Advances in Coronary Heart Disease Surgery in Latin America

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Background—The beginnings of coronary artery bypass graft in Latin America could be set in the year 1971. Since then, improvements in technique and greater experience have resulted in a rapid increase in the rate of interventions performed in the region.

Methods and Results—Searches through PubMed and Literatura Latinoamericana y del Caribe en Ciencias de la Salud, as well as personal communications from specialists from Latin America, have been the source of information. Articles were selected by their content related to the theme, and the authors’ nationality and information is mainly from Latin America. Demographic information of the population of Latin America denotes higher age averages, and this implies an increase in the severity of comorbidities in patients who undergo surgery. Longer life expectancy and improvements in medical therapy have implied that patients survive a first intervention beyond the expected time a bypass persists patent. Wall vessel properties of arterial conduits, plus a better anastomotic technique, seem to be the current solution to worsening in the coronary health of patients who undergo revascularization surgery in Latin America.

Conclusions—Despite scarce economic investment in medical sciences, many academic groups contribute to the exploration of therapeutic pharmacological combinations and inclusively apply genetic strategies. (Circulation. 2007; 115:1147-1153.)

Key Words: cardiopulmonary bypass ■ coronary disease ■ epidemiology ■ revascularization

The beginnings of coronary artery bypass graft (CABG) in Latin America could be set in the year 1971 when Dr Rene Favaloro returned to his native country to encourage coronary artery bypass surgery in the region. This technique is now performed with a median sternotomy. To minimize perioperative damage and protect the myocardium, the technique includes a period of aortic cross-clamping plus infusion of cold cardioplegia solutions. Novel techniques such as minithoracotomy (an attempt to diminish delays in patient recovery) and off-pump approaches are now used.

Coronary heart disease and CABG have evolved concurrently with more sophisticated medical approaches and improvement in technique. On the other hand, the patient himself has changed because of changes in modern lifestyle, partially related to industrialization and sedentary urban life. All of these cultural changes seem to have turned atherosclerosis into a much more aggressive process. Moreover, an increase in average life expectancy in modern civilization carries with it a great concern for quality of life. Consequently, therapeutics should not only consider the probable result achieved in mortality but also should pay considerable attention to matters that affect morbidity in the short and long term, such as neurological implications of on-pump procedures.

In addition to the developments mentioned above, the huge advances and widespread use of percutaneous coronary interventions (PCI) have mainly provoked a shift of patients with severe comorbidities to the operating room. Searches through PubMed and Literatura Latinoamericana y del Caribe en Ciencias de la Salud, as well as personal communications with specialists from Latin America, have been the source of information described below.

Changes in Patient Characteristics Between 1971 and 2005 in Latin America

In the Coronary Artery Surgery Study (CASS), operative mortality averaged 2.3%. When the Society of Thoracic Surgeons analyzed the period from 1980 to 1990, mortality related to CABG was estimated at 3.2%. However, an analysis of patient characteristics revealed both a trend toward a higher average age and an increase in reoperations as well as in emergency and urgent interventions. Some of the...
principal factors that have made an impact on CABG and its results have been analyzed in Latin America.

Age

One of the major and generally accepted determinants of increased mortality and morbidity risk is age. Insufficient evidence exists in randomized clinical trials on patients ≥80 years of age. As age increases, the odds ratio of death in coronary surgery rises exponentially. Mortality is proportionally greater in the eldest (18% in patients ≥80 years old versus 4% in those <70 years old), which correlates with the importance of age in determining the Parsonnet score. Special attention should be paid to surgery in patients ≥80 years old, because this subset of the population is expected to increase to 1 million by 2010, according to recent statistical estimations. The increase in average age of the population is a probable consequence of better medical resources in urban areas and extended healthcare advice provided by Latin American Health Care Systems in some social sectors.

When the bypass technique was first performed, the range of age of patients varied from 26 to 69 years. From 1996 to 1998, Brazilian registries showed a mean age of 59.9 years (SD 10) for patients undergoing CABG,7 and recent data revealed an increase to 63.12 years (SD 8.76). A similar trend was recently reported in Argentina, with a mean age of 63.3 years (SD 9.5). Meanwhile, women seem to be most frequently included in the series of patients ≥80 years old who are undergoing operation, with a rate of 28.57% compared with only 13.23% in the group <70 years old. On the contrary, most series with a lower average age have a predominance of male sex. This observation could correlate with the global trend in Latin America to treat women less aggressively than men.

