Effect of improvement in left ventricular ejection fraction on long-term survival in revascularized patients with ischaemic left ventricular systolic dysfunction

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Aims

The importance of improvement in the ejection fraction to the prognosis of revascularized patients with ischaemic left ventricular (LV) dysfunction is uncertain.

Methods and results

Eighty-seven patients with ischaemic LV dysfunction (mean ejection fraction 29 ± 8% by biplane Simpson’s) had dobutamine echocardiography before revascularization (coronary bypass graft surgery-81, percutaneous intervention-6). Follow-up echocardiograms were performed a mean of 4.8 ± 6.2 months after revascularization. An 8% increase in the ejection fraction was considered significant (two times the inter-observer difference of 3.7%). Patients were followed for cardiac death. During a mean follow-up of 5.2 ± 3.9 years, there were 20 (23%) cardiac deaths. Class 3/4 heart failure, increasing low-dose wall motion score, increasing % non-viable myocardium, and digoxin use in follow-up were univariate predictors of death. Beta-blocker use, ejection fraction improvement, angina, aspirin use, and increasing fractional shortening were univariate predictors of survival. Ejection fraction improvement (P = 0.02, hazard ratio (HR) = 0.26), digoxin use in follow-up (P = 0.006, HR = 5.85), and low-dose wall motion score (P = 0.017, HR = 4.78) were independent predictors of outcome. In step-wise analysis, low-dose wall motion score added incremental prognostic value to ejection fraction improvement (P = 0.003), and digoxin use in follow-up (P = 0.003) added incremental value to a low-dose score and ejection fraction improvement.

Conclusion

Ejection fraction improvement is an independent predictor of long-term outcome in revascularized patients but viability (low-dose wall motion score) and digoxin use in follow-up are also independent predictors and add incremental prognostic value to ejection fraction improvement.

Keywords

Ejection fraction improvement • Prognosis • Revascularization • Ischaemic cardiomyopathy

Introduction

Global left ventricular (LV) function as measured by the ejection fraction is one of the most important determinants of prognosis in patients with ischaemic cardiomyopathy.1 There is a direct relationship between declining ejection fraction and increasing mortality. LV dysfunction is a potentially reversible phenomenon when it is related to acute ischaemia, myocardial stunning, or hibernation or a combination of these processes. Many studies have shown that revascularization can improve LV function in patients with viability and ischaemic dysfunction, and many other studies have shown that patients with viable myocardium and ischaemic LV dysfunction have improved outcome with revascularization.2–7 However, there is conflicting evidence about whether improvement of LV function with revascularization is necessary for improved outcomes. Several studies have shown that improvement of ejection fraction with revascularization is associated with a lower risk of cardiac events over short-term follow-up but several other studies have shown no difference in cardiac mortality between those with and without improvement in ejection fraction.2–6

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The majority of previous studies has been limited by relatively short-term follow-up, have generally focused on combined cardiac events rather than mortality, and have not taken into account the effect of medical and device therapy on the outcome. Additionally, the relative prognostic value of ejection fraction improvement has not been adequately compared with the prognostic importance of other factors known to affect the outcomes of revascularized patients with ischaemic LV dysfunction.

In this study, we evaluated the impact of ejection fraction improvement on the long-term mortality of revascularized patients with ischaemic cardiomyopathy and compared the prognostic value of ejection fraction improvement with other factors affecting the outcome of these patients.

Methods

Patient selection

The study was approved by the Indiana University Institutional Review Board. Informed consent was not required for all subjects as follow-up was primarily retrospective. The study included patients with ischaemic LV dysfunction [reduced ejection fraction (<50%) and regional wall motion abnormalities in ≥25% of the myocardium] who had dobutamine echocardiography before revascularization. Out of 140 eligible patients, 102 had follow-up echocardiograms after revascularization. Fifteen of the 102 patients were excluded because of aortic valve replacement at the time of revascularization, unstable clinical status at the time of follow-up echocardiography, or performance of echocardiography >2 years after revascularization. The final study group was composed of 87 patients. Out of 87 patients, 81 patients underwent revascularization with coronary artery bypass graft surgery (CABG) and 6 patients underwent percutaneous coronary intervention.

