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Respite for hybrid coronary revascularization

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Abstract

Hybrid coronary revascularization incorporates a surgical anastomosis of the left internal mammary artery to the left anterior descending coronary artery through a thoracotomy and percutaneous implantation of drug eluting stents in diseased non-left anterior descending coronary arteries. Hybrid coronary artery revascularization can be performed as a 1-stage procedure in a hybrid operating room or as a tightly scheduled 2-stage procedure. Hybrid coronary artery revascularization is seldom the selected modality for coronary revascularization due to the lack of a hybrid operating room in many hospitals, the recommended thoracotomy approach for bypass, or the rigid schedule of surgical and endovascular revascularization. A 2-stage approach, using a sternotomy as compared to standard thoracotomy, and a flexible schedule between surgical and endovascular procedures may facilitate the adoption of hybrid coronary revascularization with non-complex multi-vessel stable coronary artery disease.

Keywords: Hybrid, coronary artery bypass, revascularization, multi-vessel, saphenous vein graft, left anterior mammary artery, percutaneous coronary intervention

INTRODUCTION

Medical therapy aiming at the stabilization and possibly the reversal of atherosclerosis in patients with stable coronary artery disease (CAD) has steadily progressed over the past 20 years[1-4]. However, patients with CAD who remain symptomatic despite optimal anti-anginal therapy or with limited life expectancy due to multi-vessel CAD (mCAD) are candidates for coronary artery revascularization (CAR)[5,6]. CAR no longer requires open heart surgery for the implantation of a coronary artery bypass graft (CABG); it

now can be achieved by percutaneous coronary intervention (PCI) with endovascular implantation of drug eluting stents (DES), which target coronary obstructions that hamper myocardial perfusion during exercise[7-12]. The indications, benefits and shortcomings of surgical and endovascular CAR are evolving and a constant source of debate[6,13]. However, two aspects of CAR are overwhelmingly agreed on: the left internal mammary artery (LIMA) is the longest-lasting and most event free conduit for CABG and the completeness of CAR is an important determinant of its long-term outcome[14-16].

Due in part to LIMA long-lasting patency, CABG surgery is considered to be the CAR procedure of choice in patients with mCAD that encompasses the left anterior descending artery (LAD)[17]. However while revascularization of non-LAD coronaries is commonly achieved with implantation of saphenous vein grafts (SVG) alongside the LIMA, another treatment option is a staged procedure, referred to as hybrid coronary revascularization (HCR), where revascularization of non-LAD coronaries is achieved by percutaneous implantation of 2nd generation DES[18,19]. Although it was advocated for ≥ 2 decades, HCR only represents < 0.5% of the total of CABG procedures performed[20].

The rationale for HCR and the barriers to its widespread adoption are first discussed. A pragmatic approach to HCR, that may facilitate its adoption by the cardiovascular community, is then advocated.

SAPHENOUS VEIN GRAFT PATENCY

Autologous saphenous vein was the conduit used by Favaloro in his landmark CABG operation 50 years ago[21]. SVG still account for > 80% of conduits used in CABG surgery[22,23]. The rate of SVG occlusions has been estimated be 15% 1-year post implantation, 1%-2% per year from year 1 to 6 and 4% per year from year 6 to 10 resulting in a patency rate of 60% at 10 years[24]. More recent data suggests 42.8% of SVG failure (defined by ≥ 75% stenosis) at 12-18 months after CABG surgery in 1828 patients who underwent angiography for clinical reasons or per protocol[25]. The rate of SVG failure was similar 12-18 months implantation in 926 patients enrolled in the Project of EX-Vivo Vein Graft Engineering via Transfection (PREVENT) IV trial[26]. The bulk of SVG patency rate data was collected in large volume University or Veterans Administration medical centers when 400,000 CABG operations were performed annually in the United States[27]. Nowadays with PCI being the most common procedure for CAR[6], CABG surgery is less performed and the current patency rate of SVG is unknown.

Rapid development of SVG atherosclerosis is the primary reason for the low SVG patency rate 5-10 years after implantation[28]. Systemic arterial pressure and harvesting-related trauma cause endothelial damage and intimal hyperplasia. An inflammatory response follows with recruitment of immune cells, activation of pro-thrombotic factors, vascular smooth muscle cells migration and extra cellular matrix degradation[29]. Macrophages and foam cells promote the development of necrotic chores that expand and eventually rupture leading to intra vascular thrombosis and clinically full-blown atherosclerosis[24]. Due to its diffuse and friable nature, SVG atherosclerosis progresses rapidly and is not mitigated by implantation of DES[28]. Further, mobilization of embolic debris and serotonin-induced vasospasm during PCI may result in a no-reflow phenomenon and in-stent restenosis[30,31]. Targeted therapy at all the steps of the atherosclerosis cascade has failed to alter the progression of atherosclerosis in SVG. Atherosclerosis is diffuse and often concentric involving 90% to 100% of the graft circumference[30,32].

