Significant prognostic impact of improvement in ventriculo-arterial coupling induced by dobutamine stress on cardiovascular outcome for patients with dilated cardiomyopathy

Kensuke Matsumoto*, Hidekazu Tanaka, Junichi Ooka, Yoshiki Motoji, Takuma Sawa, Yasuhide Mochizuki, Keiko Ryo, Kazuhiro Tatsumi, and Ken-ichi Hirata

Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

Received 19 October 2015; accepted after revision 19 November 2015; online publish-ahead-of-print 24 December 2015

Aims
The purpose of this study was to investigate the prognostic impact of the changes in ventriculo-arterial (VA) coupling during dobutamine stress on the cardiovascular events for patients with dilated cardiomyopathy (DCM).

Methods and results
For this study, 89 DCM patients with ejection fractions of 32 ± 10% and 30 normal controls were recruited. Ees was estimated with the non-invasive single-beat method using three-dimensional echocardiography at rest and during dobutamine stress (20 μg/kg/min). Effective arterial elastance (Ea) was calculated as left ventricular (LV) end-systolic pressure divided by stroke volume, and VA coupling was calculated as Ea/Ees. Event-free survival was then tracked for 32 months. At baseline, VA coupling was far from optimal in patients with DCM compared with controls (Ea/Ees: 2.49 ± 1.02 vs. 1.04 ± 0.21, P < 0.001). During the follow-up period, 22 patients developed adverse cardiovascular events. During dobutamine stress, VA coupling was significantly improved in patients without cardiovascular events (from 2.47 ± 1.09 to 1.59 ± 0.68, P < 0.001), but remained unchanged in those with cardiovascular events. A multivariate Cox proportional-hazards analysis revealed that age, NYHA functional class (>II), and the change in VA coupling during dobutamine stress were the independent determinants of cardiovascular events (P < 0.05, <0.01, and <0.001, respectively). When patients were divided into two subgroups based on the finding of receiver operating characteristic curve analysis, patients with good VA coupling reserve (cut-off: change in VA coupling ≥0.29) showed significantly favourable event-free survival than those with poor VA coupling reserve (P < 0.001).

Conclusions
Improvement in VA coupling during dobutamine stress is an important determinant of cardiovascular outcome for patients with DCM.

Keywords
dilated cardiomyopathy • ventricular contractility • ventriculo-arterial coupling • dobutamine stress echocardiography • cardiac work efficiency • left ventricular energetics

Introduction
Although remarkable progress has been made in the development of both pharmacological and non-pharmacological approaches to treat heart failure (HF), the number of HF hospitalization and deaths has increased steadily.1 It is thus important to identify HF patients with poor prognosis who are likely to suffer clinical deterioration to improve the effectiveness of care, optimize the patient outcomes, and effectively save the overall cost by focusing resources on the high-risk patients.

Dobutamine stress echocardiography is being widely used to assess left ventricular (LV) myocardial viability and patients' prognosis, and its safety and usefulness have been well established.2–7

Although the assessment of contractile reserve is well known to be useful for the prognostic risk stratification of HF patients,2,3 analysis of wall motion, such as wall motion score index (WMSI),3

* Corresponding author. Tel: +81 78 382 5846; Fax: +81 78 382 5859. E-mail: kenmatsu@med.kobe-u.ac.jp

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2015. For permissions please email: journals.permissions@oup.com.
ejection fraction (EF), or even novel speckle-tracking strain is highly load dependent. Thus, all of these measures of LV performance could lead to misleading results. On the other hand, end-systolic ventricular elastance (Ees), the slope of the end-systolic pressure–volume relationship, is thought to be a load-independent index of myocardial contractility. And its coupling with the effective arterial elastance (Ea) is considered to be the principal determinant of net cardiovascular performance. However, the potential impact of LV contractile reserve assessed by entirely non-invasively obtained Ees and ventriculo-arterial (VA) coupling on the patients’ prognosis has not been fully investigated.

