.5) vs 20.9 (8.9) ml, $p<0.001$), and the largest total atrial SV was in group III (46.5 (25.5) ml, $p<0.001$). Figure 3B shows that total atrial SV correlated well with LAV_{max} ($r = 0.82$, $p<0.001$). Total atrial EF was comparable in groups I, II and III (56.4 (13.3)%, 58.5 (10.5)% and 49.9 (15.6)%, respectively).

DISCUSSION

LA function significantly contributes to the maintenance of cardiac output, and impairment of its function contributes to circulatory failure, mitral regurgitation, atrial fibrillation and stroke.[18 19] Previous studies assessed LA function by invasive pressure–volume loop determination,[4] or by LAV changes assessed by nuclear scintigraphy, computed tomography or magnetic resonance imaging.[7 9] RT3DE is an interestingly alternative for LAV assessment because of its availability, rapid acquisition and analysis, low cost, no need for contrast or radiation, and relatively high temporal resolution. In this study LAV was assessed in the three atrial phases by RT3DE.

To the best of our knowledge, this is the first RT3DE study to describe the existence of a Frank–Starling mechanism in the left atrium. The Frank–Starling mechanism was shown by an increase in LA contractility in response to an increase in LA preload up to a point, beyond which LA contractility decreased (fig 4A).

Despite the correlation between an increase in LAV_{pre-A} and active atrial SV in patients with normal to moderately enlarged LAV, active atrial SV reached a plateau and even decreased in patients with the largest LAV. These findings are in accordance with previous non-invasive and invasive studies.[3 5 20] Active atrial SV increase in response to an increase in LAV_{pre-A} may be related not only to a pressure increase but also to an enhanced inherent inotropic state of LA myocardium. This may explain the improvement of atrial pump function after digoxin administration in patients with heart failure.[6] The clinical implication of the described Frank–Starling law in the left atrium is its role in heart failure. In early stages of heart failure, the left atrium compensates well by mechanical adaptation to

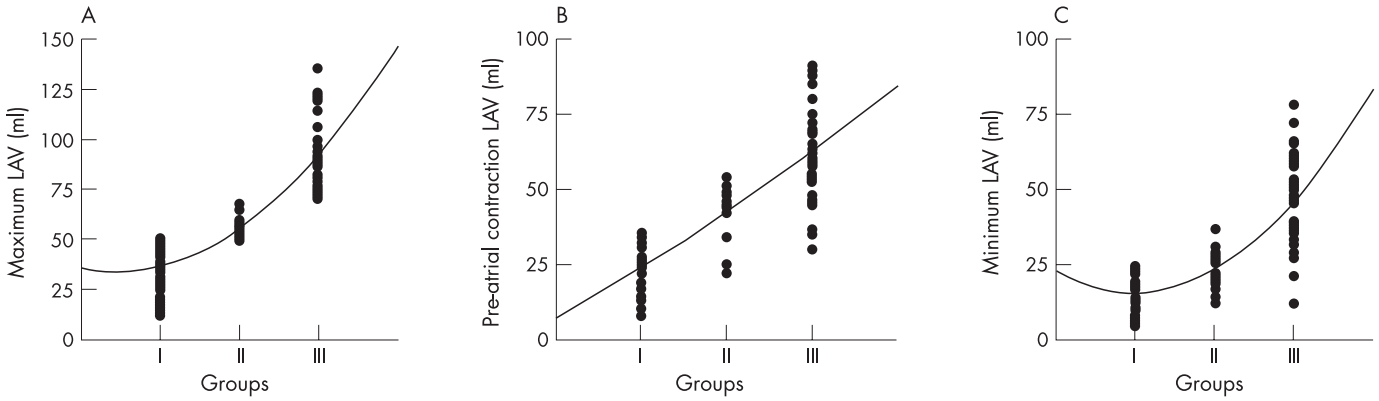

Figure 3 Left atrial volume (LAV) at three phases: (A) Maximum; (B) pre-atrial contraction and (C) minimum in the different study groups.

the increased haemodynamic load, which may prevent or delay the appearance of symptoms of heart failure.[11] Thus, evaluation of LA function in patients with heart failure will have therapeutic and prognostic value. Another clinical implication is that LA functional assessment may help as a predictor for development of atrial fibrillation and maintenance of sinus rhythm after cardioversion.[21]

LA conduit function is mainly determined by the rate of left ventricular relaxation.[22] This may explain the tendency for a reduction in passive atrial EF in group II patients, in whom LV diastolic function is impaired owing to a high incidence of hypertension and ischaemic heart disease. The increased LA conduit function in group III patients appears as a compensatory mechanism to counterbalance decreased LA pump function.[19 23] These changes in LA conduit function due to impaired left ventricular relaxation are reflected in changes in mitral inflow E/A ratio. This may explain the improvement in LA function in patients with restrictive physiology after angiotensin converting enzyme inhibitor treatment.[24]

LA reservoir function is determined by LA myocardial contraction and relaxation, and mitral annulus displacement during left ventricular contraction.[25 26] In this study there was only a non-significant decrease in LA reservoir function in patients with the largest LAV. This may be due to the multifactorial mechanisms responsible for LA reservoir dysfunction.