Echocardiography

Dobutamine was administered beginning at a dose of 5 μg/kg/min for 3 min followed by a dose of 10 μg/kg/min for 3 min. Thereafter, the dose was increased by 10 μg/kg/min increments every 2–3 min to a peak dose of 50 μg/kg/min. Echocardiograms were recorded and digitally stored at rest, at the end of the 5 and 10 μg/kg/min stages, and at peak dose.

All echocardiograms were analysed from the digitally stored images by at least one investigator blinded to the clinical, angiographic, stress testing, and follow-up data. Wall motion and thickening were assessed in 16 segments using a previously described scoring system. Dysfunctional segments exhibiting improvement in wall motion or thickening by one grade from rest to 5 or 10 μg/kg/min of dobutamine were considered viable. Segments that were akinetic or dyskinetic at rest and remained without improvement at 5 and 10 μg/kg/min were defined as ‘nonviable’. Segments that exhibited worsening of wall motion at any stage of the examination were defined as ‘ischaemic’ (except akinesis to dyskinesis). For each patient, the per cent of myocardium with normal wall motion at rest, ‘viable’ (dysfunctional with improvement at low dose), ‘non-viable’ ( akinetic at rest without improvement at low dose), and ‘ischaemic’ were determined. In each patient, the presence or absence of viability (improvement with low dose) in four or more segments with resting dysfunction was also determined.

Wall motion scores at rest, at 10 μg/kg/min (designated as low dose), and at peak dose were obtained by dividing the sum of individual segment scores by the number of segments scored.

For each patient, the ejection fraction at rest was calculated by Simpson’s biplane method from the resting images of the dobutamine study and on the follow-up study by an investigator blinded to the results of dobutamine echocardiography and follow-up. Inter-observer variability was assessed using measurements performed by a second observer and found to be 3.7% absolute ejection fraction points. Therefore, significant ejection fraction improvement was defined as an increase in the ejection fraction of ≥8% (two times the inter-observer variability). Two-dimensional echocardiographic measurements were performed according to previously published guidelines. Basal fractional shortening was determined from measurements of LV diastolic dimension and LV systolic dimension made at the level of the mitral leaflet tips using the parasternal long-axis view.

Follow-up

Follow-up was primarily retrospective and performed by medical record review and telephone interview. Medications during follow-up after revascularization were determined from clinic records. Cardiac death was the end point of the study. This was defined as death due to intractable congestive heart failure (CHF), myocardial infarction, ventricular arrhythmia, or sudden death within 1 h of symptom onset without an obvious non-cardiac cause.

Statistical analysis

Multivariate logistic regression analysis using a forward selection method was used to identify echocardiographic predictors of ejection fraction improvement. Cox proportional hazard model was used to determine univariate predictors of cardiac death with a P-value of <0.05 considered statistically significant. Multivariate analysis was done with a forward selection method including all univariate predictors. Step-wise analysis was performed using multivariate predictors of cardiac death. The agreement between digoxin use in follow-up and the severity of heart failure and ejection fraction improvement were determined by the Kappa statistic. Survival was compared between patients with and without significant improvement in the ejection fraction by the Kaplan–Meier method and log rank test. Statistical analysis was performed with SPSS version 17.0 (Chicago, IL, USA).

Results

Patient population

Clinical characteristics of the patient population are shown in Table 1. The mean age was 59 ± 10 years and the mean ejection fraction was 29 ± 8%. There were 26 (30%) females and 36 (41.4%) had NYHA class 3/4 heart failure. Seventy (80.5%) had multi-vessel disease (≥50% stenosis of two or more major epicardial coronary arteries). CABG was performed in 81 patients (93%) and 6 had percutaneous revascularization. Out of 81 patients who underwent coronary artery bypass grafting, 76 (93.8%) patients had internal mammary artery grafts. Complete revascularization (grafts to each vessel with significant stenosis) was performed in 74.7% of the patients.