The purpose of this study was therefore to investigate the prognostic impact of the changes in VA coupling using non-invasive single-beat method during dobutamine stress on the cardiovascular outcome in patients with dilated cardiomyopathy (DCM).

Methods

Study population

This study is a substudy of our previous research investigating the relationship between bi-ventricular contractile reserve and cardiovascular prognosis in patients with DCM using dobutamine stress echocardiography. Among 120 patients recruited in the previous study, we retrospectively included 101 patients who underwent simultaneous three-dimensional (3D) echocardiography during dobutamine stress test, and 30 age- and gender-matched normal controls in this study. Six of these subjects (6%) were excluded from all subsequent analyses because of suboptimal quality of images as were six (6%) with atrial fibrillation. Exclusion criteria also included the presence of other major cardiac arrhythmias and more than moderate organic valvular disease. The final study population thus comprised 119 subjects (89 patients with DCM and 30 normal controls). The diagnosis of DCM was established on the basis of the following criteria: (i) the presence of LV dilation (LV end-diastolic diameter ≥ 55 mm); (ii) reduced LV EF (all ≤ 45%); (iii) coronary anatomic evidence of the absence of coronary artery disease defined as ≥ 50% stenosis of a major epicardial vessel or a history of myocardial infarction; (iv) the absence of cardiac muscle disease secondary to any known systemic diseases; and (v) no evidence of excessive alcohol intake, toxin exposure, or history of myocarditis. At the time of enrolment, all patients were in clinically stable condition and undergoing optimal and maximally tolerated pharmacological therapy. This study was approved by the local ethics committee of our institution, and written informed consent was obtained from all subjects.

Echocardiographic examination

Transthoracic echocardiography was performed with a commercially available ultrasound system (Aplio Artida; Toshiba Medical Systems, Tochigi, Japan). Standard LV measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging. LV ejection flow waveform was acquired from apical long-axis view by positioning the pulsed-wave Doppler sample volume just below the aortic annulus. Isovolumic contraction time (ICT) was then measured as the time between the onset of QRS wave and the aortic valve opening, and ejection time (ET) was defined as the time between the aortic valve opening and the valve closure.

All 3D echocardiographic studies were performed in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging using a 2.5-MHz 3D matrix array transducer (Toshiba Medical Systems, Tochigi, Japan). Digital 3D volume data were obtained from the apical view by means of electrocardiogram-gated acquisition at baseline and during peak dobutamine stress. After gain settings were optimized for endocardial visualization, three to four data sets were acquired and stored digitally for offline analysis. Based on the time–volume curve, LV end-diastolic (EDV) and end-systolic volumes ( ESV) and LVEF were obtained. Blood pressure and heart rate were obtained continuously throughout the echocardiographic examination.

Estimation of LV end-systolic elastance, effective arterial elastance, and VA coupling

Ees was estimated by using the non-invasive single-beat technique as previously described by Chen et al. (determined from blood pressure, stroke volume, pre-ejection and total systolic periods, LVEF, and an estimated normalized ventricular elastance at arterial end-diastole). The effective arterial elastance (Ea) was calculated as the ratio of the end-systolic pressure to the stroke volume (Ea = ESP/SV). VA coupling was then obtained as the ratio of arterial to ventricular elastance (Ea/Ees), which is considered to be the principal determinant of net cardiovascular performance. LV end-systolic pressure was estimated from arterial systolic pressure × 0.9. Systemic vascular resistance (SVR), the non-pulsatile component of afterload, was determined by dividing mean arterial pressure-5/cardiac output × 80.

