

## Coronary Artery Surgery in Diabetic Patients

José M. González Santos and Mario Castaño Ruiz

Unidad de Cirugía Cardíaca. Hospital Universitario de Salamanca. Salamanca. España.

Currently, 15% to 30% of the patients that undergo coronary artery surgery are diabetics. As a group, they have less favorable anatomic and clinical characteristics than the general population. Specifically, diabetics have more extensive coronary disease, more vessels involved, and more diffuse stenosis, so they need a higher number of distal anastomoses to achieve complete revascularization. In spite of these drawbacks, they can undergo coronary artery bypass procedures with an operative mortality similar to that of non-diabetic patients. However, some postoperative complications are significantly more prevalent among diabetics, mainly renal failure, neurological accidents, sternal dehiscence, and infection. In early studies of the late results of surgical revascularization, mainly based on venous grafts, late survival and clinical improvement were less satisfactory in diabetics than in non-diabetics. However, in recent experiences, in which the internal mammary artery has been used extensively, the clinical outcome of diabetics has been similar to that of non-diabetics, confirming this procedure as the preferred one in revascularizing the coronary arteries of diabetics with multivessel disease. Off-pump surgery and extensive use of arterial grafts are becoming established strategies for reducing operative risk and improving long-term clinical results. However, continuous, strict medical management of hyperglycemia and other known coronary risk factors, especially lipid levels, is essential.

**Key words:** *Diabetes mellitus. Coronary artery bypass.*

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Correspondence: Dr. J.M. González Santos.  
Unidad de Cirugía Cardíaca. Hospital Universitario de Salamanca.  
Paseo de San Vicente, s/n. 37007 Salamanca. España.  
E-mail: [jmg@usal.es](mailto:jmg@usal.es)

### Cirugía de revascularización coronaria en el paciente diabético

Los diabéticos que precisan una derivación aortocoronaria son un grupo de pacientes cada vez más frecuente, hasta el 30% de los que se someten a este tipo de cirugía en la actualidad, y con unas características clínicas y anatómicas que los diferencian del resto de la población. En particular, suelen tener una enfermedad coronaria más extensa y difusa, con mayor número de vasos enfermos y de lesiones, y precisan más anastomosis distales para conseguir una revascularización adecuada. A pesar de que la cirugía comporta hoy día un riesgo similar al del paciente no diabético, los diabéticos desarrollan más complicaciones inmediatas, en especial, insuficiencia renal, accidentes neurológicos y problemas con la esternotomía. En estudios clásicos, en los que la cirugía se basaba fundamentalmente en los injertos venosos, la supervivencia a largo plazo y el alivio de la angina eran menores que en la población general. Sin embargo, el uso rutinario de la arteria mamaria interna ha permitido obtener unos resultados prácticamente comparables a los del paciente no diabético, por lo que en la actualidad se considera idónea la técnica de revascularización en el diabético con enfermedad multivaso. La cirugía sin circulación extracorpórea y una revascularización más extensa con injertos arteriales se están consolidando como soluciones prometedoras para disminuir el riesgo de la cirugía y mejorar los resultados a largo plazo. No se debe, sin embargo, subestimar la importancia que tienen en los resultados clínicos a largo plazo las medidas de prevención secundaria, en especial el control estricto de la glucemia y la disminución agresiva de los lípidos plasmáticos.

**Palabras clave:** *Diabetes mellitus. Cirugía coronaria.*

### INTRODUCTION

Diabetes mellitus (DM) is a disease closely related with ischemic heart disease (IHD). This metabolic disorder facilitates the development of coronary atherosclerosis, the frequency and severity of which usually increases with the severity of DM. Due to this relation, coronary accidents are the main cause of death in dia-

## ABBREVIATIONS

PTCA: percutaneous transluminal coronary angioplasty.  
ACVA: acute cerebrovascular accident.  
IMA: internal mammary artery.  
RA: radial artery.  
BARI: Bypass Angioplasty Revascularization Investigation.  
CABRI: Coronary Angioplasty versus Bypass Revascularization Investigation.  
CASS: Coronary Artery Surgery Study.  
CCS: Canadian Cardiovascular Society.  
CPB: cardiopulmonary bypass.  
IHD: ischemic heart disease.  
CABG: coronary artery bypass graft.  
DM: diabetes mellitus.  
AMI: acute myocardial infarction.  
CHF: congestive heart failure.  
ARF: acute renal failure.  
NYHA: New York Heart Association.

abetic patients and more serious clinical manifestations of IHD, like acute coronary syndrome and AMI, are up to three times more frequent in diabetics than in non-diabetics. In addition, they have a greater mortality.<sup>1,2</sup> In patients with type 1 DM, the mortality due to coronary causes is 3 to 10 times more frequent than in the normal population and 2 to 4 times more frequent than in patients with type 2 DM.<sup>3-6</sup>

