REVIEW ARTICLE

Results of Coronary Bypass Surgery in Diabetic Patient- A Review

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Introduction

Coronary atherosclerosis is more prevalent among diabetic than non-diabetic patients. In addition in diabetic patients it is more extensive and takes an accelerated course.[1-3] The reported prevalence of diabetes among patients undergoing coronary artery bypass grafting (CABG) ranges from 7% to 20%.[1.4.5]

Diabetes mellitus is an established risk factor for the development of coronary artery disease. Epidemiological data from the Framingham study [6] have shown that diabetes is a major independent risk factor for cardiovascular disease even after adjusting for other confounding risk factors such as age, hypertension, hypercholesterolemia, and tobacco abuse. Further, the incidence of congestive heart failure and cardiovascular death are even higher in female diabetic patients than in male diabetics.[7] Diabetic patients have a higher incidence of two and three-vessel disease and a lower incidence of one vessel disease than do nondiabetic patients.[8] Diabetes has been associated with higher perioperative morbidity as well as decreased survival after coronary artery bypass grafting.[9-11]. The present article reviews the underlying causes of higher perioperative morbidity and mortality in diabetic patients and the current researches on this issue to address this problem.

Study-1

Lawrie et al (1986) underwent a long term follow up study of 1,434 patients with CABG done between 1968 and 1973, 212 of whom were diabetic. All patients underwent isolated saphenous vein aortocoronary bypass graft procedures on one surgical service. Of 212 diabetics, 87(41%) patients were receiving no drug treatment, 108(51%) patients were being treated with oral hypoglycemic agents, and 17(8%) patients were receiving treatment with insulin. There were no significant difference in the demographic profiles, number of major proximal coronary lesions, left ventricular function between the diabetic and nondiabetic groups. Perioperative mortality (30 day) showed no significant differences between the two groups especially due to cardiac causes, which accounted for 60% (9/15) of mortality in the diabetic patients and 70.9% (39/55) mortality in nondiabetics. The causes of late mortality were however significantly different between the two groups. There was excessive mortality from cardiac causes, stroke, and renal causes in the diabetic group particularly in the insulin-treated patients. The results of Kaplan-Meier analysis of survival probability indicated that the diabetics had significantly lower long-term survival probability than nondiabetics (p<. 05). This difference was observed also when patients were stratified according to preoperative left ventricular function (p<. 05). Diabetics receiving no drug therapy had survival identical to that of normal patients, while patients receiving insulin therapy had the worst survival[12].

Comment

The severity of diabetes mellitus before surgery influenced the long-term survival rates negatively after coronary by-pass surgery particularly in those patients who were taking insulin. The 30-day mortality between the diabetic and non-diabetic was however comparable.

Study- 2

Cohen et al performed a prospective national cohort study, which included patients who underwent CABG in 14 medical centers in Israel during 1994. The purpose of that study was to identify factors associated with 30-day mortality after CABG among diabetic patients, and to compare them with risk

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factors among nondiabetics. Multivariate logistic regression analysis was used to identify factors associated with a 30-day mortality in diabetic and nondiabetic populations. The results showed that crude mortality was 5.0% among diabetic patients (n=1,034) and 2.5% among nondiabetics (n=3,350; p< 0.001). Crude mortality rates by gender in nondiabetics were 2.3% for men and 3.5% for women (p=NS); among diabetic patients, crude mortality rates by gender were 3.7% for men and 8.3% for women (p=0.002). Multivariate logistic regression analysis identified female gender, 3-vessel disease, and left main disease as independent risk 30-day, post-CABG mortality unique to diabetic patients, left ventricular dysfunction was found to effect a greater risk among diabetic patients, whereas chronic renal failure was associated with greater risk among nondiabetics.[13]

Comment

In contrast to the previous study the study conducted by Cohen et al demonstrated that 30-day mortality is significantly higher in diabetics than their nondiabetic counterpart particularly in female diabetic patients, and patients with 3-vessel disease, left main disease and patients with left ventricular dysfunction.

