Increase in end-systolic volume after exercise independently predicts mortality in patients with coronary heart disease: data from the Heart and Soul Study

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Aims
The predictive value of changes in global left ventricular (LV) size after exercise has not been studied. Left ventricular end-systolic volume (ESV) is a relatively load-independent echocardiographic marker of contractility that is easily measured. We investigated the role of the change in ESV at rest and after peak exercise on mortality among patients with stable coronary heart disease (CHD).

Methods and results
We performed exercise treadmill testing with stress echocardiography in 934 ambulatory subjects with CHD. End-systolic volume was measured immediately before and after exercise using 2D echocardiography. We defined ESV reversal as an increase in ESV after exercise, and we examined the association of ESV reversal with all-cause mortality during a median follow-up of 3.92 years. Of the 934 participants, 199 (21%) had ESV reversal. At the end of follow-up, mortality was higher among participants with ESV reversal than those without (26 vs. 11%; P = 0.001). After adjustment for clinical covariates, ESV reversal remained predictive of all-cause mortality (HR 2.0; 95% CI 1.4–2.9; P = 0.001). The association of ESV reversal with mortality also persisted after adjustment for exercise-induced wall-motion abnormalities (HR 1.7; 95% CI 1.1–2.3, P = 0.006). To determine if the effect of ESV reversal was independent from other echocardiographic measurements, we created a separate model adjusting for resting LV ejection fraction, ESV, end-diastolic volume, and LV mass. End-systolic volume reversal was the only significant predictor of mortality in this model (HR 2.1, 95% CI 1.4–3.0, P < 0.001).

Conclusion
End-systolic volume reversal is a novel parameter that independently predicts mortality in patients with CHD undergoing exercise treadmill echocardiography, even after adjustment for a wide range of clinical, echocardiographic, and treadmill exercise variables. Because measurement of ESV is simple, reproducible, and requires no additional imaging views, identification of ESV reversal during exercise echocardiography can provide useful complementary information for risk stratification.

Keywords
Ischaemic heart disease • Exercise stress testing • Exercise echocardiography • Risk stratification

Introduction
Left ventricular end-systolic volume (LVESV) is a marker of ventricular contractility that is relatively insensitive to loading conditions. End-systolic volume is also an indicator of remodelling after myocardial necrosis, such as from infarction,¹² and the association of resting LVESV to mortality and incident heart failure is known.³⁴ After myocardial infarction (MI), LVESV has greater predictive

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value then ejection fraction (EF) or end-diastolic volume (EDV), and EF and LVEDV do not confer added prognostic value. These findings are also demonstrated in subjects with normal EF.

Change in ventricular size in response to alterations in loading conditions may provide useful information regarding cardiac function. In the normal heart, exercise leads to both increased contractility and afterload, resulting in a normal physiologic decrease in ESV. A failure to appropriately decrease ESV with exercise may reflect afterload-contractility mismatch due to ischaemia, systolic dysfunction, or HF. End-systolic volume is easy to measure using 2D echocardiography, has low interobserver variability, and most modern echocardiography machines can calculate volumes from 2D measurements.

However, the predictive value of the magnitude of change in LV volume with exercise has not been studied. We hypothesized that changes in ESV before and after exercise treadmill testing independently predict mortality and provide incremental prognostic value in patients with stable coronary artery disease.