Also, DM is associated with more morbidity and mortality and less favorable results in the intermediate-to-long term after coronary revascularization, whether carried out surgically or by means of percutaneous techniques. Nevertheless, several prospective studies have demonstrated that, when indicated, surgical revascularization provides better clinical results in terms of survival and quality of life than medical treatment or percutaneous revascularization procedures,<sup>7-10</sup> even when intracoronary stents are used in such procedures.<sup>11</sup> Surgery also produces better results than other revascularization strategies in the context of restenosis appearing after coronary interventions.<sup>12</sup>

In this article, we proposed to review the special problems of diabetic patients for cardiac surgery and to analyze the immediate and long-term results of coronary artery bypass graft (CABG) in this difficult group of patients. Intentionally, we will not compare the results of surgery and PTCA in this review, which has been the topic of another chapter in this monographic series.

## PREVALENCE OF DIABETES MELLITUS AMONG CANDIDATES FOR CORONARY ARTERY SURGERY

The prevalence of DM among patients who undergo CABG is fairly variable, depending on ethnic or demographic characteristics. In general, most studies of populations in the western world that include all types of patients undergoing scheduled CABG cite a proportion of diabetics ranging from 12% to 30%. These percentages usually refer to diabetics who require some type of treatment.<sup>8,13-19</sup> In our population, which should be no different from the rest of Spain, more than one-third (34.9%) of the 304 patients who underwent isolated CABG in the last two years were diabetics. Most of them (18.4%) were insulin-dependent diabetics, 9.5% took oral anti-diabetics, and 6.9% controlled their condition with diet.

It is worthwhile to emphasize the fact that most studies that analyze chronological changes in the prevalence of different co-morbidities in patients undergoing CABG indicate that the percentage of patients with DM of any type is growing. In one of the most recent publications, Abramov et al<sup>20</sup> found that the percentage of diabetics had increased from 18% to 26% in patients who underwent surgery in the 1990s.

## CLINICAL AND ANATOMICAL CHARACTERISTICS OF DIABETIC PATIENTS UNDERGOING SURGERY

### Clinical characteristics

Diabetic patients undergoing CABG have less favorable demographic, clinical, and anatomic characteristics for surgery than non-diabetics. These patients are usually older, generally women, and more frequently have a history of hypertension or AMI.<sup>13,21</sup> Diabetics often have more advanced functional deterioration at the time of the intervention, CCS or NYHA grade III or IV disease, and more frequent manifestations of CHD.<sup>13</sup>

### Anatomical characteristics

DM is frequently associated to more severe coronary artery disease, with involvement of a larger number of vessels and more lesions. In addition, the diabetic patient usually has a more depressed ventricular function. In a recently published study, Wendler et al<sup>17</sup> found that patients with DM who underwent surgical revascularization had a significantly higher prevalence of three-vessel disease, 93% versus 83%, and a mean ejection fraction 5 points lower than that of non-diabetic patients. In our population, similar differences were appreciated. The diabetics had a significantly greater number of significant coronary stenoses, 3.6 versus

3.1, and a significantly lower ejection fraction, 0.49 versus 0.54, than non-diabetics. Nevertheless, the differences in the extension of coronary atherosclerosis become less marked when only patients with multivessel disease are compared. Kurbaan et al,<sup>18</sup> after analyzing the coronariographies of the patients included in the CABRI study, which compared the results of PTCA and surgery in patients with multivessel coronary disease, quantified the extension of coronary disease using different scales. Although patients with DM had a higher score before revascularization, which was indicative of a greater number of diseased segments, the difference did not reach significance. Therefore, although it seems clear that diabetics had more multivessel disease, the extension of coronary disease when only diabetic patients were considered might not differ excessively. However, this finding contrasts with clinical evidence that more distal anastomoses have to be made in diabetics to achieve complete revascularization.<sup>22-24</sup>

On the other hand, diabetics, particularly women, usually have distal beds of a smaller caliber. It has been observed that diabetics, even before developing evident coronary disease, have coronary arteries that are smaller in diameter than those of general population.<sup>25</sup> The cause could be an increase in vascular tone, incipient diffuse atherosclerosis, or both. Using angiographic quantification techniques in a group of patients undergoing percutaneous revascularization, Schofer et al<sup>26</sup> also found that the mean caliber of the coronary arteries of insulin-dependent patients was smaller than in non-diabetics. Similar observations have been made with intracoronary echography.<sup>27</sup> In addition, the distal beds of these patients often show diffuse disease and have more extensive zones of calcification. These circumstances, although difficult to quantify and record, can make conventional surgery difficult or impossible, and compromise the intermediate and long-term patency of coronary grafts. These unfavorable anatomic abnormalities are more important in older patients, when diabetes is prolonged and other vascular complications are associated.<sup>28</sup>

### Comorbidity

As a result of the microvascular and macrovascular disturbances that it produces, DM is associated more frequently to a series of structural and functional anomalies in organs other than the heart that influence the surgical act itself and the perioperative treatment of patients. The deterioration of kidney function as a result of diabetic nephropathy and peripheral vascular disease, especially in the lower limbs and supra-aortic trunks, are of special interest. These points are commented further ahead, when the preoperative assessment is discussed.