Estimate of LV energetics

For simplicity, we assumed that the PV loop could be regarded as a rectangle whose height was end-systolic pressure and whose width was stroke volume (figure 1). Under the simplifying assumption, stroke work (SW) was approximated as the product of SV and end-systolic pressure. In addition, the pressure–volume area (PVA) can be defined as the sum of potential energy (PE) and SW, which has been defined by Suga et al. as the total mechanical energy required for ejection of
the blood. As an index of the energy efficiency of ventricular contraction, cardiac work efficiency was calculated as the ratio of SW to the PVA.16

Dobutamine stress test
All patients underwent dobutamine stress echocardiography in incremental stages lasting 5 min each. The initial dose was 5 μg/kg/min and was increased first to 10 μg/kg/min and finally to the maximal dose of 20 μg/kg/min.18 LV contractile reserve was defined as the absolute differences between baseline stroke volume index (SVI), cardiac index (CI), LVEF, WMSI, Ees and VA coupling, and corresponding values obtained at peak stress (ΔSVI, ΔCI, ΔLVEF, ΔWMSI, ΔEes, and ΔVA coupling, respectively). Ongoing medical therapy including β-blockers remained unchanged at the time of stress testing.

Long-term follow-up analysis
Unfavourable events were pre-specified as primary endpoints of death from or hospitalization for deteriorating HF, and sudden cardiac death. Follow-up was conducted for a median of 31.8 (16.8–52.6) months.

Statistical analyses
Continuous variables were expressed as mean values ± SD or percentages for normal distribution. For non-normally distributed data, the median and inter-quartile ranges are shown. Group comparisons were performed by using the unpaired t-test, and the paired t-test was used for comparison of continuous variables. Proportional differences were evaluated by means of Fisher’s exact test or the χ² test as appropriate. Receiver operating characteristic (ROC) curves were computed to determine the optimal cut-off points for predicting cardiovascular events. The Kaplan–Meier curve was constructed to assess cardiovascular event-free survival during the follow-up period, and event rates were compared by means of the log-rank test. The associations of clinical and echocardiographic parameters with cardiovascular events were identified by Cox proportional-hazards model for both univariate and multivariate analyses. In the selection of the univariate variables, all the established clinical and echocardiographic prognostic markers were selected as dependent variables regardless of the results of the group comparisons. Variables with a univariate value of P < 0.10 were incorporated into the stepwise selection, while age and gender were forced into the multivariate analysis regardless of their association on univariate analysis. To avoid collinearity in situations where >2 variables measured a pathophysiological parameter (e.g. LV end-systolic volume index and LV EF as markers of LV contraction), clinically more relevant parameter was entered into stepwise selection. The intra-class correlation coefficient was used to determine inter- and intra-observer reproducibilities from 10 randomly selected subjects. For all steps, a P-value of <0.05 was considered statistically significant. MedCalc 12.3.0 (MedCalc Software, Mariakerke, Belgium) was used for all statistical analyses.

Results
Long-term follow-up
Of the 89 DCM patients who met all inclusion criteria, none were lost to follow-up. During the median follow-up period of 31.8 months, 22 patients (25%) developed adverse cardiovascular events, with 2 patients dying of HF, 4 of sudden cardiac death, and the remaining 16 being hospitalized due to worsening HF.

Baseline characteristics
The baseline clinical and echocardiographic characteristics of the 89 DCM patients and 30 age- and gender-matched normal controls are summarized in Table 1. As expected, patients with DCM exhibited significant global LV remodelling along with the reduced LV contraction in comparison with normal controls. With respect to the baseline haemodynamic characteristics, baseline Ees was significantly smaller for patients with DCM. Of note was that, Ees was nearly equal to Ea in the normal control, while Ees was less than one-half of Ea in patients with DCM (1.04 ± 0.21 vs. 2.49 ± 1.02, P < 0.001). This coupling ratio resulted in increased PE (3181 ± 1484 vs. 1742 ± 514 mmHg mL/m², P < 0.001) and decreased cardiac work efficiency (46 ± 9 vs. 66 ± 9%, P < 0.001) for patients with DCM.