Parallel to the above-mentioned increase in age ranges is the cumulative increase in the number and severity of comorbidities of patients undergoing surgery. Reports from different South American countries describe the following associated diseases: renal insufficiency, 1.6%; gastrointestinal disease, 1%; peripheral vascular arterial disease, 3%; stroke, 3%; and chronic obstructive pulmonary disease, 4.7%.

Diabetes Mellitus

The prevalence of diabetes mellitus in Latin America is expected to double within the next couple of decades. Type 2 diabetes mellitus is already among the top 10 causes of mortality in the Latin American adult population because of chronic complications related to premature and accelerated atherosclerosis.

From a surgical technical point of view, this factor seems to be related to a poor distal vascular runoff. Some articles have reported that 22% of cases of diabetic patients were referred for CABG from 1997 to 2001, a percentage which is similar to that of larger series that include patients from 1997 to 2005 and slightly inferior to data reported in global registries (27% of diabetic patients in 2005). This emerging situation and the question of how a diabetic patient should preferably be revascularized, PCI with drug-eluting stents versus CABG, has lead to the design of the Future Revascu-
limited by the deteriorated state of the distal microvasculature and endothelial dysfunction. A perspective from Latin America’s pathologists, surgeons and clinicians is described in the present summary.

**Improvement in CABG Technique and Subsequent Outcomes in Latin America**

No global record has been performed to analyze CABG results in Latin America. However, many results from this region deserve to be outlined. In Chile, between 1971 and 1998, ≈5000 CABG procedures were conducted from most of Chile’s active and tertiary hospitals. The information provided indicates that the number of grafts per patient in Chile increased from 1.9 to 3.4 between 1971 and 1998, the use of arterial conduits increased from 0.18% to 0.81%, and perioperative mortality remained constant in 1.6% of cases.

In 2003, a Brazilian group financed by the Ministry of Health reported that mortality results of CABG were mainly dependent on the number of procedures per year. Recent reports show mortality event rates of 7.8%. Overall, ≈35 000 CABG per year (ie, 205 CABG per million inhabitants) are performed in Brazil (personal communication from E. Buffolo, November, 2005).

The database from the Favaloro Foundation in Argentina includes a total of 7697 CABG procedures from 1997 to 2005, of which 14% are combined with valvular surgery and 1% are associated with carotid intervention. The overall mortality rate in this single site declined from 5.9% to 4.4%. The proportion of bypass surgeries performed in the elderly (>80 years old) increased from 1.7% to 6.3% in 2005. In these series, 84.7% of the total number of myocardial revascularization surgeries were on-pump.

It is worth noting that Latin America’s medical institutions have also dealt with the consequences of economic difficulties, which have caused transitory alterations in which surgical interventions are selected. This could be observed in recent data supplied from Argentina, which suffered a financial collapse between 2000 and 2004 (Figure 1).

![Figure 1. Impact of financial crisis on PCI and on CABG in Argentina.](http://circ.ahajournals.org/)

As a consequence, despite financial difficulties, patients are taken into the operating room at older ages and with a greater number of comorbidities than in the past; patients undergo invasive procedures even with concomitant illnesses that were previously considered to be a reason for exclusion, and overall perioperative mortality has remained quite unchanged in this region.

Since an initial period of skill acquisition and technical learning in the 1970s, when the mortality rate was extremely high in patients with severe obstruction of the left main coronary artery, mainly because of the use of the patch-graft technique, CABG has become widely applied, and patients with left main coronary artery lesions have benefitted. The next step after disappointing patch-graft results was a saphenous vein graft, which used end-to-end anastomoses, renamed as an interposed technique.

At first, the venous graft interposition was indicated in short localized segmental occlusion at the middle and distal thirds of the right coronary artery. This approach was extended to the rest of the native vessels. Patients with diffuse coronary artery disease showed definite areas of myocardial damage and worse ventricle function. This group of patients was excluded from surgery at the beginning of the 1970s, whereas such a patient now constitutes a frequent candidate for revascularization surgery. Essentially, inappropriate distal vascular runoff has been identified as an independent predictor of mortality in the long term and is also related to the rate of reintervention during follow-up.

Physics applied through the Poiseuille law has demonstrated that the diameters of the chosen conduits play a major role in the flow and pressure gradient developed in the graft that reaches the distal vascular runoff. This has led to the development of new techniques to Anastomose grafts sequentially with primarily arterial conduits because they remain patent for longer periods.