## INDICATIONS FOR SURGERY IN DIABETICS

In general, the indications for surgical revascularization in diabetics are the same as in the general population. Nonetheless, as indicated in the guidelines of the American College of Cardiology and American Heart Association for the treatment of patients with chronic stable angina,<sup>29</sup> when the patient's clinical situation is an indication for revascularization and multivessel disease exists, surgery must be chosen regardless of coronary anatomy, given the evident long-term advantages of CABG on PTCA.

A situation that requires special assessment is that of patients with diabetic nephropathy. In insulin-dependent patients with chronic kidney failure and significant stenosis of at least one of the three main vessels, it has been demonstrated that surgical revascularization significantly reduces the incidence of ischemic episodes and improves survival in comparison with medical treatment.<sup>30</sup> Patients with diabetic nephropathy who require kidney transplantation are of special interest. Up to one-third of them may have severe IHD, even in the absence of symptoms or other clinical markers of IHD.<sup>30,31</sup> In this group of patients, precise knowledge of the coronary anatomy is justified and the surgical revascularization in the presence of multivessel disease is necessary.

## PREOPERATIVE ASSESSMENT

As has been commented, patients with DM more frequently have associated extracardiac pathologies that have a significant influence on the appearance of postoperative complications. Peripheral vascular disease, especially of the carotid arteries, and kidney dysfunction are the most frequent of all of them and must be carefully investigated before surgery.

A thorough interview should investigate especially the presence of intermittent claudication or other manifestations of arterial involvement of other territories, particularly the cerebral and intestinal territories. In the physical examination, the presence of carotid, abdominal, or femoral bruits, the abolition of peripheral pulses, or the presence of pulsatile masses, findings suggestive of stenosis or arterial occlusion, or aneurysm of the abdominal aorta or other arterial territories. The correct assessment of an associated peripheral vascular disease is very useful for selecting the most suitable limb for obtaining the saphenous vein. It alerts us to the possible presence of obstruction of the subclavian arteries, which contraindicates the use of pediculated internal mammary artery (IMA) with conservation of its origin on the subclavian artery. In addition, it allows us to choose a suitable site for the insertion of a counter-pulsation balloon, if needed, or, in extreme cases, it may be a contraindication for its use.

The absence of a carotid bruit or previous neurological symptoms does not exclude the presence of significant cerebrovascular disease, which is why it is recommended that echo-Doppler of the supra-aortic trunks be performed to exclude it in patients with a high-risk profile for carotid disease. Since DM has been identified as a determinant factor of significant carotid disease,<sup>32</sup> it is recommended that this test be made in diabetics over 65 years old whenever other risk factors coexist, like female sex, a history of smoking habit or cerebral ischemic accident, or disease of the common left coronary trunk, given its narrow relation with cerebrovascular disease.<sup>33,34</sup> What to do when the test is positive exceeds the objectives of this monograph.

The renal function of patients with DM must also be evaluated carefully before surgery by routine tests and, if necessary, the determination of creatinine clearance. The finding of abnormal renal function requires adequate preoperative hydration of the patient, as well as special caution in the use and dosage of nephrotoxic drugs. In general, non-steroid anti-inflammatory drugs and angiotensin converting enzyme inhibitors should be discontinued in all clinically stable diabetics 48 h before surgery, regardless of their renal function.<sup>35</sup>

Another important and specific aspect of these patients is the control of glycemia before and after the intervention. The patients who are well-controlled at time of surgery must receive the same doses of insulin or oral anti-diabetics that they were taking up until the morning of the surgical intervention. However, slow-acting insulins should be replaced by intermediate-action insulins one or two days before surgery.<sup>36</sup> On the morning of the operation, continuous intravenous insulin administration is begun in all the patients and maintained until postoperative day 3, following a protocol designed to keep glycemia between 150 mg/dL and 200 mg/dL throughout this period.<sup>37</sup> Patients who are not well-controlled at the time of admission must be assessed by endocrinology specialists in order to maintain glycemia in this optimal range.

Insulin-dependent patients who are using protamine preparations have a greater risk of presenting adverse reactions to this drug when heparin is discontinued after cardiopulmonary bypass.<sup>38</sup> Since transdermal exposure is of limited value in identifying protamine allergy, it is prudent to give a test dose to detect hemodynamic changes suggestive of an adverse reaction, like systemic hypotension with elevation of cardiac output and severe pulmonary hypertension with possible secondary right ventricular dysfunction.<sup>39</sup>

## SURGICAL ASPECTS

There are some differential aspects in the strategy of CABG in diabetic patients that should be commented

in greater extension, especially with respect to the choice and treatment of coronary grafts.