Dobutamine stress echocardiography
Table 2 shows the comparisons of haemodynamic and echocardiographic parameters between subgroups with and without cardiovascular events, and changes in these parameters during dobutamine stress. And group-averaged pressure–volume loops before and after dobutamine stress are schematically presented in Figure 2. As for the echocardiographic indices of LV contraction, in patients without cardiovascular events both LVEF and WMSI improved significantly along with a significant decrease in LV volumes in response to dobutamine, while these responses were blunted in patients with cardiovascular events. In terms of haemodynamic parameters, dobutamine infusion significantly increased the total mechanical energy consumption as evidenced by an increase in PVA (from 5937 ± 2107 to 7542 ± 3384 mmHg mL/m², P < 0.001). On the other hand, VA coupling improved significantly in patients without cardiovascular events (from 2.47 ± 1.09 to 1.59 ± 0.68, P < 0.001), so that cardiac work efficiency improved significantly in response to dobutamine (from 47 ± 9 to 57 ± 9%, P < 0.001) in these patients. On the other hand, VA coupling did not change at all during dobutamine stress in patients with cardiovascular events (from 2.55 ± 0.82 to 2.39 ± 0.99), so that total mechanical energy consumption increased significantly but without improvement in cardiac work efficiency (from 45 ± 8 to 47 ± 10%) for this group.

Prognostic factor of cardiovascular events
Based on the findings of ROC curve analyses, we divided the patients into two subgroups according to LVEF (ΔLVEF: cut-off value of 6.4%), Ees (ΔEes: cut-off value of 0.29 mmHg/mL), and VA coupling response (ΔVA coupling: cut-off value of 0.86), respectively. Patients with good LVEF response showed significantly favourable event-free survival than those with poor response (Figure 3A). Similarly, patients with good Ees response and good VA coupling response exhibited significantly favourable survival than the others, respectively (Figure 3B and C). When adverse cardiovascular events were restricted to only hard event (i.e. death from HF or sudden cardiac death), patients with good VA coupling response experienced significant favourable survival than the others (Figure 4A). Similarly, when adverse cardiovascular events were restricted to only soft event (i.e. hospitalization from HF), patients with good VA coupling response showed significant favourable survival than the others (Figure 4B).
The hazard ratio (HR) and 95% confidence interval (CI) for each of the variables of the univariate and multivariate Cox proportional-hazards analyses are shown in Table 3. An important finding of the multivariate analysis was that not only age and NYHA functional class but also DVA coupling (HR: 0.162, P = 0.001) were independently associated with cardiovascular events.

Feasibility and reproducibility of measurements

The feasibility of the 3D echocardiography in our study was as high as 94%. The intra-observer variability assessed in terms of intraclass correlation coefficient was 0.993 (95% CI: 0.972–0.998) for LVEF, 0.990 (95% CI: 0.959–0.998) for Ees, 0.993 (95% CI: 0.973–0.998) for Ea, and 0.991 (95% CI: 0.965–0.998) for VA coupling. The inter-observer variability for these measurements was 0.979 (95% CI: 0.915–0.995), 0.973 (95% CI: 0.891–0.993), and 0.991 (95% CI: 0.962–0.998), respectively.

The additional time required for obtaining 3D images was markedly short at 2.6 ± 0.8 min for patient, and only 3.2 ± 0.8 min was needed to analyse 3D echocardiographic data during both resting condition and during dobutamine infusion.

Discussion

The study reported here is the first to demonstrate the prognostic capability of the assessment of changes in VA coupling using 3D echocardiography.
in terms of change in the WMSI was the independent predictor of stress echocardiography and found the contractile reserve assessed et al. VA coupling proved to be highly effective for prognostic risk stratification for patients with DCM. Moreover, the quantitative assessment of changes in non-invasive single-beat method during dobutamine stress for patients with DCM. Left ventricle and vasculature were found to be effectively coupled to maximize SW (i.e. \( E_a = Ees \)) in the normal heart, while in patients with DCM, coupling ratio was far from ideal condition, which could no longer maintain SW properly and resulted in the mechanical uncoupling. In response to low-dose dobutamine, Ees, VA coupling and cardiac work efficiency improved significantly in patients without cardiovascular events, but total mechanical energy increased without improvement in cardiac work efficiency in those with cardiovascular events. Moreover, the quantitative assessment of changes in VA coupling proved to be highly effective for prognostic risk stratification for patients with DCM.