Ejection fraction improvement and follow-up

Forty-two patients (48%) had improvement of the ejection fraction with revascularization and 45 patients had no significant improvement. Multivariate logistic regression analysis showed that the %
of ischaemic myocardium \( P = 0.029 \) [hazard ratio 0.970 (0.943–0.997)] was the only independent predictor of ejection fraction improvement. Measures of viability such as low-dose score, % of viable myocardium, and viability (augmentation) in four or more segments with dysfunction were not predictive of ejection fraction improvement. The patients were followed for a mean duration of 5.2 ± 3.9 years. Echocardiograms were performed a mean of 4.8 ± 6.2 months after revascularization. There were 20 (23%) cardiac deaths during the follow-up period with 70% (14 of 20) of the deaths due to heart failure.

### Table 1  Clinical characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n = 67)</th>
<th>Cardiac death (n = 20)</th>
<th>( P )-value</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.9 ± 10.5</td>
<td>62.4 ± 8.3</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Gender (males)</td>
<td>61 (70%)</td>
<td>16 (80%)</td>
<td>0.232</td>
<td></td>
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<tr>
<td>Diabetes</td>
<td>40 (46%)</td>
<td>9 (45%)</td>
<td>0.955</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>58 (66.7%)</td>
<td>12 (60%)</td>
<td>0.963</td>
<td></td>
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<tr>
<td>Hyperlipidaemia</td>
<td>54 (62.1%)</td>
<td>10 (50%)</td>
<td>0.342</td>
<td></td>
</tr>
<tr>
<td>Tobacco use</td>
<td>57 (65.5%)</td>
<td>16 (80%)</td>
<td>0.200</td>
<td></td>
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<tr>
<td>Family h/o CAD</td>
<td>48 (55.2%)</td>
<td>9 (45%)</td>
<td>0.288</td>
<td></td>
</tr>
<tr>
<td>Prior CABG</td>
<td>45 (67.6%)</td>
<td>16 (80%)</td>
<td>0.364</td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>44 (50.6%)</td>
<td>10 (50%)</td>
<td>0.199</td>
<td></td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>46 (65.7%)</td>
<td>10 (50%)</td>
<td>0.342</td>
<td></td>
</tr>
<tr>
<td>LAD disease</td>
<td>43 (61.2%)</td>
<td>6 (30%)</td>
<td>0.200</td>
<td></td>
</tr>
<tr>
<td>CHF class 3/4</td>
<td>30 (46%)</td>
<td>13 (65%)</td>
<td>0.004</td>
<td>3.99 (1.56–10.21)</td>
</tr>
<tr>
<td>Angina prior to revasc</td>
<td>53 (79.1%)</td>
<td>11 (55%)</td>
<td>0.038</td>
<td>0.39 (0.16–0.95)</td>
</tr>
<tr>
<td>ASA in FU</td>
<td>59 (88.05%)</td>
<td>15 (75%)</td>
<td>0.011</td>
<td>0.26 (0.09–0.73)</td>
</tr>
<tr>
<td>Digoxin use in FU</td>
<td>23 (36.5%)</td>
<td>16 (80%)</td>
<td>&lt;0.001</td>
<td>6.75 (2.25–20.26)</td>
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<tr>
<td>BB use in FU</td>
<td>50 (74.6%)</td>
<td>8 (40%)</td>
<td>0.002</td>
<td>0.24 (0.09–0.60)</td>
</tr>
<tr>
<td>ACE-I in FU</td>
<td>55 (82.08%)</td>
<td>16 (80%)</td>
<td>0.915</td>
<td></td>
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<tr>
<td>CCB in FU</td>
<td>15 (22.4%)</td>
<td>4 (20%)</td>
<td>0.483</td>
<td></td>
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<tr>
<td>Statin in FU</td>
<td>49 (73.1%)</td>
<td>11 (55%)</td>
<td>0.15</td>
<td></td>
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<tr>
<td>Nitrates in FU</td>
<td>37 (55.2%)</td>
<td>10 (50%)</td>
<td>0.478</td>
<td></td>
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<tr>
<td>Aldosterone anta in FU</td>
<td>11 (16.4%)</td>
<td>4 (20%)</td>
<td>0.589</td>
<td></td>
</tr>
<tr>
<td>ICD in FU</td>
<td>7 (10%)</td>
<td>4 (20%)</td>
<td>0.396</td>
<td></td>
</tr>
</tbody>
</table>