Methods

Participants

The Heart and Soul Study is an ongoing prospective cohort study designed to determine how psychosocial factors affect health outcomes in patients with coronary artery disease. A total of 1024 patients were enrolled between September 2000, and December 2002, from two Veterans Affairs Medical Centers (San Francisco and Palo Alto, CA, USA), one university-based medical centre (University of California, San Francisco, CA, USA), and nine public health clinics in the Community Health Network in San Francisco. Eligible participants had at least one of the following: (i) history of MI, (ii) angiographic evidence of ≥50% stenosis in ≥1 coronary vessels, (iii) evidence of exercise-induced ischaemia by treadmill ECG or stress nuclear perfusion imaging, or (iv) a history of coronary revascularization. Participants were excluded from the Heart and Soul Study if they were unable to walk one block, had an MI within the previous 6 months, or were planning to move from the local area within 3 years. Of the 1024 study participants, 934 (91.2%) had complete stress echocardiographic measurements and are the subjects of this secondary data analysis. The remaining 90 participants (8.8%) were not able to complete treadmill exercise testing for orthopaedic or mechanical reasons. The research protocol was approved by the appropriate institutional review boards and all participants provided written, informed consent. Details regarding methods and study design have been previously published.

Measurements

Predictor variable

Complete resting and post-stress 2D echocardiograms with Doppler imaging were performed by two trained and experienced echocardiographers using a standardized protocol on one of three identical cardiac ultrasound systems with a 3.5 MHz transducer (Acuson Sequoia Ultrasound System, Mountain View, CA, USA). Echocardiographic images of the LV were obtained at rest immediately prior to exercise and in early recovery (within 1 min after peak exercise) according to a research protocol based on American Society of Echo-cardiography (ASE) guidelines. A single experienced reader (NBS) blinded to the clinical history, physical examination, laboratory data, stress test results, and outcome variables, interpreted all echocardiograms and verified the measurements used for calculation of ventricular volumes. Left ventricular ESV was calculated using the biplane method of discs (modified Simpson's rule) at end-systole in apical four-chamber and apical two-chamber views as recommended by the ASE and as has been validated elsewhere.

Other variables

Each participant underwent a symptom-limited graded exercise treadmill test according to a standard Bruce protocol. To achieve maximum heart rate, participants who were unable to continue the standard Bruce protocol (due to orthopedic or other reasons) were switched to slower settings on the treadmill and encouraged to exercise for as long as possible. Continuous 12-lead electrocardiographic monitoring was recorded during testing, and exercise capacity was calculated as total metabolic equivalent tasks (METs) achieved at peak exercise (1 MET = 3.5 mL of oxygen uptake per kilogram of body weight per minute). For participants who required modification of the Bruce protocol, exercise capacity was determined as total METs achieved at peak exercise. These subjects were included in all analyses. After achieving maximal workload, subjects were immediately placed supine on an exam table, and echocardiographic images were obtained within 60 s after completion of treadmill testing. Heart rate was measured 1 min after termination of exercise to compensate for the effects of physiological venous blood redistribution in the immediate post-exercise period.

Ejection fraction at rest and post-stress was calculated as: [end-diastolic volume – end-systolic volume]/[end-diastolic volume]. We calculated a wall motion score index after peak exercise using the following method. Each of the 16-wall segments in the LV was scored on the basis of contractility after exercise, (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, 5 = aneurysm, 0 = not visualized). The wall motion score index was defined as the sum of all segmental wall motion scores divided by the number of segments visualized. A normally contracting LV thus received a wall motion score index of one (16/16), with higher wall motion score indices representing worse contractility.

Outcomes

The primary outcome was time to death. We conducted annual, scheduled telephone follow-up interviews with participants or their proxy to inquire about death. The last date of follow-up was 5 April 2006. For any reported event, medical records, death certificates, and coroner’s reports were retrieved and reviewed by two independent and blinded adjudicators. If the adjudicators agreed on the outcome classification, their classification was binding. If they disagreed, they conferred, reconsidered their classification, and requested consultation from a third-blinded adjudicator as necessary.

Statistical analysis

The primary predictor variable was the change in ESV with exercise, defined as the difference between resting and post-stress ESV (ESV_change = ESV_rest – ESV_stress). We also created a binary predictor that indicated an abnormal increase in ESV after exercise (ESV reversal). Normally, ESV decreases with exercise due to enhanced contractility, augmented stroke output, and shorter diastolic filling time. End-systolic volume reversal was defined as ESV_change < 0 (ESV_stress > ESV_rest).