### Choice of grafts

DM has been related to an accelerated progression of atherosclerosis in native coronary arteries, revascularized or not, and in coronary grafts, especially saphenous vein grafts.<sup>18,40-42</sup> Although the first progression of atherosclerosis cannot be modified with surgery, longer-lasting grafts can be used to improve the long-term clinical results of surgical revascularization. The histological and histochemical characteristics of the IMA provide natural resistance to atherosclerosis,<sup>43</sup> which makes it the graft of choice in diabetic patients. From a clinical viewpoint, it has been widely demonstrated that revascularization of the anterior descending coronary artery with the IMA significantly improves mortality and the delayed incidence of unfavorable episodes (recurrence of angina, new AMIs, and new bypass procedures).<sup>44,45</sup> This advantage is even greater in diabetic patients, in which surgery improves the 7-year survival by more than 20 points, fundamentally at the expense of the group of patients in which the IMA is used, a has been demonstrated convincingly by the BARI study.<sup>8</sup> In addition, the use of both IMAs in «T» or «Y» grafts allows all the branches of the left coronary to be revascularized with arterial grafts and, sometimes, the distal branches of the right coronary.<sup>46</sup>

Nevertheless, the use of this graft in diabetics, especially both IMAs, is associated to a significant increment in sternal complications. It has been demonstrated that dissection of the IMA according to the classic technique, that is to say, as a musculo-aponeurotic pedicle with the artery and its two satellite veins, greatly reduces sternal vascularization, especially in the case of bilateral dissection.<sup>47,48</sup> Although this phenomenon reverts completely in about a month, it inevitably compromises sternal healing and can condition the appearance of dehiscence and surgical wound infection. Although some investigators have found that even the dissection of a single pediculated IMA is an independent factor for mediastinitis,<sup>37</sup> more exhaustive studies have not confirmed this finding.<sup>49,50</sup> However, this is not the case when both IMAs are used. Various studies with a large number of patients have confirmed that this technique increases 5 to 15-fold the risk of mediastinitis in diabetic patients.<sup>49,51,52</sup> These results have caused most teams to conclude that the use of two IMAs is contraindicated in diabetic patients.

This disadvantage can be overcome with a «skeletalized» IMA preparation. The isolated vessel is totally dissected and the musculo-aponeurotic tissue surrounding it is conserved. It has been demonstrated experimentally<sup>53</sup> and clinically<sup>54</sup> that this technique reduces the loss of sternal vascularization by preserving the collateral branches. These branches are perfused from

the thoracic aorta through the intercostal arteries.<sup>55</sup> This favors the healing of the sternal wound and reduces the incidence of dehiscence and mediastinitis. In a recent retrospective study, Matsa et al<sup>56</sup> report an incidence of mediastinitis of only 2.6% using both skeletonized IMAs in diabetic patients, which is not significantly greater than the 1.7% seen in non-diabetics. Nevertheless, the incidence of mediastinitis was 15% in obese diabetic women, so the authors recommend avoiding this technique in this subgroup. In another retrospective study by Calafiore et al,<sup>57</sup> the incidence of mediastinitis in diabetics in which skeletonized IMAs were dissected was 2%, similar to that seen in non-diabetics and significantly lower than the 10% observed in patients with DM in which the IMAs were dissected conventionally. On the other hand, Pevni et al<sup>58</sup> have used this technique in 206 diabetic patients, obtaining an incidence of deep wound infection of only 1.9%, almost identical to the 1.7% found in non-diabetics. Finally, Bical et al<sup>59</sup> have operated on 63 diabetic patients using this technique without sternal complications. Therefore, and although no prospective, randomized studies that conclusively guarantee these results have been made to date, it seems that the low incidence of wound complications, together with the apparent long-term benefit that is obtained using both IMAs, make the use of this technique advisable in most diabetic patients.

Skeletonization offers another advantage for these patients who, as mentioned earlier, usually have more diseased vessels and more distal lesions than non-diabetic patients. This technique frees the vessel from musculo-aponeurotic bridges that restrict their expansion and longitudinal stretching, thus making it possible to obtain a longer graft than when the vessel is dissected as a pedicle.<sup>60</sup> This makes it possible to reach more distal segments of the coronary arteries. In association with the increased facility for making side-to-side anastomosis, it makes it easier to achieve complete arterial revascularization.<sup>57</sup>

In patients in which this technique is not possible or who present other circumstances that make the use of IMAs inadvisable, alternative vessels can be used, like the radial arteries and, more rarely, the right gastroepiploic arteries or lower epigastric arteries.