After the great results of left internal mammary artery grafting in myocardial revascularization, wider use of arterial grafts was attempted. Then the 2 internal thoracic arteries were used. The radial artery (RA) gave poor results when initially used, mainly because of errors in handling of the conduit. After surgeons learned how to prepare the RA after it was dissected, its use was restarted, and many trials have dealt with the search for the best anastomotic location for this arterial conduit.

Composite grafts of the left internal mammary artery and the RA anastomosed with “Y” technique to the left internal mammary artery, or a modified technique with the left internal mammary artery anastomosed to the RA, which was
previously sequentially anastomosed to the left main anterior descending coronary artery and marginal branches, solved the problem of disproportionate diameters. The modified technique improved the mean peak velocity of the graft, and total blood supply to the revascularized left main anterior descending coronary artery and its branches was satisfactory with both composite techniques. The RA has also proven to be a satisfactory conduit in patients >70 years of age.

In 1997, in this region, endarterectomy was performed in 0.001% of cases and increased to 2% in recent years according to database analyses. An average of 2.83 bypasses per surgery are accomplished. Exclusive arterial revascularization accounted for 42% of cases, and 73% of cases used double internal thoracic arteries.

In the 1990s, arterial conduit usage was encouraged by previous results with the internal thoracic artery. Other arteries, such as the epigastric and gastroepiploic, are less used (0.007 per surgery in 1997 and 0.003 per surgery in 2004), primarily because of more difficult and complex accessibility, and they have been replaced by improved techniques with free grafts with radial and internal thoracic arteries.

Meanwhile, since the beginning of the present century, the increased frequency of previous stenting performed in native arteries significantly compromises the quality of the distal anastomotic point within the vessel. A 2-fold increase in the antecedent of prior stenting in patients derived for CABG from 1997 to 2004 (8.6% to 15%) has been observed (personal communication from the Favaloro Foundation database center, October, 2005).

Consequently, wall vessel properties of arterial conduits plus a better anastomotic technique that applies the Poiseuille equation seem to be the solution for the time being to the worsening condition of the coronary anatomy of patients referred for revascularization surgery in Latin America.

Longer survival and the previously mentioned improvements in therapy imply that patients survive a first CABG longer than the time that bypass patency is expected to persist. Consequently, the need for a second intervention on the same patient has become a frequent reality.

Mean time from the first coronary surgery to reoperation is estimated according to observational data as 12.5 years. Reoperation is frequently seen with previously stented vessels or diabetic patients. Despite the fact that reductions in mortality rates from 2% to 6% for reoperation have been achieved with the technological advances in CABG and with the introduction of PCI for bypass graft lesions, in-hospital mortality still increases significantly from 3.8% to 10.1% when patients from first surgery are compared with those referred for reoperation.

Development of better techniques and a reduction of surgical times have been important advances in CHD surgery. These advances were achieved by off-pump surgery, retrograde cardioplegia infusion for severely deteriorated ventricles, ventricular remodeling surgical techniques, and improved arterial conduit selection.

Even physiological experiments consider the possible role of certain anesthetics to induce preconditioning and, thus, ischemia tolerance. Another important factor in better results with off-pump surgery is the development of more efficient stabilizers, such as Octopus.

The Brazilian experience with off-pump revascularization has yielded positive results. A report from Curitiba includes a total of 1440 off-pump CABG from 1999 to 2004. In 1999, almost 50% of myocardial revascularized patients underwent off-pump surgery. Use of this surgical technique grew to 21% during the last 23 years and 49% in the last 5 years with a mean of 1.9 grafts per patient.

In some reports from Argentina, this technique is mainly reserved for elderly patients >80 years of age (4.6% off-pump versus 2.5% on-pump), with fewer postoperative complications and a significantly lower mortality rate (4.3% in the group that ranged from 70 to 79 years of age and 11% in the group >80 years of age with off-pump CABG versus 7.9% and 13% with on-pump CABG, respectively). Historical concepts about the limitations of off-pump surgery for complete revascularization are still a question of debate.

Tendencies in Latin America reflect differences in the rate of application of this technique all around the continent. Although off-pump surgery is the rule in certain institutions, other institutions apply selection criteria related to the patient’s risk when this kind of procedure is chosen.

With regard to remodeling techniques for the failing and dilated left ventricle, special care must be taken if remodeling of akinetic muscle or even diskinetic regions is considered. Remodeling is performed in some Brazilian teams in almost 9% of cases (personal communication from E. Buffolo, November, 2005), whereas in Argentina the rates of remodeling technique use are estimated at 2.23%.