### Assessment of ventricular contractility and its inotropic reserve

Dobutamine stress echocardiography is used to assess the prognosis for HF patients and its usefulness is well recognized.\(^2\)\(^-\)\(^7\) Pratali et al.\(^1\) studied 184 patients with DCM with high-dose dobutamine stress echocardiography and found the contractile reserve assessed in terms of change in the WMSI was the independent predictor of cardiac death. On the other hand, Ramahi et al.\(^4\) have shown that an increase in LVEF during high-dose dobutamine echocardiography is a strong predictor of survival for patients with DCM, independent of the baseline value of LVEF. However, analysis of wall motion, such as WMSI\(^2\) and LVEF\(^1,4\) during dobutamine infusion, is subjective as well as highly load dependent, and its accuracy depends largely on the experience of the operators. On the other hand, we recently reported the prognostic utility of contractile reserve assessed by means of quantitative speckle-tracking strain in patients with DCM, and that contractile reserve assessed on 3D global circumferential strain was found to be a more robust prognostic parameter than that assessed by WMSI or LVEF to predict adverse cardiovascular events.\(^5\) Thus, the application of quantitative speckle-tracking echocardiography to the arena of dobutamine stress test was expected to remove the subjective nature associated with visual assessment during stress testing. In patients with HF, however, it is known that dobutamine stress has varied effects on afterload depending on the severity of HF.\(^7\) Actually, dobutamine infusion showed the heterogeneous effects on the vasculature with this relatively low-dose protocol in this study. Although SVR decreased during dobutamine stress from 1323 \(\pm\) 441 to 1096 \(\pm\) 434 dynes s/cm\(^5\) in the entire