ASA in FU, aspirin use in follow-up; Aldosterone anta in FU, aldosterone antagonist use in follow-up; CCB in FU, calcium channel blocker use in follow-up; CI, confidence intervals; HR, hazard ratio; ICD in FU, implanted cardioverter-defibrillator implantation during follow-up; Revasc, revascularization. Rest of the abbreviations as per Table 1.

### Table 2  Clinical characteristics of survivors and patients with cardiac death

Univariate clinical and echocardiographic predictors of outcome

Clinical predictors of cardiac death are shown in Table 2. Advanced heart failure (NYHA class 3/4) and digoxin use in follow-up were univariate predictors of death. Beta-blocker use in follow-up, angina prior to revascularization, and aspirin use in follow-up were predictive of survival. Among echocardiographic variables (Table 3), an increasing low-dose wall motion score and increasing % non-viable (akinetic at low dose) myocardium were univariate predictors of death. Increasing fractional shortening and ejection fraction improvement were predictive of survival.

### Multivariate analysis

The results of multivariate analysis are shown in Table 4. Ejection fraction improvement (\( P = 0.003 \)) was an independent predictor of survival. Increasing low-dose wall motion score (\( P = 0.006 \)) and digoxin use in follow-up (\( P = 0.017 \)) were independent predictors of cardiac death. There was fair agreement between the presence of Class 3/4 heart failure and digoxin use in follow-up.
There was also a fair agreement between digoxin use in follow-up and lack of improvement in the ejection fraction ($P = 0.05$, Kappa $= 0.221$).

Long-term survival in patients with and without ejection fraction improvement

Figure 1 compares survival in patients with significant improvement in the ejection fraction and patients without significant improvement in the ejection fraction. Survival curves begin to diverge after 2.5 years of follow-up. Survival was maintained at 89% through 8 years of follow-up in patients with ejection fraction improvement compared with 54% in those without significant ejection fraction improvement.

Incremental value of viability and digoxin use in follow-up to ejection fraction improvement

The low-dose wall motion score added incremental prognostic value to the combination of ejection fraction improvement and low-dose wall motion score ($P = 0.003$).

**Discussion**

In this long-term outcome study of patients with severe ischaemic LV systolic dysfunction, improvement in the ejection fraction with revascularization was a strong independent predictor of survival. However, the extent of viable myocardium as assessed by the low-dose wall motion score and the use of digoxin in follow-up were also independent predictors of outcome adding incremental prognostic value to ejection fraction improvement.

**Improvement of ejection fraction and prognosis**

Improvement in global LV function is often assumed to be the primary reason for the improvement of outcome of patients with ischaemic LV dysfunction who undergo revascularization. Evidence supporting this reasoning includes the observation that patients with more extensive viable myocardium have better outcomes after revascularization than those with less extensive or limited viability. The strong correlation of improvement in global LV function with significant viability has lent credence to the reasoning that ejection fraction improvement is essential to improvement of prognosis with revascularization. As a result, various non-invasive imaging studies are used to identify those patients with significant viability who will have improvement of global LV systolic function and outcome with revascularization. This is a particularly important exercise in those who have severe ventricular dysfunction since the risk of surgical revascularization may be substantial.$^{5,10}
In support of the link between improved ejection fraction and outcome, Bax et al.\textsuperscript{6} found that patients with ejection fraction improvement (≥5%) had lower cardiac event rates (17 vs. 47% over 2 years) compared with those without significant improvement. However, there was no significant difference in mortality. Meluzin et al.\textsuperscript{5} found that patients with a mean improvement of the ejection fraction of 12% had lower cardiac event rates than those with a lesser degree (mean 6%) or no improvement in ejection fraction. The study was underpowered to compare mortality among the three groups. In a third study, Rizzello et al.\textsuperscript{10} found that patients with viability and ejection fraction improvement ≥5% had lower event rates (4 vs. 21%) than those with viability and no ejection fraction improvement, but there was again no difference in mortality.