More advanced technologies such as robotics applied to myocardial revascularization are still under investigation, and no clear guidelines of indication are available in Latin America because of scarce experience in this field. However, morbidity currently seems to be the actual difficulty to be worked out, and a tendency toward less invasive procedures and shorter pump times is the gold standard. In any case, atherosclerosis continues to progress even in the best arterial conduit, and microvascular damage still represents a limitation to resolve.

Pharmacological Therapy in CABG

The Impact of Cardioplegia

Favorable outcomes with respect to postoperative ventricular function are in large part dependent on optimal intraoperative myocardial protection. Early cardioplegia techniques relied on cold crystalloid to initiate and maintain intraoperative cardiac arrest. Blood cardioplegia facilitates myocardial aerobic metabolism and reduces lactate production. Novel approaches with separate administration or additional additives such as sodium–hydrogen exchange myocardial protectants are under investigation.

Pharmacological Approaches After CABG

The early occlusion of arterial bypass grafts is a frequent situation that historically has oscillated at around 15% of cases during the first month after an intervention. Mechanical reasons such as small lumen size of the grafted vessel, slower
flow within the venous grafts, and even kinking phenomena of the conduits constitute the principal causes.

However, thrombotic occlusion in distal anastomoses, largely composed of platelets, is not infrequent. During a prolonged time period, it was observed that platelet disposition in mechanical anastomotic sites predisposed to very early intimal hyperplasia, which was capable of reducing the vessel lumen diameter in $\sim 30\%$ of cases, and this observation has been the basis for rational antithrombotic therapy.

Many years ago, pharmacological combination of aspirin and dipyridamol, both administered before the surgical procedure, was the motif of attention in clinical assays that compared drug effect versus placebo. The initial results were encouraging: $3\%$ distal occlusion versus $10\%$ in the placebo group. Angiographies performed at 1 year of follow-up still revealed extremely positive results: $22\%$ distal occlusions versus twice that value in the placebo group.$^{31}$

This pharmacological combination proved to be safe from the standpoint of hemorrhagic events. Nevertheless, routine use did not extend universally, and the drug dipyridamol was discarded from therapy as it became understood that the benefit was essentially derived from the aspirin prescription.$^{32}$ Latin America was a pioneer in these experiences on antithrombotic pharmacological combinations, particularly in mechanical heart valve replacement.$^{33}$

The rapid and wide familiarity of cardiologists with the use of clopidogrel in patients who undergo PCI, such as those patients who are not prescribed an early invasive strategy for acute coronary syndrome, does not correlate with the situation of patients who undergo CABG. At the moment, no solid experience with consistent evidence exists. Nor has Latin America introduced this tiengoprin under such circumstances, with the exception of formal contraindication for salicylic acid administration. With regard to anticoagulation, some randomized trials suggested an early benefit to this strategy.$^{34}$ However, ticlopidine,$^{35}$ like aspirin, has been shown to be as effective as anticoagulation added to aspirin in terms of continuation and maintenance of graft conduit patency.$^{36}$ The sustained role of anticoagulation in the context of coronary surgery could be defied by the recent assays on bivalirudina administered during the intervention itself. The first reports on this matter are currently being published.$^{37}$

Undoubtedly, beyond the initial months after CABG, survival challenge of the grafts depends on the aggressive intensity of the atherosclerotic process. Patency of the conduits is greatly menaced by inappropriate control of the traditional risk factors such as hypercholesterolemia and hyperglycemia. After multiple-vessel CABG, patients who require only 1 PCI ($3.9\%$ cases) accounted mainly for a native artery ($67\%$) and to a lesser extent to a venous graft ($29.4\%$); less frequently, an arterial conduit required PCI ($3.5\%$). When $>1$ stent was implanted after CABG, $40\%$ were a combination of native and venous grafts, and $53\%$ of cases used a native artery as observed in some series (Favaloro Foundation Database).

