Predictors of long-term outcome in patients with left ventricular dysfunction following coronary artery bypass grafting

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Abstract

Background: Prognostic significance of clinical and non-invasive risk markers in patients after surgical revascularisation remains unclear, especially in post-infarction patients with left ventricular (LV) dysfunction.

Aim: The single-centre, prospective study was designed to assess survival and the predictive power of several clinical and non-invasive risk markers of all-cause (ACM) and cardiovascular mortality (CVM) in post-CABG patients with LV dysfunction.

Methods: A cohort of 61 patients (age 59±9 years, 49 males, LVEF 33±6%) 6-12 months after CABG was prospectively followed for a median of 46 months. Demographics, clinical data, medication, LVEF, QRS >120 ms or late potentials (LP) presence, QT dispersion ≥80 ms, premature ventricular contractions (PVC) ≥10/h, non-sustained ventricular tachycardia (nsVT), and SDNN ≤70 ms in ambulatory ECG were analysed. The ACM and CVM were evaluated. The prognostic value of analysing parameters was determined.

Results: Fourteen patients died, 10 of them due to cardiovascular causes. Univariate Cox analysis showed that incomplete revascularisation, history of angina, heart failure, low LVEF, use of nitrates, digitalis or diuretics, and presence of LP or prolongation of QRS complex were predictors of poor outcome. Combination of angina and low LVEF was the best model in a multivariable Cox analyses for the prediction of both types of death.

Conclusions: The present study showed that in post-CABG patients with LV dysfunction, angina class and low LVEF are the main predictors of ACM and CVM. Combination of LVEF <30% with the presence of QRS >120 ms or LP may also be helpful in the identification of high-risk subjects. Other common non-invasive risk markers, particularly arrhythmic and autonomic, seem to lose some of their predictive power in patients after CABG and receiving beta-blocking agents.

Keywords: left ventricular dysfunction, heart failure, CABG, survival, risk factors

Introduction

Moderate to severe impairment of left ventricular (LV) function is a major problem in patients with coronary artery disease (CAD). Several observational studies and retrospective analyses showed that patients with LV dysfunction caused by CAD responded better to myocardial revascularisation than to medical therapy alone [1, 2]. Surgical revascularisation reduced sudden cardiac death (SCD) in a population with normal, or mildly reduced LV function – lessons learned from the Coronary Artery Surgery Study [3]. Post hoc analysis of the SOLVD trial also showed that in patients with LV ejection fraction (LVEF) ≤35%, prior coronary artery bypass grafting (CABG) was independently associated with significant reduction in risk of death and SCD [4]. Moreover, insights from implantable cardioverter-defibrillator (ICD) recipients suggest that apart from lack of CABG revascularisation and enlarged LV, the use of diuretics and digitalis influenced appropriate ICD discharges during follow-up [5]. The first prospective randomised study designed to compare long-term benefit of surgical and medical treatment in patients with ischaemic cardiomyopathy, the STICH trial, is still ongoing [6].

On the other hand, numerous clinical, haemodynamic, biochemical, electrocardiographic and electrophysiological variables have been related to prognosis in patients with LV dysfunction [7]. However, it is unclear whether these results can be extrapolated to patients after CABG.

This single-centre, prospective study was designed to assess survival and the predictive power of several clinical and non-invasive risk markers of all-cause mortality (ACM) and cardiovascular mortality (CVM) in patients with LV dysfunction after CABG.

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Methods

Study group

A cohort of 61 consecutive patients after myocardial infarction with LVEF ≤40% who underwent CABG within the preceding 6-12 months in the years 1998-99 was studied. Data were collected prospectively.

Reasons for ineligibility were as follows: acute coronary syndrome, heart surgery or percutaneous revascularisation within the last 6 months, decompensated heart failure (NYHA IV), coexisting significant valvular heart disease, pericardial disease, prior episode of sustained ventricular tachycardia (sVT) or ventricular fibrillation (VF), chronic atrial fibrillation or paced rhythm, predicted life expectancy <1 year.

Surgical therapy

Patients were considered suitable for CABG if they demonstrated proximal lesions (>70%) in at least two coronary arteries. All CABG procedures were performed by means of a median sternotomy using cardiopulmonary bypass. Complete revascularisation was performed in forty patients (66%) (2-5 vein grafts, median 3; in 12 patients an internal thoracic graft was used) and incomplete in 21 patients (34%) (2-4 vein grafts, median 2; in 6 patients an arterial conduit was used). The most common reason for incomplete revascularisation was occlusion of at least one vessel with poor distal visualisation, making the possibility of grafting in this distribution uncertain.