In contrast to the previous studies, investigations by Samady et al.\textsuperscript{3} and Acampa, et al.\textsuperscript{2} came to the opposite conclusion regarding the importance of ejection fraction improvement to better outcomes. In the study of Samady et al.\textsuperscript{3} survival was 94% in those with ejection fraction improvement (≥5% increase) and 93% in those without ejection fraction improvement after 32 months of follow-up. In the study of Acampa et al.\textsuperscript{2} survival was 80% in those with ejection fraction improvement (≥5% increase), and 81% in those without ejection fraction improvement with a mean of 4 years of follow-up.

In our study, patients with ejection fraction improvement had markedly improved long-term survival compared with those without significant improvement. Interestingly, the survival benefit of an improvement in the ejection fraction did not become apparent until well after 2 years of follow-up, which may explain why some studies with follow-up limited to durations of 2–3 years showed no significant survival benefit of ejection fraction improvement.\textsuperscript{3,6}

Our results also emphasize the importance of long-term follow-up and the mode of revascularization of patients with ischaemic LV dysfunction. The study of Acampa et al.\textsuperscript{2} also evaluated the long-term impact of ejection fraction improvement on outcome. At 5 years of follow-up, there was 100% survival in patients with ejection fraction improvement compared with 85% survival in those with no ejection fraction improvement. However, the survival of patients with ejection

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**Figure 1** Survival of patients with and without ejection fraction improvement.
fraction improvement declined after 7 years and the curves converged at 8 years of follow-up, leading the authors to conclude that ejection fraction improvement does not improve the long-term outcome. In contrast, the survival advantage of patients with ejection fraction improvement in our study continued to increase beyond 8 years of follow-up (Figure 1). The differences in long-term survival in the study of Acampa et al. and in our study may be reconciled by examining the methods used for revascularization in the two studies. CABG was the method of revascularization for 57% of patients in the study of Acampa et al. compared with 93% of patients in our study. Additionally, 94% of patients who underwent CABG in our study had at least one arterial conduit. The importance of arterial grafts in the long-term survival of patients with advanced coronary disease is well recognized and the greater use of CABG and arterial conduits in our study likely contributed to the excellent and sustained survival (89%) of patients with ejection fraction improvement.11

The 8% threshold value used to define a significant increase in ejection fraction in our study may be another reason why our study demonstrated an association between ejection fraction improvement and better survival. The threshold value of 8% was twice the mean inter-observer difference in ejection fraction measurements. Except for the study of Meluzin et al., prior studies defined significant ejection fraction improvement as a 5% increase based on nuclear angiographic studies.12–14 The 8% threshold used in our study may have ensured that those patients included in the ejection fraction improvement group truly had significant increases in global LV systolic function with revascularization. The data of Meluzin et al.5 who showed that patients with larger mean increases in the ejection fraction with revascularization had lower event rates and a trend towards better survival than those with lesser or no increases in the ejection fraction provide supportive evidence that clinically meaningful improvements of ejection fraction may be higher than the 5% increase used in most studies.