In recent years, the frequency with which radial arteries (RA) are used as the second arterial graft has increased. This vessel has been used as a coronary graft for almost two decades, although it was initially rejected due to the scant rate of early permeability due to a greater tendency to suffer spasms.<sup>61</sup> Nevertheless, improvements in perioperative pharmacological treatment and improved patient selection have made it possible to achieve better short and intermediate-term permeability results than with the saphenous vein, about 80% at 5 years.<sup>62</sup> These results justify the increasing use of RAs. When used with an IMA, complete

arterial revascularization can be achieved, at least in the territory of the left coronary. This allows the controversial use of two IMAs in diabetic patients to be avoided. Although the arteries of diabetics show changes in endothelial function that lead to an exaggerated vascular reactivity, RAs used as aortocoronary grafts respond to vasodilator and vasoconstrictor stimuli, whether or not dependent on the endothelium, in a way similar to the IMAs.<sup>62</sup>

Nevertheless, there are some limitations to the use of RAs in diabetics. One problem is that the frequency of calcification of the medial layer is significantly greater in diabetic than in non-diabetic patients. This sometimes impedes the use of grafts that have already been dissected.<sup>61</sup> Another problem is that the thick muscular layer of the RA means that in the presence of competitive flow due to more severe coronary obstruction or a diseased distal vascular bed, with scant runoff, the graft can suffer spasm and early occlusion. For that reason, the coronary artery selected must have severe stenosis and a distal vascular bed of good caliber, free of distal lesions. These requirements are often not met due to diffuse distal disease in diabetic patients.

Finally, the right gastroepiploic artery can be used to revascularize the lower face of the heart, taking advantage of the fact that the long-term patency of this graft is also superior to saphenous vein grafts.<sup>63,64</sup> As in the case of the RAs, and due to the developed muscular layer of the gastroepiploic artery, it should only be used when the coronary artery that it is destined to supply has a severe proximal obstruction.<sup>65</sup> No specific studies exist on the clinical and angiographic results of this graft in diabetics, so it is difficult to make recommendations about its use in these patients. Nevertheless, the absence of atherosclerotic lesions in the grafts that remain permeable at 5 years allow us to recommend their use in young patients, who can benefit more from complete revascularization with arterial grafts.

## IMMEDIATE RESULTS

### Early mortality

DM has traditionally been related with more early mortality in patients who undergo surgery with cardiopulmonary bypass (CPB),<sup>66,67</sup> which also is true in the context of CABG. Herlitz et al<sup>68</sup> found in a prospective study that the hospital mortality of diabetic patients (6.7%) was significantly greater than the 3.0% observed in non-diabetics. The authors related this fact to the greater prevalence of certain circumstances in diabetic patients, such as previous AMI, AHT, obesity, symptoms of CHD, and coexistent peripheral vascular disease, all which are associated with increased risk in coronary artery surgery. When the influence of these

factors was eliminated by multivariate analysis, diabetes was only a weak or even null predictor of early mortality in two larger multicenter studies.<sup>22,69</sup>

Fatal or not, certain postoperative complications are more frequent in diabetic patients.

### Neurological complications

In general terms, the incidence of perioperative acute cerebrovascular accident (ACVA) in the context of coronary artery surgery ranges from 1% to 5%. The etiopathogenic mechanisms cited most frequently are the embolization of particles from the aortic wall or CPB circuit,<sup>70</sup> and the coexistence of significant carotid disease. Although the degree of atheromatosis and aortic manipulation is difficult to quantify, the presence of carotid lesions of 75% or more increases almost 10-fold the risk of neurological complications, even in asymptomatic patients.<sup>34</sup> Diabetes is also clearly associated, although more weakly, to an increase in ACVA after coronary artery surgery. In two studies that analyzed the influence of DM on the appearance of neurological complications after CABG, diabetes increased the risk of ACVA by 1.5 to 3-fold.<sup>70,71</sup> Patients with DM frequently have diffuse atherosclerosis of the cerebral vessels and disturbances in the vasomotor regulation of the central nervous system, circumstances that condition a marginal cerebral flow, even in baseline conditions, and favor the appearance of ischemic lesions.<sup>34</sup> Systematic performance of intraoperative epiaortic echocardiography can help to detect atheroma plaques susceptible to fragmentation and guide the placement of the cannula and aortic clamp. The information obtained may even entail a modification in the revascularization strategy to avoid aortic manipulation entirely.<sup>72</sup>

### Renal complications

Postoperative acute renal failure (ARF) is a serious complication after coronary artery surgery because it greatly increases mortality, especially when extra-renal filtration procedures must be used.<sup>73</sup> The absence of a pulsatile flow during CPB, together with the redistribution of splanchnic and renal flow that takes place during CPB, the release of inflammatory molecules and catecholamines, microembolisms from the CPB circuit or aorta, and the release of hemoglobin from traumatized red blood cells have been implicated in the etiopathogenesis of renal failure after coronary artery surgery.<sup>73</sup> Diabetes mellitus also constitutes an independent risk factor for the development of postoperative ARF. In a major multicenter study that analyzed this problem in coronary artery surgery,<sup>74</sup> the presence of type 1 diabetes doubled the risk of suffering postoperative ARF. Other risk factors that were independently associated with the appearance of pos-

toperative ARF in the general population were plasma creatinine >1.4 mg/dL, NYHA functional class III or IV, and previous coronary artery surgery. When type 1 diabetes coincides with any of these factors, the risk of ARF triples for any of the age categories. In addition, in the 70 to 80-year-old age group, the risk of ARF was 4 times greater in patients with DM and 6 times greater in patients over 80 years old.