Risk factor analysis

Demographic, clinical and medication data at enrolment were obtained. Age, gender, use of digoxin, diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and lipid-lowering agents were registered. Patients underwent a non-invasive risk stratification protocol that included measurement of echocardiographic and electrocardiographic variables. The LVEF was determined with 2D echocardiography (Sonos 2000, Hewlett Packard, USA). The QRS duration and QT dispersion (QTd) were measured from a standard 12-lead ECG recorded at a speed of 50 mm/s (Mac 5000, Marquette-GE, USA). At least 18 hours of data were obtained from ambulatory ECG recording (Oxford Excel, Marquette-GE, USA) and the presence of premature ventricular contractions (PVC) or ventricular fibrillation (VF), chronic atrial fibrillation or paced rhythm, predicted life expectancy <1 year.

-arrhythmia signal (<40 μV) in the terminal portion of the averaged QRS complex was >38 ms. Patients with bundle branch block or intraventricular conduction defects (QRS >120 ms on standard ECG) were excluded from LP analysis.

Non-invasive scoring procedure included the following cut-off points used for further analyses: QTd ≥80 ms, PVC ≥10/h, nsVT, SDNN ≤70 ms, and QRS >120 ms or LP presence.

The study protocol was approved by the local Ethics Committee.

Follow-up and endpoints

Patients were followed prospectively at 3-6 month intervals. The primary endpoint of the study was ACM. Causes of death were established from the family members and from the hospitals to which patients had been admitted. Deaths were defined as cardiovascular or non-cardiovascular.

Statistical analysis

Continuous variables are shown as mean ± SD and categorical variables as absolute numbers or proportions. Continuous data were compared with Student’s t-test and categorical variables with the chi-square test or Fisher’s exact test. Receiver operator characteristic (ROC) curve were used to assess the optimal cut-off point for LVEF in identification patients at risk. Univariate and multivariate proportional hazard Cox regression analysis with the forward stepwise procedure for presumed risk factors was performed. Survival were estimated by the Kaplan-Meier method and compared with a log-rank test. The p value of <0.05 was considered significant. Statistical analysis was performed with the Statistica 7.1 PL package.

Results

The baseline clinical characteristics is summarised in Table I. The mean LVEF was 33±6%. Forty (66%) patients underwent complete revascularisation.

Late potentials or QRS wider than 120 ms were frequently present in this population (61%): QRS >120 ms was found in 20% and LP in 41% of patients. In patients with incomplete revascularisation QRS >120 ms or LP were slightly more frequent (55 vs. 45% and 60 vs. 48%, respectively; NS) than in those with complete grafting. However, subjects with SDNN ≤70 ms were rarely present – 5% (Table II).

During the long-term follow-up (4 to 61 months, mean 44±16, median 46 months) there were 14 (23%) deaths. Ten of them were from cardiovascular causes: 4 SCD and 6 non-sudden deaths (advanced heart failure – 1, stroke – 4, abdominal aneurysm – 1). Survival rates were 90%, 79% and 70% at 2, 4 and 5 years, respectively. Sustained VT was not observed in the study population. No patient received an ICD. No patient was lost to follow-up.
Predictors of all-cause mortality

Univariate predictors of survival are presented in Table III. Incomplete revascularisation, a history of more advanced angina and heart failure, use of nitrates, digitalis or diuretics, and presence of LP or prolongation of QRS complex were found to adversely affect survival. Left ventricular EF analysed as a continuous value was also found to be an important and significant predictor of total mortality. The ROC analysis showed that the best predictive values were obtained for LVEF $\leq 30\%$ (cut-off point 30.2\%, area under the curve 0.716; Figure 1) with sensitivity of 60\%, specificity of 71\%, positive and negative predictive values of 85.5 and 34.5\%, respectively. Severe LV dysfunction (LVEF $\leq 30\%$), when analysed alone, was found to be an important but not significant (p=0.0765) predictor of all-cause mortality. However, combinations of LVEF $\leq 30\%$ with either frequent or repetitive PVCs (HR=4.30, 95\% CI 1.38-12.58, p=0.0108) or LP/QRS $> 120 \text{ ms}$ (HR=5.14, 95\% CI 1.77-14.87, p=0.0029) were found to be significant predictors.

Multivariate analysis showed that only Canadian Angina Class (CCS) and LVEF value were independent factors, affecting all-cause mortality (p=0.0134 for this model, with hazard ratio – HR=5.12 (1.547-16.971) for angina class and HR=0.86 (0.755-0.972) for LVEF). This model identified patients at risk of death with sensitivity of 75.0\% and specificity of 84.9\%; positive and negative predictive values were 42.9\% and 95.7\%, respectively.