Study limitations

LA tracing can be problematic owing to (*a*) decreased resolution of three-dimensional imaging compared with two-dimensional imaging; (*b*) the left atrium being in the far field and (*c*) some LA walls suffering from lateral resolution by which pixels will become lines in the image display. Because the objective of our study was to prove a physiological concept rather than to demonstrate the feasibility of three-dimensional assessment for LA volumes we only included patients with good image quality in our study (representing about one-third of routinely referred patients). Because of this selection, we cannot make recommendations for the routine clinical value of LAV measurements and assessment of LAV changes. For such recommendations intra- and interobserver variabilities and the accuracy of such measurements (compared with a ''gold standard'') should be assessed in the whole spectrum of image qualities.

CONCLUSION

In this RT3DE study, the presence of a Frank–Starling mechanism was shown by an increase in LA contractility in response to an increase in LA preload up to a point, beyond which LA contractility decreased. RT3DE assessment of LAV may help in understanding LA physiology and clinical assessment.

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Conflict of interest: None declared.

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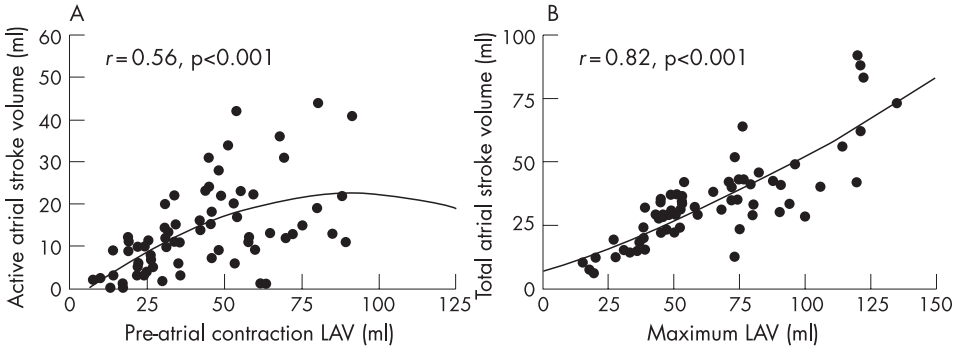

Figure 4 (A) Relation between pre-atrial contraction left atrial volumes (LAV) and active atrial stroke volume; (B) maximum left atrial volumes and total atrial stroke volume.

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Autodiagnosis of systolic dysfunction

Please visit the *Heart* website [www.heartjnl.com] for a link to the full text of this article.

Systolic dysfunction could in future be routinely diagnosed with an automated blood test, it has been disclosed, for the first time.

The automated assay for serum N terminal B type natriuretic peptide prohormone (NTproBNP) outperformed an assay for N terminal atrial natriuretic peptide prohormone (NTproANP) in a direct comparison in over 700 randomly selected patients from general practice, with echocardiography and left ventricular ejection fraction as the diagnostic benchmarks for ventricular systolic dysfunction.

It performed significantly better at all values of left ventricular ejection fraction (LVEF) and showed significantly better clinical utility in this group of patients at LVEF $\leqslant$40%—indicating definite left ventricular dysfunction—with areas under the curve in receiver-operator characteristic curves >0.9 compared with >0.7 for NTproANP.

The assay was performed in parallel with a manual assay for NTproANP on aliquoted blood samples taken from 734 patients with no known ventricular dysfunction from seven general practices in north London. Patients were aged >45 (median 58 (range 45–89)) years and comprised 349 men and 385 women. All were tested between January 2000 and December 2001.

The commercially available NTproBNP assay carries the obvious advantage of large throughput over manual assays for atrial natriuretic peptide and NTproANP currently used to determine ventricular dysfunction in high risk patients, making it potentially suitable for testing in primary care. Whether its performance was comparable, however, was until now unknown; whether it will also outperform the assay for B type natriuretic peptide remains to be seen.

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