| Table 2 | The comparisons of haemodynamic and echocardiographic parameters between subgroups with and without cardiovascular events, and changes in these parameters during dobutamine stress |
|-----------------|-----------------|-----------------|-----------------|
|                | Event free \((n = 67)\) | Event \((n = 22)\) |
|                | Baseline | Dobutamine | Baseline | Dobutamine |
| **Haemodynamics** | | | | |
| Systolic BP, mmHg | 98 \(\pm\) 16 | 128 \(\pm\) 31\(^*\) | 99 \(\pm\) 23 | 121 \(\pm\) 34\(^i\) |
| Diastolic BP, mmHg | 57 \(\pm\) 14 | 66 \(\pm\) 18\(^*\) | 55 \(\pm\) 11 | 65 \(\pm\) 18\(^i\) |
| Heart rate, bpm | 68 \(\pm\) 13 | 88 \(\pm\) 18\(^*\) | 68 \(\pm\) 13 | 85 \(\pm\) 18\(^*\) |
| Stroke volume index, mL/m\(^3\) | 41 \(\pm\) 12 | 49 \(\pm\) 14\(^*\) | 36 \(\pm\) 11 | 42 \(\pm\) 16\(^i\) |
| Cardiac index, L/min/m\(^2\) | 2.70 \(\pm\) 0.74 | 6.77 \(\pm\) 1.93\(^*\) | 2.44 \(\pm\) 0.75 | 5.49 \(\pm\) 2.25\(^*\) |
| SVR, dynes s/cm\(^5\) | 1274 \(\pm\) 386 | 1024 \(\pm\) 340\(^*\) | 1473 \(\pm\) 563 | 1317 \(\pm\) 601 |
| Ees, mmHg/mL | 0.87 \(\pm\) 0.34 | 1.44 \(\pm\) 0.52\(^*\) | 0.95 \(\pm\) 0.41 | 1.15 \(\pm\) 0.53 |
| Ea, mmHg/mL | 1.91 \(\pm\) 0.62 | 2.06 \(\pm\) 0.55 | 2.36 \(\pm\) 1.29\(^i\) | 2.50 \(\pm\) 1.07 |
| VA coupling, unit | 2.47 \(\pm\) 1.09 | 1.59 \(\pm\) 0.68\(^*\) | 2.55 \(\pm\) 0.82 | 2.39 \(\pm\) 0.99 |
| SW, mmHg mL/m\(^3\) | 2736 \(\pm\) 965 | 4306 \(\pm\) 1950\(^*\) | 2619 \(\pm\) 1317 | 3404 \(\pm\) 1790\(^*\) |
| PE, mmHg mL/m\(^3\) | 3201 \(\pm\) 1463 | 3236 \(\pm\) 1723 | 3122 \(\pm\) 1582 | 3880 \(\pm\) 2205\(^i\) |
| PVA, mmHg mL/m\(^2\) | 5937 \(\pm\) 2107 | 7542 \(\pm\) 3384\(^*\) | 5736 \(\pm\) 2730 | 7284 \(\pm\) 3721\(^i\) |
| Cardiac work efficiency, % | 47 \(\pm\) 9 | 57 \(\pm\) 9\(^*\) | 45 \(\pm\) 8 | 47 \(\pm\) 10 |
| LV volume index, mL/m\(^3\) | | | | |
| End-diastole | 96 \(\pm\) 26 | 90 \(\pm\) 28\(^i\) | 118 \(\pm\) 41\(^*\) | 113 \(\pm\) 38 |
| End-systole | 65 \(\pm\) 23 | 54 \(\pm\) 25\(^*\) | 89 \(\pm\) 40\(^i\) | 83 \(\pm\) 39 |
| LVEF (%) | 33 \(\pm\) 9 | 43 \(\pm\) 12\(^*\) | 27 \(\pm\) 13\(^*\) | 29 \(\pm\) 14 |
| WMSI | 1.99 \(\pm\) 0.22 | 1.71 \(\pm\) 0.39\(^*\) | 2.17 \(\pm\) 0.18\(^i\) | 1.98 \(\pm\) 0.37\(^i\) |

WMSI, wall motion score index. All other abbreviations as in Table 1.

\(^{*}\) \(p < 0.001\) vs. baseline.

\(^{i}\) \(p < 0.001\) vs. patients without events.

\(^{*}\) \(p < 0.001\) vs. baseline.

\(^{i}\) \(p < 0.05\) vs. baseline.

\(^{*}\) \(p < 0.01\) vs. patients without events.

\(^{i}\) \(p < 0.01\) vs. patients without events.

\(^{i}\) \(p < 0.05\) vs. patients without events.
group of the patients, dobutamine infusion reduced SVR > 10% in 57 (64%), remained unchanged in 16 (18%), and increased >10% in 16 patients (18%), respectively. Thus, conventional measures of LV contractile reserve including LVEF, WMSI, and even novel speckle-tracking strain, which are highly dependent on loading conditions, may not accurately reflect the changes in ventricular contractility during dobutamine stress.

On the other hand, the concept of contractility is an intrinsic property of ventricular contraction relatively independent of preload and afterload. Thus, one can speculate that the changes in ventricular contractility may be a more robust and reliable marker to assess true inotropic reserve. In the 1970s, Suga et al. and Sagawa established the concept of end-systolic elastance as a reliable marker of ventricular contractility. Although Ees is considered to be the theoretical gold standard of LV contractility, its clinical applicability has been limited due to its invasiveness and complex measurement procedure. To resolve these problems, several investigators have proposed single-beat estimation of end-systolic elastance without changing the loading conditions. More recently, by using two-dimensional echocardiography, completely non-invasive single-beat estimation of Ees has been advocated and validated against invasive measurements both at rest and during dobutamine stress. When an entirely non-invasive single-beat Ees is obtained, we can quantify LV end-systolic elastance and LV energetics by measuring only several easily obtainable echocardiographic parameters. In this regard, accurate and reproducible quantitative assessment of LV volumes and function are pivotal for the assessment of non-invasive single-beat method. Three-dimensional echocardiography allows more accurate quantification of LV volumes than with two-dimensional method and has an accuracy that is similar to magnetic resonance imaging.