Differences in baseline characteristics between patients with and without ESV reversal were compared using chi-square tests for categorical variables and the Student’s t-test for continuous variables. Cumulative event-free survival was measured by the method of
Kaplan–Meier, and unadjusted differences were compared using the log-rank test. To assess the independent value of ESV on mortality, we performed Cox regression analysis and adjusted for baseline variables. All variables that had an unadjusted association with ESV reversal and \( P < 0.1 \) were included on our models. We also included pre-specified covariates that were selected on the basis of face validity. Using this strategy, we created pre-specified nested models to assess the incremental prognostic value of ESV reversal adjusting for clinical variables, wall motion abnormalities, wall motion score, and parameters of treadmill testing. To determine the independent effect of ESV reversal with respect to other echocardiographic parameters, we created a separate multivariate model adjusting for other echocardiographic measurements selected on the basis of face validity. For all Cox regression models, the assumption of proportional hazards was found to be valid by using the log-minus-log curves and the Schoenfeld test. We verified the log-linearity assumption by adding quadratic and cubic terms of ESV change to the model, which did not significantly improve the fit of the model by post-estimation likelihood ratios. This confirmed that the log-linear model adequately represented the association between ESV change and time to death. All statistical tests were two-sided, and a \( P \)-value of \( < 0.05 \) was considered significant. Statistical analyses were performed using STATA 9.0 (College Station, TX, USA). The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

**Results**

Among the 934 participants, ESV change was normally distributed, with a mean of 6.4 ± 12 mL. End-systolic volume reversal was present in 21% of the cohort (Figure 1). The mean EF was 62 ± 10%, and the resting EF was normal (≥55%) in 82% of subjects. Baseline characteristics are shown in Table 1. Subjects with ESV reversal were older and had higher baseline rates of diabetes, prior MI, angiotensin blockade use, and beta-blocker use. They also had higher baseline ventricular volumes, LV mass, and stress and resting wall motion scores. Subjects with ESV reversal also had lower exercise workload, one-minute and peak heart rates, and systolic blood pressure. There were no differences in mean body mass index, EF, or the proportion with heart failure, prior revascularization, ST changes with exercise, or angina with exercise.

During a median follow-up of 3.92 years (interquartile range 2.99–4.06 years), there were 132 deaths (14% of cohort). A mean adjusted locally weighted time series (LOWESS) plot revealed a threshold effect near the point at which stress ESV exceeded resting ESV (ESV reversal; Figure 2). Of note, risk ratios using a cutoff at the inflection point on this graph at ESV change = 4 cc were similar to those using a cutoff of 0 cc (ESV reversal). We therefore chose ESV reversal as our binary cut point for simplicity.

Mortality was higher in the group with ESV reversal compared with those without ESV reversal (26 vs. 11%, \( P < 0.001 \)). Univariate and sex- and age-adjusted models showed that ESV reversal predicted mortality (Table 2) in univariate (HR 2.3; 95% CI 1.6–3.2, \( P < 0.001 \)) and sex- and age-adjusted (HR 2.1; 95% CI 1.5–3.0; \( P < 0.001 \)) models. After adjustment for age, sex, hypertension, diabetes, heart failure, prior MI, and medical therapy, ESV reversal remained significantly associated with mortality (Table 2, adjusted HR 2.0; 95% CI 1.4–2.9; \( P < 0.001 \)). For each standard deviation (12 cc) increase in ESV with exercise, the adjusted relative hazard of death increased by 19% (HR 1.19; 95% CI 1.01–1.40; \( P = 0.039 \)).

