High Mortality Associated With Precluded Coronary Artery Bypass Surgery Caused by Severe Distal Coronary Artery Disease

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Background—Patients with extensive coronary artery disease (CAD) have better prognosis when treated with coronary artery bypass grafting surgery (CABG), especially when left ventricular dysfunction (LVD) is present. However, there are scanty data about the clinical course of patients not referred to CABG because of extensive and severe atherosclerotic involvement of distal coronary arteries (ENDCAD). The aim of this study was to evaluate patients with multivessel (MV) or left main CAD (LM) who had CABG precluded because of ENDCAD.

Methods and Results—Between August 1999 and July 2001, 51 patients who had clinical indication but were not eligible for CABG because of ENDCAD were followed for at least 12 months or until death. There were 32 men and 19 women (age 61±9 years). Previous acute myocardial infarction (AMI) was present in 31 (60.8%), diabetes mellitus (DM) in 28 (54.9%), systemic arterial hypertension in 37 (72.5%), LVD (left ventricular ejection fraction <40%) in 26 (51%), 3 vessel CAD in 31 (60.8%), and LM in 4 (7.8%). During follow-up there were 20 cardiac (39.2%) deaths, 19 (37.2%) AMI, and 3 (5.8%) patients developed congestive heart failure. There were 2 (3.9%) noncardiac deaths. Patients with DM (60.7% versus 13%; P = 0.001; odds ratio [OR], 10.30; 95% confidence interval [CI], 2.46 to 43.09), LVD (76.9% versus 0%; P = 0.0001; OR, 4.33; 95% CI, 2.14 to 8.74), 3-vessel CAD (51.6% versus 20%; P = 0.039; OR, 4.26; 95% CI, 1.16 to 15.69), and LM (100% versus 34%; P = 0.019; OR, 1.25; 95% CI, 1.004 to 1.556) were more likely to die. There was no deaths in patients with 2-vessel CAD but they had more nonfatal AMI (43.8% versus 14.3%; OR, 4.667; 95% CI, 1.188 to 18.332).

Conclusions—Patients in whom CABG could not be performed because of ENDCAD had high mortality, especially in the presence of LVD. DM (particularly insulin-dependent), LM CAD, and 3-vessel CAD were independent markers of increased risk.


Key Words: atherosclerosis ■ coronary disease ■ grafting ■ mortality ■ prognosis ■ revascularization ■ surgery ■ survival

Coronary artery disease (CAD) is the leading cause of death worldwide and it is expected that 82% of the future increase in CAD mortality will occur in developing countries.1–2 Annually, in Brazil there are >76 000 deaths caused by CAD.3 Improvements in medical therapy and recent advances in percutaneous coronary angioplasty (PTCA) have changed referral patterns for coronary artery bypass grafting surgery (CABG) and have increased the number of high-risk patients proceeding to surgery.4–6 Several reports call attention to the benefits of CABG in patients with left main coronary stenosis (LM), multivessel coronary stenosis (MV) with extensive myocardial ischemia, and left ventricular dysfunction (LVD).7–10 However, there is scanty literature about the prognosis of patients that has a coronary anatomy unsuitable for CABG.

The aim of this study was to follow-up patients with LM or MV who had CABG precluded because of extensive and severe atherosclerotic involvement of distal coronary arteries (ENDCAD).

Study Population

Between August 1999 and July 2000, a nonconsecutive series of 51 patients with documented myocardial ischemia by stress testing or spontaneous angina, angiographically documented significant LM of >50%, or MV of >70%, with or without LVD, and diffuse coronary atherosclerosis extending to the periphery of the epicardial conductance vessels were considered for inclusion into the study. Patients were enrolled if there was agreement on the part of 2 surgeons and 1 clinical cardiologist that CABG could not be attained. Exclusion criteria included CAD amenable to PTCA or CABG, single-vessel
CAD, life-threatening noncardiovascular comorbidities, valvular heart disease, congenital heart disease, cardiomyopathy, previous PTCA or CABG in the past 6 months, and ventricular aneurysm requiring surgical repair. Patients were also excluded if they were unable to give informed consent or to return for follow-up.