Myocardial viability and prognosis

Few studies have compared the value of ejection fraction improvement with the extent of viability for prediction of prognosis of patients with ischaemic dysfunction. In our study, the extent of viability as measured by the wall motion score during low-dose dobutamine infusion was an independent predictor of outcome and added incremental prognostic value to ejection fraction improvement. Increasing scores were associated with lesser amounts of viability and poorer survival. In the study of Acampa et al. the only independent predictor of outcome in revascularized patients was the extent of non-viable myocardium. In the majority of previous studies, binary classification schemes for assessment of viability have been used assigning viability or non-viability on the basis of the presence or absence of a threshold amount of viable myocardium.9 More recently, the prognostic value of assessing the extent of viability with more continuous measures such as the low-dose score have been recognized.15

There are various reasons why survival is improved in revascularized patients with more extensive viability apart from improvement in the ejection fraction. Myocardium with non-transmural infarction and preserved epicardial viability may not exhibit improvement of rest function with revascularization. However, preservation of viability in regions with non-transmural infarction prevents or delays adverse ventricular remodelling and progression to clinical heart failure. The relief of ischaemia by revascularization in regions with partial viability may reduce a potential trigger for ventricular arrhythmia, and prevention of more extensive scar in vulnerable regions with chronic ischaemia may reduce the substrate for malignant arrhythmias.16–19

Medical and device therapy and prognosis

In this study, we included in our analysis the use of medicines and implantable cardioverter-defibrillators after revascularization. Beta-blocker use in follow-up was a univariate predictor of survival and digoxin use was predictive of cardiac death. The protective effect of beta-blockers was expected, but on multivariate analysis beta-blocker use was not an independent predictor of outcome. Digoxin use in follow-up, however, remained predictive of cardiac death on multivariate analysis. The relationship between digoxin use in follow-up and cardiac mortality may be one of causation or just association. Digoxin use may reduce hospitalizations for heart failure but higher serum levels of the drug are associated with higher mortality, especially in women, suggesting a possible direct adverse effect of the medication.20,21

Alternatively, digoxin use in follow-up may have been associated with increased mortality simply because use of the drug was a marker of more severe heart failure. In our study, digoxin use in follow-up correlated with more severe heart failure on presentation (Kappa = 0.27). Heart failure severity is a powerful predictor of adverse outcomes in ischaemic LV dysfunction.22,23 Unfortunately, we did not have accurate assessments of heart failure severity after revascularization to evaluate the correlation between digoxin use in follow-up and heart failure class after revascularization. In patients with ischaemic LV dysfunction, the lack of improvement in the heart failure class with revascularization correlates with lack of improvement in the ejection fraction.6 In
our study, digoxin use in follow-up correlated with the lack of improvement in the ejection fraction, suggesting that after revascularization digoxin use and severe heart failure were also correlated.

Limitations
Follow-up was primarily retrospective in this study, and there was no uniform time for ejection fraction assessment after revascularization. The study group was relatively small. The use of beta-blockers, angiotensin-converting enzyme inhibitors, and implantable defibrillators was not optimal but was comparable with other studies enrolling patients within the last 10 years. In our study, 82% of patients were receiving angiotensin-converting enzyme inhibitors and 13% had implanted defibrillators. In the recently published EMPHASIS-HF trial in patients with severe ventricular dysfunction, 77% of patients were receiving angiotensin-converting enzyme inhibitors and 13% had implanted defibrillators at the time of enrolment in the trial. Over two-thirds of the deaths in our study were due to heart failure rather than sudden death, suggesting that the underutilization of defibrillators may not have had a significant impact on cardiac mortality in our study.

Conclusion
The finding that ejection fraction improvement is an important driver of the long-term survival of patients with ischaemic ventricular dysfunction supports the value of viability testing to identify subjects likely to have improvement of global function with revascularization. Sustained improvement in survival in those with ejection fraction improvement may be dependent on coronary revascularization with arterial conduits. The finding that the extent of viability as measured by the low-dose score is also an independent predictor of survival indicates that an additional goal of viability testing should be to accurately assess the extent of viability in each patient. Finally, the outcome was adversely affected by digoxin therapy, either because of a direct effect of the drug or because the medication was a marker for severe heart failure.

Conflict of interest: none declared.

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