We created additional incremental models to determine if the association of ESV reversal with mortality was independent from other measurements obtained in routine stress echocardiography. After adjustment for clinical variables and the presence of any new wall motion abnormality, the association between ESV reversal and mortality remained significant (adjusted HR 1.7; 95% CI 1.1–2.3; \( P = 0.006 \)). Adjusted Kaplan–Meier estimates for this model demonstrate a separation of survival curves within the first several months of follow-up and continue to diverge until the end of follow-up (Figure 3). The findings were similar when adjusted for a change in wall motion score (adjusted HR 1.6; 95% CI 1.04–2.4; \( P = 0.01 \)) in addition to clinical variables. In both of these models, addition of ESV reversal as a binary predictor significantly improved the fit of the multivariate models by likelihood ratio chi-square testing (\( P < 0.05 \) for all).

These findings remained consistent when adjusting for exercise data. After adjustment for clinical variables, total workload (METs), one-minute HR recovery (\( \text{HR}_{\text{peak exercise}} - \text{HR}_{\text{one-minute post exercise}} \)), presence of angina with exercise, presence of ST changes with exercise, and peak systolic blood pressure, ESV reversal remained associated with mortality (adjusted HR 1.5; 95% CI 1.01–2.2; \( P = 0.05 \)) and provided added prognostic value (\( P = 0.05 \) for LR chi-square test).

We also created a separate model to determine if the effect of ESV reversal was independent from other resting echocardiographic measurements (Table 2). After adjustment for LV EF, resting ESV, baseline EDV, and LV mass, ESV reversal remained predictive of mortality (adjusted HR 2.1; 95% CI 1.5–3.0; \( P < 0.001 \)).
In the subgroup of patients with normal resting EF (≥55%), ESV reversal remained a significant predictor in most multivariate models (Table 2). Of note, in univariate analysis, ESV reversal did not predict the presence of ST segment changes ≥1 mm with exercise.

**Discussion**

The principal finding of this observational study is that in patients with stable coronary heart disease (CHD), undergoing exercise treadmill echocardiography ESV reversal after exercise is associated with increased mortality, even after adjustment for cardiovascular risk factors, heart failure, MI, medical therapy, and abnormal stress test and echocardiographic findings. Addition of ESV reversal as a predictor added significant prognostic value to clinical, treadmill, and echocardiographic multivariate models.

Multiple large observational studies have demonstrated that the detection of exercise-induced wall motion abnormalities or changes in wall motion score index provide incremental prognostic value to stress electrocardiography parameters. However,
few studies have examined stress-induced changes in post-exercise LV end-systolic size. In a study of patients with abnormal echocardiograms and normal exercise, end-systolic size, as determined visually from 2D echo view was associated with cardiovascular events, but did not confer added prognostic value to treadmill ECG variables. Another pair of studies examined LV end-systolic size. In a study of patients with abnormal echocardiograms and normal exercise, end-systolic size, as determined visually from 2D echo view was associated with cardiovascular events, but did not confer added prognostic value to treadmill ECG variables.

Table 2  Association of end-systolic volume reversal with all-cause mortality

<table>
<thead>
<tr>
<th>Unadjusted (univariate analysis)</th>
<th>Entire cohort (n = 934)</th>
<th>EF ≥ 55% (n = 773)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Unadjusted (univariate analysis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>2.3 (1.6–3.2)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for clinical variables (age, sex, HTN, diabetes, HF, previous MI, ACE/ARB, statin, and beta-blocker use)</td>
<td>2.1 (1.5–3.0)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for clinical variables above and presence of exercise wall motion abnormality</td>
<td>2.0 (1.4–2.9)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for clinical variables above and exercise wall motion score</td>
<td>1.7 (1.1–2.3)*</td>
<td>0.006</td>
</tr>
<tr>
<td>Adjustment for clinical variables above and exercise wall motion score</td>
<td>1.6 (1.04–2.4)*</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjustment for clinical variables above and treadmill test variables [total workload (METs), one-minute HR recovery, presence of angina with exercise, presence of ST changes with exercise, and peak systolic blood pressure]</td>
<td>1.5 (1.01–2.2)*</td>
<td>0.05</td>
</tr>
<tr>
<td>Adjustment for echo variables (resting EF, resting end-diastolic volume, resting ESV, LV mass)</td>
<td>2.1 (1.5–3.0)*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HTN, hypertension; HF, heart failure; MI, myocardial infarction; ACE/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker.