**Importance of VA coupling and LV energetics**

The conditions for coupling of ventricular contractility with arterial load have been predicted theoretically and validated experimentally. Previous investigators clearly showed that SW is maximized when effective arterial elastance equals end-systolic elastance (i.e. Ees = Ea), whereas cardiac work efficiency is maximized when effective arterial elastance is approximately one-half of end-systolic elastance (i.e. Ees = 2Ea). In this study, the left ventricle and vasculature were observed to be effectively coupled to maximize the SW (i.e. Ees = Ea) in the normal heart, while coupling ratio was far from ideal condition, which could no longer maintain SW properly and resulted in the mechanical uncoupling in the failing heart.

During dobutamine stress, improvement in VA coupling was found to be important determinants of cardiovascular outcome for HF patients, while change in Ees and LVEF was not an independent determinant of adverse cardiovascular events. Thus, when one considers the compensatory mechanisms of the cardiovascular system, the ability to adjust VA coupling may be more important for maintaining a stable compensated condition in patients with chronic HF than the ability to augment the LV contractility in response to sympathetic stimulation. On the other hand, in patients with cardiovascular events, VA coupling did not change during dobutamine stress. As a result, dobutamine stress significantly increased total mechanical energy consumption without improvement in cardiac work efficiency.
work efficiency (i.e. ‘energy wasting effect’) in this group. This indicates that cardiac oxygen consumption would increase without improvement in cardiac work efficiency in the setting of haemodynamic stress or exertion without effective increase in cardiac output. This may be a reason why patients without VA coupling reserve experienced more cardiovascular events in this patient population.

Previous investigators used end-systolic pressure–volume ratio (i.e. ESP/ESV), as a simplified surrogate of LV end-systolic elastance, and have reported that inotropic reserve assessed by pressure–volume ratio and VA coupling can be used as a robust surrogate of LV contractile reserve and used for the risk stratification of the patients with various heart diseases.25,26 Bombardini et al.25 studied 51 patients with systolic HF who underwent exercise stress radionuclide angiography and observed LV functional reserve during stress testing. The patients who were able to increase SV during stress testing showed a decrease in arterial elastance during exercise, which lead to better VA coupling and improved cardiac efficiency. Furthermore, they also reported that event-free survival was significantly better in these patients than the others. More recently, same authors26 expanded these results to study 891 patients with negative stress echocardiography results. They demonstrated that LV end-systolic elastance assessed by pressure–volume ratio and VA coupling reserve could predict cardiac events even in patients with negative stress echocardiography. At a glance, these results appear to be similar to ours, but both the absolute values of LV end-systolic elastance and arterial elastance are more than two times higher than previously reported values27,28 for patients with systolic HF. Using invasive haemodynamic study, Ishihara et al.27 reported the changes in Ees, Ea, and VA coupling ratio during low-dose dobutamine stress for 23 patients with idiopathic DCM (mean EF 33 ± 2%). During dobutamine infusion, Ees increased from 0.80 ± 0.12 to 1.31 ± 0.13 mmHg/mL, Ea remained relatively unchanged from 2.14 ± 0.19 to 2.33 ± 0.22 mmHg/mL, and Ea/Ees ratio significantly decreased from 3.12 ± 0.43 to 1.86 ± 0.15. Although these results are quite similar to ours, it appears that pressure–volume ratio (i.e. ESP/ESV ratio) apparently overestimates the LV contractility. The reason of this overestimation of ventricular contractility may be based on the concept of pressure–volume ratio, which assumes $V_0$, the volume axis intercept at zero pressure, is negligibly small. However, as shown in the invasive haemodynamic study, $V_0$ was not negligibly small especially in HF patients with dilated failing heart.29 These results indicate that pressure–volume ratio can