**Future Directions: Gene Therapy in Latin America**

Inadequate distal territory in patients who undergo bypass surgery usually means an obstructive atherosclerotic lesion in epicardial arteries of a size so small that no surgical connections can be made, or in plaques that extend through most of the artery length, such as those that occur in diabetic patients.$^{38}$ However, it must be considered that most of the coronary circulation is intramyocardial and forms part of the distal arterial territory as well. Most of these arteries range in diameter between 10 and $300 \mu m$ and are part of what is usually defined as “microcirculation,” a rather vague term that encompasses vessels with different functions, such as small arteries and capillaries; the only property these vessels share is a size between 0.2 to $3 \ mm$. These arteries are considered to be partially responsible for the coronary flow reserve. They act as resistance vessels so that the aortic pressure (mean, $90 \ mm Hg$) is brought down to a precapillary pressure of $45 \ mm Hg$. It is well known that vascular reactivity in nonstenotic segments of the coronary circulation in patients with angiographically documented coronary artery stenosis is abnormal as well.$^{39,40,41}$

Noncoronary factors comprise both functional, such as abnormal vasodilatation, and structural abnormalities in the macro- and microvasculature, respectively, as well as increased extravascular resistance that results from left ventricular hypertrophy, interstitial fibrosis, and abnormal structure of the microcirculation.$^{42}$ Under these circumstances, restitution of the coronary flow can be obtained in most patients who undergo bypass surgery; in $\sim 10\%$ to $\sim 20\%$ of patients, symptoms persist despite the presence of a patent artery.$^{43,44}$

At the present time, an intensive search for methods that may induce angiogenesis and/or arteriogenesis is underway. Angiogenesis refers to the sprouting of capillaries from preexisting vessels. Arteriogenesis refers to the blood vessel remodeling, and to the enlargement of new and existing vessels, primarily arterioles, to establish if the decrease in coronary reserve is due to modification of the capillaries, of the arteries, or of both, and is important for the design of strategies tending to increase that reserve.

To find out which patients may eventually benefit from that therapy, studies have been carried out on the size of the arteriolar compartment in human hearts with different pathologies (eg, hypertensive hypertrophy or nonischemic dilated and hypertrophic cardiomyopathy). All these conditions presented a significant decrease in the length density (mm of arterioles contained in $1 \ mm^3$ of myocardium) as compared with normal hearts, especially in small arteries 20 to $100 \mu m$ in diameter.

Some Latin American institutions have been engaged during the last few years with the effect of transfection with genes coding for growth factors on the evolution of chronic and acute myocardial ischemia in large animal models. The main results of those studies are that transfection with a relatively high dose of human vascular endothelial growth factor 165 gene induces a marked arteriogenesis in pigs with chronic ischemia and in sheep with acute myocardial infarction.$^{47}$ In addition, it induces replication and hyperplasia of adult cardiomyocytes and an improvement in ventricular function$^{48,49}$ (Figure 2).

These results provided the basis for a phase I trial,$^{49}$ which started in the present year, on the effect of transfection with the same gene, as well as with a relatively high dose, in “no
option” patients with chronic ischemia and in patients undergoing bypass surgery with nonrevascularizable territories or with pathologies susceptible to development of microcirculation alterations, such as diabetes mellitus or secondary hypertrophies. The trial will be started with a high dose of vascular endothelial growth factor 165, despite recent reports with low doses of vascular endothelial growth factor 165.30

Conclusions
The Latin American region is protagonist and witness of the cardiovascular surgery evolution in recent decades. One of the most transcendental steps beyond manual technological developments has probably been medical education and teaching in this region by qualified skilled surgeons. Heterogeneity of the Latin world, frequently affected by social crisis, has succeeded in defying such limitation with particular devotion.

The great rate of healthcare demand for a population of ~400 million probably contributes to the reduced number of articles published from this part of the continent, comprising <0.5% of scientific publications. Despite scarce economic investment in medical sciences (<1% of the region’s gross domestic product), many academic groups are exploring therapeutic pharmacological combinations and applying techniques practiced seriously in animal models and inclusive genetic strategies. In this context, the kindness of everyone who has collaborated in providing data to transmit to the scientific community through this generous supplement deserves our recognition. However, we are aware that the coronary bypass graft is not the final goal. The objective, still far away in this part of the world, will continue to be prevention as the main standard. Continuing medical education, like teaching, will always be the foundation for more sophisticated advances in Latin America’s medicine.

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Disclosures
None.

References

Figure 2. Histological analysis of myocardial tissue sections 10 days after coronary artery ligation revealed increased adult cardiomyocyte mitosis in sheep that receive high doses of plasmid coding for human vascular endothelial growth factor gene,47 which confirms previous observations of entrance in mitosis after vascular endothelial growth factor gene transfer in chronic myocardial ischemia.48 Left, cycling cardiomyocytes at different stages of mitosis showed deeply stained chromosomes (A) after sarcomeric alpha-actin and Ki67 antigen immunostaining. Right, trichrome staining showed the same findings (B).