In diabetic patients, it is important to maintain a good perfusion pressure and flow during CPB to minimize renal damage.<sup>75</sup> However, even in anephric patients, the aggressive use of hemodialysis during and after surgery makes it possible to carry out interventions with CPB with a mortality and incidence of complications comparable to those found in patients with conserved renal function. Definitively speaking, since DM is a risk for the development of postoperative ARF, the use and dosage of nephrotoxic drugs or contrast agents in these patients should be judiciously assessed. In addition, hydration before and after surgery must be adequate and the perioperative control of hemodynamic parameters must be strict in order to maintain high perfusion pressures and reduce CPB times. Intraoperative hemodialysis should be used in selected cases. In addition, when the anatomy of coronary artery disease permits, the possibility of carrying out revascularization without CPB must be assessed as a way of preventing renal morbidity associated with CPB.

### Sternal complications

The most devastating surgical wound complication is mediastinitis. Although its incidence is sometimes higher, it usually affects 1% to 2% of the patients who undergo medial sternotomy.<sup>49,76,77</sup> The importance of this complication derives from its high mortality, which can reach 47%.<sup>78</sup> As in the case of other complications, DM has been identified as a determinant factor of postoperative mediastinitis after CABG.<sup>79</sup> The incidence of this complication in diabetics and its relation with the type of graft used was discussed above. When this complication appears in patients with DM, early mortality increases 2 to 3-fold.<sup>80</sup> For these reasons, in diabetics who will be undergoing coronary artery surgery factors that are important for preventing this complication should be kept in mind, like adequate selection and management of grafts, particularly IMAs, and strict control of glycemia in the immediate postoperative period, as has been mentioned.

### Decompensated diabetes

Hyperglycemia reduces the body's resistance to infection. It has been demonstrated that periods of hyperglycemia are associated with accelerated glycosylation and deactivation of immunoglobulins and C3

complement component.<sup>81,82</sup> In the same way, hyperglycemia produces glycosylation of newly synthesized collagen, activation of collagenase, and a reduction in the proportion of collagen in surgical wounds.<sup>83</sup> On the other hand, leukocytes show disturbances in adhesion, phagocytosis, and chemotaxis, and a reduced bactericidal capacity.<sup>37</sup>

Different studies have demonstrated that when glycemia remains elevated during the first postoperative days, the risk of infectious complications increases, especially mediastinitis.<sup>37</sup> The beginning of a continuous intravenous insulin infusion protocol, known as the *Portland Protocol*, to keep glycemia below 200 mg/dL significantly reduced the incidence of mediastinitis from 2.4% to 1.5%. This decrease was equivalent to a reduction in relative risk of 66%, despite the fact that the treated group included a significantly greater number of obese patients and patients revascularized with the IMA. Although, for obvious reasons, no later randomized studies have been made that can confirm these findings, prospective studies of populations at similar risk have been made. In some of them, the incidence of mediastinitis has been completely eliminated.<sup>84</sup> For that reason, we think that glycemia should be controlled in diabetic patients undergoing any type of cardiac surgery according to this system.

## LONG-TERM RESULTS

### Survival

It is evident that DM is clearly related with a lower survival after coronary artery surgery. This tendency was demonstrated in one of the first large-scale prospective studies of the clinical results of CABG, the CASS study, which included more than 8000 patients. Analysis of the results of this registry show that DM is an independent determinant factor of delayed mortality, with a clear divergence of the risk curves from the first year of follow-up.<sup>85</sup> However, given the time that has passed since this study was made, current trends could be different. Nevertheless, in a recent review by one of the groups that have most investigated the influence of DM on the results of coronary artery surgery, from the Gotenburg University Hospital, Herlitz et al<sup>15</sup> found that the percentage of patients who had died in the first 5 years after surgery was 6 times greater in diabetics than in non-diabetics (12.1% versus 2.1%, respectively). In this and other similar studies,<sup>13,16</sup> DM appears as a factor with an independent influence on long-term survival. Nevertheless, other investigators have concluded that only type 1 diabetes is associated with a less favorable survival.<sup>86</sup> In general, most studies that analyze the long-term results of CABG find significantly lower 5-year actuarial survival rates in diabetics, 15 to 20 points lower.<sup>13,16</sup>