Study –3

Thourani et al did a short and long term follow up study on 12,198 patients who underwent routine CABG operation between 1978 through 1993 at Emory university hospital. During the 16 years, 9,920 of these patients were classified as nondiabetic and 2,278 as diabetic according to the definition given by American college of cardiology. Compared with nondiabetic patients, the group with diabetes was older (62±10 years versus 60±10 years), comprised more women (31% versus 19%), had a greater incidence of hypertension (61% versus 44%) and previous myocardial infarction (51% versus 48%), had class III-IV angina more commonly (69% versus 63%), showed a higher incidence of congestive heart failure (11% versus 5%) or triple-vessel or left main disease (60% versus 50%), and had lower ejection fractions (0.54 versus 0.57) (all, p£ 0.05). Diabetic patients had a higher incidence of postoperative death (3.9% versus 1.6%) and stroke (2.9% versus 1.4%)(both, p£ 0.05), but not Q wave myocardial infarction (1.8% versus 2.9%). Diabetics had lower survival (5 years, 78% versus 88%; 10 Years, 50% versus 71%; both, p£ 0.05) and lower freedom from percutaneous transluminal coronary angioplasty (5 years, 95% versus 96%; 10 years, 83% versus 86%; latter, p£ 0.05), but diabetics did not have lower freedom from either myocardial infarction (5 Years, 92% versus 92%; 10 years, 80% versus 84%) or additional coronary artery bypass grafting (5 years, 98% versus 99%; 10-years, 90% versus 91%). Multivariate correlates of long-term mortality were diabetes, older age, reduced ejection fraction, hypertension, congestive heart failure, number of vessel diseased, and urgent or emergent operation.[7]

Comment

This study clearly established the higher preoperative risk factors, early and late morbidity and mortality in diabetics than their nondiabetic counterpart.

Study: 4

Magee M J et al compared the influence of diabetes on mortality and morbidity between off-pump CABG and CABG with cardiopulmonary bypass. A total of 9,965 patients, from January 1995 through December 1999, of whom 2,891(29%) had diabetes, underwent isolated CABG. Twelve percent (346 of 2,891) of diabetic patients and 12% (829 of 7074) of nondiabetic patients underwent CABG without cardiopulmonary bypass. Patients undergoing CABG without cardiopulmonary bypass compared with those having CABG with cardiopulmonary bypass had higher mean predicted mortalities (diabetic, 3.96% versus 3.72%, p=0.83; non-diabetic, 3.03% versus 2.86%, p=0.79). In nondiabetic patients, coronary artery bypass grafting without cardiopulmonary bypass provides an actual and risk-adjusted survival advantage over coronary artery bypass grafting with cardiopulmonary bypass (1.81% versus 3.44%, p=0.0127; risk-adjusted mortality, 1.79% versus 3.61%, p=0.007). The survival benefit of coronary artery bypass grafting without cardiopulmonary bypass was not seen in diabetic patients (2.89% versus 3.69%, p=0.452; risk-adjusted mortality, 2.19% versus 2.98%, p=0.42) Diabetic patients undergoing coronary artery bypass grafting without cardiopulmonary bypass had fewer complications, including decreased blood product use

(31.39% versus 58.4%, p=0.001), and reduced incidence of prolonged ventilation (6.94% versus 12.10%), p=0.005), atrial fibrillation (15.90% versus 23.26%, p=0.002), and renal failure requiring dialysis 10.87% versus 2.75%, p=0.036).[14]

Comment

The survival advantage in nondiabetic patients treated with coronary artery bypass grafting without cardiopulmonary bypass was not apparent in diabetic patients. Coronary artery bypass grafting without cardiopulmonary bypass in diabetic patients was nevertheless associated with significant reduction in morbidity.

Study: 5

Szabo et al in Sweden studied the early post-operative outcome and medium-term survival in diabetic and nondiabetic patients undergoing CABG.

A total of 2,779 consecutive patients undergoing isolated CABG during 1999 were studied, 19.4% of whom had diabetes mellitus. Demographic and peri-procedural data were registered prospectively in a computerized institutional database.

The diabetic group was younger and included a higher proportion women, and patients with hypertension, triple- vessel disease, unstable angina. They required a higher number of bypasses, and a longer cross clamp and cardiopulmonary bypass times. Intensive care of hospital stays were prolonged and for inotropic agents, hemotransfusions, and dialysis was higher in the diabetic group. Renal failure, stroke (4.3%versus 1.7%), mediastinitis, and wound infections were more frequently encountered. Thirty-day mortality was 2.6% versus 1.6%(p=0.15). Cumulative 5-year survival was 84.4% versus 91.3%($p < 0.001$).

Comment

Short-term mortality was acceptable in diabetic patients after CABG but they had increased postoperative morbidity in comparison with nondiabetic patients, particularly with regard to renal function, cerebral complications, and infections. Midterm survival was impaired in diabetic patients mainly because of a less favourable outcome of patients treated with insulin.[15]

Discussion

The above five studies clearly established the unfavorable outcome in terms of morbidity and mortality in diabetic patients than their nondiabetic counterparts. Several studies have been done to determine the underlying cause of unfavourable outcome of diabetic patients undergoing CABG compared to non-diabetic patients. Verma et al showed that increased endothelin-1 production in diabetic patients after cardioplegic arrest and reperfusion impairs coronary vascular reactivity. Hyperglycemia is a potent stimulus for endothelin-1 production. The coronary effluent release of endothelin-1 is higher in diabetic than in nondiabetic patients after cardiopulmonary bypass and reperfusion, diabetic coronary micro vessels respond to bypass and reperfusion with greater endothelin-1 mediated vasoconstriction and diminished nitric oxide-mediated vasodilatation, and these effects are attenuated by endothelin antagonism. The diabetic heart elicits an exaggerated response to ischemia-reperfusion, with altered neutrophil adhesion, endothelial dysfunction, myocyte contractility, oxidative stress, and myocardial energetics.[16]