After enrollment the patients were contacted by direct telephone interview or by hospital chart review from August 2000 to July 2001 to evaluate their vital and clinical status. All patients were followed-up for at least 12 months or until death. They were placed on state-of-the-art pharmacological and nonpharmacological measures recommended in chronic ischemic heart disease.

The primary end-point of the study was cardiac death. Secondary end-points were nonfatal AMI, noncardiac death, and development of congestive heart failure (CHF).

AMI was defined as the presence of significant new Q wave in at least 2 electrocardiographic (ECG) leads or symptoms compatible with AMI associated with creatine kinase MB fraction concentrations that were more than twice the upper limit of the reference range. LVD was considered to be present when the left ventricular ejection fraction (LVEF) measured by 2-dimensional echocardiogram was $<40\%$. All non-witnessed deaths or deaths without necropsy were considered of cardiac origin.

Statistical Analysis
Comparison between continuous variables was performed by Student $t$ test, and to compare categorical variables the Fisher exact test was used. All tests were 2-tailed and $P<0.05$ was considered statistically significant. We did not perform multivariate logistic regression analysis because there were an insufficient number of patients. Statistical analysis was performed with the commercially available software (Statistica 6.0; StatSoft Inc, Tulsa, Calif).

Results
Baseline patient characteristics are depicted in the Table. There were 32 men (62.7\%) and 19 women (37.3\%) with a mean age of 61±9 years. Thirty-seven patients (72.5\%) had systemic arterial hypertension (HAS), 28 (54.9\%) had diabetes mellitus (DM), of which 9 (17.6\%) were insulin-dependent, 31 (60.8\%) had previous AMI, 26 (51\%) had LVD, 16 (31.4\%) had 2-vessel CAD, 31 (60.8\%) had 3-vessel CAD, and 4 (7.8\%) had LM CAD.

During the follow-up a total of 22 patients died (43.1\%). Of these, 20 were of cardiac origin (39.2\%). Nineteen patients (37.2\%) had a nonfatal AMI and 3 (5.8\%) developed CHF (Figure 1). Patients with DM (60.7\% versus 13\%, $P=0.0001$, odds ratio [OR], 10.30, 95\% confidence interval [CI], 2.46 to 43.09), LVD (76.9\% versus 0\%, $P<0.0001$, OR, 4.33, 95\% CI, 2.14 to 8.74), 3-vessel CAD (51.6\% versus 20\%, $P=0.039$, OR, 4.26, 95\% CI, 1.16 to 15.69), and LM (100\% versus 34\%, $P=0.019$, OR, 1.25, 95\% CI, 1.004 to 1.556) were more likely to die (Figure 2). There were no cardiac death in patients with 2-vessel CAD, but they had more nonfatal AMI (43.8\% versus 14.3\%, $P=0.0033$, OR, 4.66, 95\% CI, 1.18 to 18.33). Eight of 9 (88.9\%) patients with insulin-dependent DM died during the follow-up, and the remaining patient has experienced a nonfatal AMI.

Discussion
Clinical cardiologists dealing with CABG know that the quality of distal coronary vessels is one of the critical issues that make cardiac surgeons hesitant whether the surgical revascularization is feasible or not. Graham et al in a pilot study have demonstrated that diffuse distal CAD was a powerful independent predictor of surgical death. However, the extent of disease in distal coronary vessels has not been included in predictive models of CABG because it was considered subjective and prone to interobserver bias.

Currently there are few data on the prevalence and prognosis of patients with symptomatic CAD not amenable by revascularization. In a recent report from Mukherjee et al,

<table>
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<th>Baseline Patient Characteristics (n=51)</th>
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<tr>
<td>Age, mean (SD), y</td>
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<tr>
<td>Men, n (%)</td>
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<td>Women, n (%)</td>
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<tr>
<td>Stable angina, n (%)</td>
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<td>Unstable angina, n (%)</td>
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<td>Congestive heart failure, n (%)</td>
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<td>2-vessel CAD, n (%)</td>
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<td>LM CAD, n (%)</td>
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<td>LVD, n (%)</td>
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<td>LVEF, mean (SD)</td>
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AMI indicates acute myocardial infarction; CAD, coronary artery disease; LM, left main coronary artery; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction.