Predictors of cardiovascular mortality

Univariate analysis revealed that CVM was higher in patients with a history of more advanced angina and heart failure, lower LVEF, treated with digitalis or diuretics,
and also those who had wide QRS complexes or presence of LP (Table IV). The Kaplan-Meier curves showed that patients with LVEF ≤30% had significantly higher CVM than patients with preserved LVEF (Figure 2). There was a trend towards lower CVM in patients who underwent complete revascularisation (Figure 3). The risk of CVM was higher when presence of LP or wide QRS complex was combined with LVEF ≤30% (HR 10.73, 95% CI 1.11-103.37, p=0.0238).

In multivariate analysis, the only independent significant predictor of CVM was again the model with angina class and LVEF [p=0.0002 for this model with HR=5.76 (1.819-366.382) for angina and HR=0.846 (0.634-0.915) for LVEF]. This model identified patients at higher risk of CVM with sensitivity of 83.3% and specificity of 90.2%; positive and negative predictive values were 50.0% and 97.9%, respectively.

**Discussion**

The main findings of this study are that in post-CABG patients with LV dysfunction (LVEF ≤40%) increased mortality was independently associated with clinical factors such as angina class (but not incomplete revascularisation) and degree of impairment of LVEF. Combined assessment of LVEF and duration of QRS complex, or in the case of normal QRS in standard ECG, presence of LP, also identified a cohort with poor prognosis. The presence of LVEF ≤30% and QRS >120 ms or LP was associated with higher CVM and ACM. Additionally, medications such as diuretics, nitrates and especially the use of digitalis significantly influenced the outcome.

In a retrospective analysis of the SOLVD trial, Cooper et al. demonstrated that non-potassium sparing diuretics independently increased the rate of arrhythmic death [8]. Recently, Ahmed et al. in a retrospective analysis of the DIG study confirmed that chronic non-potassium sparing diuretics use was associated with increased long-term mortality and hospitalisation in a wide spectrum of heart failure patients [9]. The use of nitrates, very scarcely discussed in the literature, in our study was also associated with worse outcome.

Digitalis was used very seldom (8%) in our study population. However, in univariate analysis the use of digitalis was a strong predictor of ACM (HR 7.84) and CVM

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**Table IV. Univariate predictors of cardiovascular mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (HR)</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete revascularisation</td>
<td>0.292</td>
<td>0.082-1.040</td>
<td>0.0576</td>
</tr>
<tr>
<td>CCS class (continuous)</td>
<td>4.608</td>
<td>1.43-18.546</td>
<td>0.0318</td>
</tr>
<tr>
<td>Digitalis</td>
<td>26.88</td>
<td>2.43-297.88</td>
<td>0.0003</td>
</tr>
<tr>
<td>Diuretics (continuous)</td>
<td>4.351</td>
<td>1.20-15.636</td>
<td>0.0244</td>
</tr>
<tr>
<td>LVEF ≤30%</td>
<td>5.413</td>
<td>1.06-27.567</td>
<td>0.0420</td>
</tr>
<tr>
<td>LVEF (continuous)</td>
<td>0.811</td>
<td>0.69-0.947</td>
<td>0.0081</td>
</tr>
<tr>
<td>LP or QRS &gt;120 ms</td>
<td>2.402</td>
<td>1.03-5.577</td>
<td>0.0416</td>
</tr>
<tr>
<td>NYHA class (continuous)</td>
<td>4.263</td>
<td>1.44-12.574</td>
<td>0.0086</td>
</tr>
</tbody>
</table>

**Abbreviations:** see Table I and II

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**Figure 2.** Kaplan-Meier cumulative survival plot of CVM: impact of LVEF

**Figure 3.** Kaplan-Meier cumulative survival plot of CVM: impact of complete/incomplete CABG
Our post-CABG patients with LVEF ≤30% increased QT dispersion was not associated with higher mortality risk. Problems with accurate measurement of QTd may explain why the predictive value of this electrocardiographic measure is limited [22].

The main purpose of risk stratification is to identify high-risk patients and to optimise therapy. In our study population high-risk post-CABG patients could be identified with positive predictive values of 42.9% for ACM and 50% for CVM by the presence of angina symptoms (probably due to incomplete revascularisation, closure of bypass grafts or progression of atherosclerosis) and severely depressed LVEF.

Study limitations
The small study population and low number of deaths, especially SCD (28.6% of total mortality), may prevent generalisation of the results to other post-CABG populations. There are other variables, not assessed in the study, such as heart rate turbulence, T wave alternans, QT/RR relationship or baroreceptor sensitivity.