*For these models, ESV reversal added significant incremental prognostic value than (P-value of LR chi-square < 0.05 for all).

Several studies have suggested that stress-induced changes in ESV may be a more sensitive indicator of myocardial ischaemia and can be more easily assessed than EF. Stress-induced ESV reversal is associated with a higher risk of cardiovascular events, even in patients with normal EF. In our study, ESV reversal was a stronger predictor of adverse outcomes than EF.

Figure 3  Proportion surviving in 934 participants with CAD, stratified by change in end-systolic volume with exercise (adjusted for age, sex, HTN, diabetes, HF, previous MI, use of ACE/ARB, statin, or beta-blocker, and the presence of an exercise-induced wall motion abnormality).

One explanation is that ESV reversal may be a more sensitive indicator of myocardial ischaemia and can be more easily assessed than EF. Stress-induced ESV reversal is associated with a higher risk of cardiovascular events, even in patients with normal EF. In our study, ESV reversal was a stronger predictor of adverse outcomes than EF.

Another explanation is that ESV reversal may be a more sensitive indicator of myocardial ischaemia and can be more easily assessed than EF. Stress-induced ESV reversal is associated with a higher risk of cardiovascular events, even in patients with normal EF. In our study, ESV reversal was a stronger predictor of adverse outcomes than EF.

Finally, assessment of change in EF requires measurement of ESV and EDV at rest and post-stress. Calculation of ventricular volumes requires manual tracing of endocardial contours in two apical...
views. Therefore, as these values are summed and multiplied to calculate EF, any measurement error is compounded. This may lead to a greater standard error of measurement for EF than for ESV and, in turn, lead to a stronger association between ESV and mortality. Furthermore, because of the consolidation of the ventricular mass and architecture in systole, endocardial boundaries in end-systole tend to be easier to visualize than in diastole.

Limitations

This is an observational study. Confounding due to unidentified factors may be present. Our modelling approach was to create incremental models with larger and larger sets of variables to demonstrate the persistent association between ESV reversal and mortality. Although the association between ESV reversal and mortality was still significant in our largest (15-variable) model, adjustment with multiple interrelated variables could result in model over-fitting.

Since the ability to walk one block was an inclusion criterion, subjects with poor functional status are underrepresented. Treadmill testing with echocardiography was used to measure ESV reversal, and 8.8% of the cohort could not complete treadmill testing for mechanical or orthopaedic reasons. Since we could not assess ESV in patients who did not undergo treadmill testing, these patients were excluded from the analysis. Therefore, our findings may not be generalizable to patients undergoing other mechanical or pharmacological stress testing methods, or to other imaging modalities. Patients with very large ventricular volumes, or very low EF are underrepresented. However, this may be a relative strength, since ESV reversal had significant prognostic value even in patients with normal EF and ambulatory functional status. Almost half of subjects were enrolled at Veterans Affairs medical centres, which could limit generalizability, especially to women. Volumetric measurements were performed by three skilled sonographers. If these measurements are performed by less-experienced technicians or at a different time-point after exercise, then increased measurement error and variability may attenuate the observed associations, thus limiting reproducibility.

In summary, ESV reversal is a novel parameter that is an independent predictor of mortality in patients with CHD, even after adjustment for a wide range of clinical, echocardiographic, and treadmill exercise variables. End-systolic volume reversal provides significant incremental prognostic value to clinical, echocardiographic, and haemodynamic parameters. Since ESV is easy to measure, requires no additional imaging views, and is highly reproducible,9,10 identification of ESV reversal can provide complementary information for risk stratification in patients with CHD undergoing stress echocardiography.

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Conflicts of interest: none declared.

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