Figure 3 Shown are Kaplan–Meier curves of event-free survival from the primary endpoint according to ejection fraction (LVEF) (A), Ees (B), and VA coupling response (C) during dobutamine stress.
lead to the significant overestimation of LV end-systolic elastance and can lead to misleading results especially in the patients with remodelled heart.

**Clinical implications**

In the assessment of the HF patients, the quantitative evaluation of haemodynamic condition, including the ventricular contractility, vascular tone, and also its interaction will be needed for the treatment of individual HF patients. By using non-invasive single-beat method, we can repeatedly assess the changes in LV contractility in a short time at bedside due to its fully non-invasive nature. And based on the quantitative assessment of coupling condition and LV energetics, comprehensive tailored treatment approach could serve to optimize the VA coupling to stabilize acute exacerbation, reduce readmission, enhance quality of life, and optimize HF therapy.

**Study limitations**

There are certain limitations to this study. First, this pilot study covered a relatively small number of patients in a single centre, so that further studies with larger patient populations in multicentre basis will be needed to validate our findings. Second, simultaneous invasive haemodynamic study was not performed, but the assessment of non-invasive single-beat method was previously validated in comparison with invasive measurement both at rest and during dobutamine stress.13 Third, we enrolled chronic HF patients with reduced EF using the arbitrary cut-off point of LVEF ≤45% in this study. Although the cut-off of LVEF 40% or less is generally applied in the majority of similar studies dealing with HF with reduced EF, there is no consensus about the optimal cut-off value of LVEF for the diagnosis of this group of patients. We believe that cut-off value of LVEF for patient enrolment would not have a significant effect on the overall results of this study. Finally, β-blockers were left unchanged in all patients during dobutamine stress. Although this may have affected the response to dobutamine infusion, ethical

![Figure 4](https://example.com/figure4.png)

**Figure 4** Shown are Kaplan–Meier curves of event-free survival from hard events (death from heart failure or sudden cardiac death) (A) and soft events (HF hospitalization) (B) in patients with good or poor VA coupling response during dobutamine stress, respectively.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Univariate and multivariate Cox proportional-hazards analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
<td><strong>Univariate analysis</strong></td>
</tr>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td><strong>Clinical variables</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.036</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.487</td>
</tr>
<tr>
<td>NYHA functional class (&gt;II)</td>
<td>3.315</td>
</tr>
<tr>
<td>Serum BNP concentration (pg/mL)</td>
<td>5.609</td>
</tr>
<tr>
<td><strong>Echocardiographic variables</strong></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic volume index (mL/m²)</td>
<td>1.017</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.942</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>1.036</td>
</tr>
<tr>
<td><strong>Variables under dobutamine stress</strong></td>
<td></td>
</tr>
<tr>
<td>ΔSVI (mL/m²)</td>
<td>0.965</td>
</tr>
<tr>
<td>ΔLVEF (%)</td>
<td>0.890</td>
</tr>
<tr>
<td>ΔWMSI</td>
<td>0.376</td>
</tr>
<tr>
<td>ΔEes (mmHg/mL)</td>
<td>0.010</td>
</tr>
<tr>
<td>ΔVA coupling</td>
<td>0.128</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidential interval.
All other abbreviations as in Table 1.
Conflict of interest: none declared.

Conclusions

Improvement in VA coupling during dobutamine stress was identified as an important determinant of cardiovascular outcome for patients with DCM. The quantitative assessment of VA coupling reserve using 3D non-invasive single-beat method may thus lead to better management of these patients.

References