Long-term outcome is affected by many other factors, e.g. conventional coronary risk factors, measured late after surgery. Treatment efficacy of these factors was not systematically assessed in this study. It should be stressed that among the cardiovascular causes of death there were 5 deaths of vascular origin (stroke – 4, abdominal aneurysm – 1). Non-fatal cardiovascular events during follow-up such as non-fatal myocardial infarction or stroke and hospitalisation due to heart failure were not evaluated in the study.

Conclusions
The present study showed that angina class and the degree of impairment of LVEF are the main determinants of all-cause and CVM in post-CABG patients with LV dysfunction. The results of our study also suggest that combination of low LVEF with the presence of wide QRS complexes or LP may be helpful in the identification of high-risk subjects. Other common non-invasive risk markers, particularly arrhythmic and autonomic, seem to lose some of their predictive power among patients after CABG and receiving beta-blocking agents.

The use of nitrates, diuretics, and in particular digoxin, may be associated with a higher mortality rate and therefore should be administered only when necessary.

References


Czynniki wpływające na przeżycie chorych z pozawałowym uszkodzeniem lewej komory poddanych chirurgicznej rewaskularyzacji mięśnia sercowego

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Streszczenie

Wstęp: Pomimo wielu badań poświęconych poszukiwaniu markerów zagrożenia u chorych po zawale serca z dysfunkcją lewej komory, istnieje sporo kontrowersji na ten temat. Szczególną, odrębną grupę tworzą chorych po chirurgicznej rewaskularyzacji mięśnia sercowego.

Cel: Jednośrodkowa, prospektywna analiza przeżywalności oraz znaczenia prognostycznego danych klinicznych i nieinwazyjnych wskaźników w przewidywaniu śmiertelności ogólnej (ang. all-cause mortality, ACM) i zgonów z przyczyn sercowo-naczyniowych (ang. cardiovascular mortality, CVM) u chorych z pozawałową dysfunkcją lewej komory po chirurgicznej rewaskularyzacji mięśnia sercowego (CABG).

Metody: Badana populacja obejmowała 61 osób po zawale serca [wiek 59±9 lat, 49 mężczyzn, frakcja wyrzutowa lewej komory (LVEF) 33±6%] włączanych do badania w okresie 6–12 miesięcy po CABG, a następnie obserwowanych prospektywnie przez okres 4–61 miesięcy (mediana 46). Analizowano dane demograficzne, kliniczne, w tym stosowane leki, LVEF, dyspersję repolaryzacji (QTd ≥80 ms), szerokość zespołów QRS >120 ms lub obecność późnych potencjałów komorowych (LP), przedwczesne pobudzenia komorowe (PVC) ≥10/godz., epizody nieuwierdzonego częstokurzu komorowego (nSVT) i parametr czasowy zmienności rytmu SDRR ≤70 ms. Oceniano częstotliwość wystąpienia ACM i CVM, a następnie określono znaczenie prognostyczne wymienionych wskaźników.

 Wyniki: Zmarło 14 chorych, w tym 10 z przyczyn sercowo-naczyniowych. Jednoczynnikowa analiza Coksa wykazała, że czynnikami zwiększającymi ryzyko wystąpienia zgonu (zarówno ACM, jak i CVM) są: niepełna rewaskularyzacja, stopień nasilenia dławicy, obecność niewydolności serca, niższa LVEF, stosowanie azotanów, naparstnicy lub diuretyków oraz obecność LP lub poszerzenie zespołu QRS. Współistnienie obniżenia LVEF ≤30% z obecnością LP lub poszerzeniem QRS powodowało istotne zwiększenie ryzyka CVM (HR=10,73, p=0,0238). W wieloczynnikowej analizie Coksa połączenie stopnia nasilenia dławicy i obniżenia LVEF cechowało się największą wartością predykcyjną dla ACM i CVM, a pozytywna i negatywna wartość przewidywania wynosiły odpowiednio: 42,9% i 95,7% oraz 50,0% i 97,9%.

Wnioski: Obecność dużego stopnia dysfunkcji lewej komory w połączeniu z gorszą klasą wydolności wieńcowej u chorych z pozawałowym uszkodzeniem lewej komory leczonych CABG cechuje się największą siłą predykcyjną dla ACM i CVM, a pozytywna i negatywna wartość przewidywania wynosiły odpowiednio: 42,9% i 95,7% oraz 50,0% i 97,9%.

Słowa kluczowe: pozawałowe uszkodzenie lewej komory, niewydolność krążenia, CABG, śmiertelność, czynnik ryzyka

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