Figure 1. Primary and secondary events during follow-up.

Figure 2. Incidence of mortality according to the presence of left ventricular dysfunction (LVD), diabetes mellitus (DM), 3-vessel coronary artery disease (3v), and left main coronary artery disease (LM).

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analyzing patients eligible for direct myocardial revascularization and angiogenesis, showed that almost 12% of 500 patients with symptomatic CAD were not suitable for CABG or PTCA. A Swedish survey of patients referred for coronary angiography because stable angina pectoris showed that 9.6% of the patients were rejected for revascularization despite severe symptoms. A report from Duke University based on their most recent experience showed that patients with advanced CAD accounted for >15% of the catheterization laboratory population. Annually, at our institution almost 1200 patients were submitted to CABG or PTCA; therefore, we admit that ~4.2% (51 of 1200) had a revascularization procedure rejected because of ENDCAD.

Our study demonstrated that patients with ENDCAD have high mortality and morbidity (Figure 1). At 1-year follow-up, 39.2% of the patients with ENCAD had a cardiac death, 37.2% had an AMI, and another 5.8% developed CHF. As a result, at the end of 1-year of follow-up 82.2% of patients with ENDCAD developed a cardiac event. This dismal outcome is similar to the results of an study reported by Kandzari et al., in which of 487 patients with advanced CAD defined as 3-vessel CAD, or LM CAD and left ventricular ejection fraction <50%, or severe angina, who did not undergo coronary revascularization procedures within 30 days of catheterization, found a 2-year mortality rate of 37.8%, and 10% incidence of AMI. In contrast to our study, despite the advanced CAD, almost 25% of the patients included in this study have had a revascularization procedure during the follow-up. Landolfo et al. studying 34 patients with severe diffuse CAD not amenable to PTCA or CABG who were considered eligible for transmyocardial laser revascularization (TMR), found a 1-year mortality rate of 14.7% and 8.8% of nonfatal AMI. In a prospective, randomized, multicenter trial comparing the safety and efficiency of TMR with medical therapy alone in 275 patients with medical refractory class IV angina and CAD that could not be treated with PTCA or CABG, the survival at 1 year was 89% for medical therapy alone and 84% for TMR.

Several studies have showed that LVD and the location and severity of CAD are factors associated with adverse outcome in patients with CAD treated medically. We demonstrated that patients with LVD had a mortality of 76.9%, or a risk of dying almost 4-times more than those without LVD (Figure 2). This high mortality is much higher than those that has been observed in randomized trials involving patients with congestive heart failure or LVD.

We also showed that patients with 3-vessel disease had higher mortality rates than those without (51.6% and 20%, respectively) or a risk 4-times greater. LM CAD also increased the risk of dying by 25% (Figure 2).

Although there is some controversy about the influence of DM on the severity and extension of CAD, DM is linked to an increased short-term and long-term adverse outcome after CABG. Almost 55% of the patients included in our study had diabetes, and they had a 10-times greater chance of dying than those without DM (Figure 2). In addition, of 9 patients with insulin-dependent DM included in this study, 8 of them died (88.9%) at the end of the follow-up. To the best of our knowledge, this is the worst outcome ever described in the medical literature about patients with DM.

Limitations
This is a small study involving a special class of patients whose decision not to be a candidate for CABG was taken by a group of clinical cardiologists and cardiac surgeons based on the visual aspect of a coronary arteriography. As we mentioned, this is a subjective measure, and we do not know whether other groups of cardiologists or cardiac surgeons would agree with our decision. To minimize this bias, we tried to follow the coronary angiographic criteria proposed by Graham et al.

Clinical Implications
Given the high-risk profile of patients with ENDCAD, especially those with LVD, further rationale should be provided to submit them to new therapeutics options like percutaneous or direct transmyocardial angiogenesis and heart transplantation.

Conclusions
Patients in whom CABG could not be performed because of ENDCAD had high mortality, especially in the presence of LVD. DM (particularly insulin-dependent), LM CAD, and 3-vessel CAD were independent markers of increased risk.

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