It is interesting that some investigations that centered on subgroups of patients at greater risk, such as patients with poor ventricular function, found no unfavorable effect of DM on intermediate-term mortality. Analyzing the results of the CABRI study, a clinical trial designed to demonstrate the benefits of the implantable defibrillator in patients with severely depressed ventricular function, Whang et al<sup>87</sup> found no significant differences in the poor 2-year survival rate (26% in diabetics and 24% in non-diabetics), although diabetics needed to be hospitalized more frequently for cardiac causes. In another high-risk group, diabetics with nephropathy who required permanent hemodialysis, survival after surgery is especially poor. Although coronary artery surgery can be carried out with little morbidity and mortality in patients of these characteristics, as demonstrated recently by Hosoda et al,<sup>88</sup> the 5-year survival is poor, barely more than 20%, although better than in patients who do not undergo revascularization. This figure contrasts with 89% seen in patients on hemodialysis for causes other than diabetes.

Some authors have identified certain factors that are independently associated with delayed mortality. Among these, kidney failure and depressed left ventricular function are constants in most studies.<sup>15,16,86</sup> Other factors more unequally related with a lower survival are advanced age, female sex, AHT, and smoking.<sup>15,16,87</sup> The influence of certain atherogenic factors could be related to a more rapid progression of coronary artery disease after revascularization, as reported by some investigators.<sup>18,89</sup>

The causes of delayed death also vary in prevalence between diabetics undergoing CABG and other patients. Diabetics undergoing CABG die more frequently of cardiac causes, especially sudden death<sup>16</sup> or refractory heart failure, generally related to new AMIs.<sup>15</sup>

### Relief of symptoms

There is less symptomatic benefit after CABG in diabetics than in non-diabetics, and it is less lasting. In a population of fewer than 2000 patients undergoing CABG in Sweden, Herlitz et al<sup>90</sup> found that 35% of the diabetics and 29% of the non-diabetics had angina 2 years after the intervention, although it only limited physical activity in 19% and 17% of patients, respectively. The persistence or reappearance of manifestations of CHF after revascularization surgery was more frequent in patients with DM. In the same study, only 31% of the diabetics were free of dyspnea at 2 years, a symptom that was absent in 57% of the non-diabetics. In the experience of these investigators, dyspnea is the main symptom responsible for the limitation of activity in diabetics who undergo coronary artery surgery.

## Need for new revascularization procedures

Less consistent relief of the symptoms of IHD after CABG in diabetics makes it possible to predict a greater need for performing new revascularization procedures. Thus, in a numerous group of patients operated on at the University of Emory, the need for PTCA after 5 and 10 years was significantly greater in diabetics.<sup>13</sup> In this same study, new CABG were not performed more frequently in patients who had undergone surgery. This could reflect a more conservative attitude toward the recurrence of angina in these patients, considering the greater possibility of early complications and the less favorable long-term clinical results.

## Quality of life

As can be deduced from the remarks made, DM is accompanied by a poorer quality of life after CABG. Investigators of the University of Gotemburg,<sup>91</sup> using three different scales to assess mental and physical well-being, found that DM, in addition to chronic obstructive pulmonary disease, was the only extracardiac condition to independently determine quality of life 5 years after the intervention. Nevertheless, these results are partly influenced by the worse situation of diabetics before surgery. In fact, quality of life before surgery is a fundamental determinant of the quality of life after the intervention. In another publication by the same group,<sup>92</sup> in which the same scales were used, only the Physical Activity Score showed a more modest, and statistically non-significant, increment in diabetics than in non-diabetics.

## Graft patency

Classic studies of the long-term permeability of saphenous vein grafts identified DM as one of the factors related to the accelerated development of atherosclerosis in venous grafts and, consequently, with their mean long-term permeability.<sup>41</sup> Nevertheless, although the greater atherogenic and thrombogenic load of diabetics could be expected to indicate a worse future for aortocoronary grafts, this has not been demonstrated conclusively, at least when platelet antiaggregants and lipid-lowering drugs are used after surgery. In the Post Coronary Artery Bypass Graft Trial, the influence of these drugs on the long-term permeability of venous grafts and other objectives was analyzed. Hoogwerf et al<sup>93</sup> found no differences in the percentage of grafts occluded per patient at 4 years in diabetics (15.0%) and non-diabetics (13.2%), or in the percentage of grafts per patient with significant angiographic changes (34.5% versus 33.3%, respectively). With regard to IMA grafts, which are more resistant to atherosclerosis, no differences in patency have been documented between diabetics and non-diabetics. Markwitsch et al<sup>94</sup>

have recently investigated the intermediate-term patency of IMA grafts, used as a compound «T» graft for the purpose of achieving complete revascularization with arterial grafts. In their experience, the permeability of IMAs was excellent, better than 98%, in patients with both type 1 and type 2 DM. No data are currently available on the patency in the intermediate and long term of other types of arterial grafts, like RAs, in diabetics, although the initial experiences seem promising.