Endothelin-1 is one of the most potent vasoconstrictors known and has been implicated in the development of a number of cardiovascular diseases, including congestive heart failure, pulmonary hypertension, endothelial dysfunction, atherosclerosis, and vasospasm.[16]

Verma et al in another study showed that cardiomyocytes might also produce endothelin-1, which might directly impair myocyte contractility by increasing intracellular calcium levels. This impairment of endothelium and cardiomyocyte could be antagonized by endothelin receptor blockers (BQ-123 and Bosentan)[17].

The mature 21 amino acid peptide endothelin-1, or ET-1, is synthesized from a 38 amino acid precursor, known as “big endothelin.”Big ET” is then converted to the biologically active ET-1 by an ET converting enzyme. The diverse physiologic actions of ET-1 appear to be mediated through two receptor subtypes, the ET_A and ET_B receptors.

The production of ET was first described in endothelial cells, but the synthesis of ET has now

been identified to occur in a number of cell types including smooth muscle cells and cardiac myocytes[18]. ET causes potent vasoconstriction of several vascular systems[18]. Potent constriction of vascular smooth muscle occurs primarily through binding of ET to the ET_A receptor and through several intracellular signaling events, increases calcium availability to the contractile elements. The ET_B receptor contributes to the regulation of vascular smooth muscle tone in several different ways. First, ET_B receptors located on endothelial cells mediate vasodilatation via the release of nitric oxide and prostacyclins. Second, this receptor subtype also exert vasoconstriction when located on the smooth muscle cells. Therefore contractile effect of ET depends mainly on the relative density of ET_A and ET_B receptors on smooth muscle cells and of ET_B receptors on endothelial cells. The vasoconstrictive effects of ET are more pronounced in arteries with atherosclerotic disease, ET amplifies coronary artery constrictions induced by nor epinephrine, serotonin.[18]

Whereas the vasoconstrictive effects of ET are widely recognized, activation of the ET_A receptor has direct effects on myocyte biology, including contractile protein interactions, inotropic state, protein expression, and electro physiology.

Fundamental intracellular events that have been reported to occur after ET_A receptor activation are the release or release and mobilization of intracellular calcium (Ca^{+2}) and intracellular pH changes[18]. Since ET_A receptor activation can cause increased release of intracellular Ca^{+2}, then activation of this receptor system after cardioplegic arrest and reperfusion would potentially exacerbate intracellular Ca^{+2} homeostasis and contractile function. An important sarcolemmal exchange system that directly influences intracellular pH is the Na^+/H^+ exchanger. Intracellular pH under normal ambient conditions is maintained relatively alkaline when compared with the environment; this is achieved through the transport of protons out of the myocyte. This exchange system has the capacity to correct an intracellular acid load during periods of ischemia through the acceleration of H^+ extrusion and intracellular accumulation of Na^+. This increased intracellular Na^+ can in turn, increase the exchange rate of the Na^+/Ca^{+2} exchanger with a subsequent accumulation of intracellular Ca^{+2}. Several studies have demonstrated that the Na^+/Ca^{+2} exchanger directly contributes to the increased influx and accumulation of Ca^{+2} during ischemia and reperfusion. Thus during early reperfusion, intracellular Ca^{+2} homeostasis could be further aggravated by the activation of the Na^+/H^+ exchanger[18].

A three to six fold increase in systemic levels has been documented to occur immediately after cardioplegic arrest and reperfusion. A number of clinical studies have demonstrated that increased ET levels persist well during the postoperative period. Potent and specific ET_A receptor antagonists, as well as combined ET_A/ET_B receptor antagonists, have been described. These new nonpeptide ET receptor antagonists are constructs with significant bioavailability, prolonged half-life, and high specificity. ET receptor antagonists have been successfully used in patients with pulmonary hypertension and heart failure. These ET receptor antagonists have been successfully used in several animal models of cardioplegic arrest and CPB. The ET receptor antagonist with greatest clinical profile to date is the nonselective antagonist bosentan. Specifically, the immediate administration of bosentan in patients with heart failure has provided favorable effects on systemic homodynamic and pulmonary hypertension.[18]

Conclusion

Increased endothelin release and activation is an important cause of unfavorable outcome in diabetic patients undergoing CABG, and the use of endotheline antagonist may be a novel approach to counteract this problem.

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