## STRATEGIES TO IMPROVE THE RESULTS OF SURGERY IN DIABETICS

### Use of arterial grafts

The clinical advantages of using IMAs to revascularize the anterior descending coronary artery are undeniable.<sup>44,45</sup> More debated, although evident in certain anatomic situations or age groups, are the advantages of complete revascularization with arterial grafts, especially in the territory of the left coronary artery.<sup>46</sup> One of the groups that seem to benefit most from the extensive use of arterial grafts are, indeed, diabetic patients. Unfortunately, until now, arterial grafts have been used cautiously in patients with DM, especially two IMAs, for fear of sternal complications.

It is generally accepted that the use of IMAs improves the long-term survival of diabetic patients. In a retrospective study with a long follow-up, Yamamoto et al<sup>95</sup> found that diabetics revascularized with at least one IMA had a survival rate at 13 years of 82%, almost identical to that of non-diabetics in which IMA was used. The advantages of using IMA in diabetics have been clearly demonstrated in prospective studies like the BARI trial,<sup>9</sup> in which it was shown that delayed mortality due to cardiac causes in surgically revascularized diabetics is fairly similar to that of non-diabetics (76.4% versus 86.4%) as long as at least one IMA is used. The difference in survival is more evident and early in patients with more severe DM, who are treated with insulin. The survival benefit obtained from CABG seems to derive from a greater capacity to survive a new AMI due to the fact that perfusion of the anterior face of the heart is ensured by a patent IMA graft. Other investigators have found similar survival results, as well as the relief of symptoms.<sup>14</sup>

### Revascularization without CPB

CABG without CPB is a technique that generally has a lower incidence of hematological, neurological, and renal complications,<sup>96</sup> which is why it could be especially advantageous in diabetics. Nevertheless, as we have already commented, the less favorable characteristics of the coronary arteries in patients with DM, in which diffuse atherosclerosis and calcifica-



tions are more frequent, and left ventricular hypertrophy is usually present, make these patients poor candidates for this strategy. This is probably why the reduction in operative mortality that has been seen in CABG without CPB in the general population has not been demonstrated, at least not consistently, in diabetics.<sup>97</sup>

Although coronary surgery without CPB reduces manipulation of the aorta and eliminates the cardiopulmonary bypass circuit, it has not been demonstrated clearly that this strategy reduces the incidence of neurological complications in diabetic patients.<sup>97</sup>

In spite of these limitations, it seems that eliminating CPB reduces the incidence of certain types of complications in patients with DM, especially the need to administer hemoderivates, prolonged mechanical ventilation, atrial fibrillation, and kidney failure, which are of special interest in diabetics. In a series published recently by Magee et al<sup>97</sup> diabetic patients operated on without CPB had to be dialyzed less frequently than patients who underwent cardiopulmonary bypass, in spite of having a greater incidence of preoperative ARF. Similar findings have been confirmed in other studies<sup>96</sup> that, nevertheless, demonstrate that the reduction in renal morbidity is limited fundamentally to patients at high risk of postoperative kidney dysfunction. These results coincide with those of other investigations in which exhaustive measurements of kidney function were made, such as glomerular filtration rate, effective renal plasma flow, renal and systemic vascular resistance, and creatinine clearance before, during, and after CPB, revealing that it induces scant changes in these parameters in patients without previous ARF.<sup>98</sup>

Nevertheless, fewer distal anastomoses are made in CABG without CPB<sup>96,97</sup> because it is more difficult to carry out an extensive revascularization of the inferior and lateral face on a beating heart. In clinical practice, the diabetic requires a larger number of distal anastomoses to achieve complete revascularization,<sup>22-24</sup> it is to be expected that only a selected group of these patients can benefit from surgery without CPB, if the aim is complete revascularization.

### Better medical treatment

The strict control of glycemia is important, not only in the immediate postoperative period, but also in the long term. The UK Prospective Diabetes Study<sup>99</sup> demonstrated that strict control of glycemia, maintaining plasma glucose below 6 mmol/L, reduces microvascular complications and acute cardiac accidents. Based on this result, it can be ventured that maintaining glycemia within normal range also should reduce the incidence of delayed coronary accidents after surgery. In addition, other secondary prevention measures, which often are underused, have been demonstrated to be as

effective or more effective in diabetics than in non-diabetics. Consequently, in the specific context of diabetics undergoing CABG, the Post Coronary Artery Bypass Graft Trial<sup>93</sup> demonstrated that an aggressive reduction of plasma lipids, keeping LDL cholesterol below 85 mg/dL significantly reduces the appearance of ischemic complications and improves the permeability of aortocoronary grafts. Other investigators have found similar advantages with this strategy.<sup>100</sup>

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