Redo revascularization is currently the only therapeutic option for diseased SVG[31,33], and is seldom achieved by repeat CABG surgery due to technical difficulties and a mortality that is 5-fold greater than that of the initial operation[34-36]. Redo revascularization through PCI with implantation of bare metal stents or DES is also problematic[37-39]. Percutaneous interventions on diseased SVG are associated with a high-rate of in-stent restenosis, target vessel revascularization, peri-procedural myocardial infarction and in-hospital mortality[40,41]. Current wisdom advocates to focus revascularization efforts on the native vessel lesions and not on the diseased SVG[40,41].

LIMA PATENCY AND OUTCOME

The LIMA is the conduit used for bypass of a diseased LAD in 95% of patients who undergo CABG surgery[42]. In patients with a LAD obstruction that decreases resting blood flow, the LIMA patency rate is > 90% at 10 years post implantation[12,43]. Failure of LIMA graft mostly occurs in patients with competitive flow between the LIMA and the native vessel as the result of low grade LAD lesion. The long-term patency of a LIMA graft to a diseased LAD guarantees normal perfusion to ≥ 50% of the total myocardial mass for many years[17,44,45]. In contrast to DES that only remedy a single focal LAD obstruction, a LIMA graft protects proximal and mid segments of the LAD against the development of new atherosclerotic lesions[46-48]. Further, by restoring normal LAD blood flow at rest and during exercise a LIMA graft enhances downstream vascular endothelial function and thereby delays the progression of atherosclerosis[47]. The LIMA endothelium is abundant in inducible nitric oxide (NO) synthase and thereby has a high NO concentration. The LIMA endothelium prevents graft thrombosis, slows the progression of target vessel atherosclerosis and maintains distal vessel patency[46,48].

Observational rather than evidence-based data led to the overwhelming use of LIMA in CABG surgery[49-51]. In the absence of evidence based data, one can only speculate on the role that the LIMA plays in the superiority of CABG surgery over PCI with 2nd generation DES in patients with complex mCAD[47,52,53]. The absence of LIMA was found to be associated with redo operation and high mortality in patients after CABG surgery[14,54].

In summary, despite a lack of evidence-based data, the LIMA to LAD bypass graft is largely thought to underlie the long-lasting and favorable outcome of contemporary CABG surgery.

DES

CABG surgery is rarely performed without implantation of a LIMA graft. Thus, the outcome of patients who undergo surgical revascularization with only SVG cannot be compared to that of patients who undergo PCI revascularization with current 2nd generation DES. In the absence of evidence-based data comparing the effects of SVG *vs.* DES on outcome measures, data must be compared from findings of individual therapeutic trials of these different CAR modalities[55]. The incidence of in-stent thrombosis (ST) and SVG occlusions was similar at 5 years with 1st generation DES like the paclitaxel eluting stent (PES) in the SYNTAX trial[56]. Advancements of stent technology, with the development of everolimus eluting stent (EES), have provided improvements in immediate 1-year ST rate (0.60% *vs.* 1.59%)[57] and 5-year ST rate (1.30% *vs.* 1.86%)[16] when compared to first-generation DES. However, as ST exerts a greater effect on mortality than SVG occlusion[56], ischemia-driven target lesion revascularization (ID-TLR) may be a more apt comparison with SVG graft failure. In a meta-analysis from 2016, 5-year ID-TLR incidence was 7.53% with EES and 11.50% with PES[58], which is favorable compared to a 75%-86% patency for SVG in 5-7 years[42] [Table 1].

In summary we do not have randomized trials of surgical CAR with exclusive implantation of SVG *vs.* PCI endovascular revascularization with implantation of 2nd generation DES. Therapeutic trials of these 2 CAR modalities point to similar patency rate and outcome with SVG and 2nd generation DES at 5 years.

MULTI-VESSEL REVASCULARIZATION IN ACUTE CORONARY SYNDROME

Acute coronary syndrome, with its spectrum in disease from unstable angina to ST-elevation myocardial infarction (STEMI), portends future repeat cardiovascular events[59]. CABG in STEMI is very rare, comprising about 5%-8% of STEMI presentations in the ACTION registry per year[60]; 39% of those CABG cases were after primary PCI and median angiogram-to-CABG time was 23.3 h. Numerous studies have shown a correlation between total ischemia time and overall cardiovascular mortality in STEMI[61-63].

Table 1. Rates of drug eluting stent target lesion revascularization[1], saphenous vein graft failure[2], and LIMA-LAD arterial graft failure[2]

	1-year	5-year	10-year
1st generation DES- Paclitaxel (PES)/Sirolimus (SES)	3.97%[3]	11.50%[4]	16.4%[6]
2nd generation DES- Everolimus (EES)	6.03%[3]	7.53%[4]	14.8%[6]
Saphenous vein graft	2.1%-19%[5]	14%-25%[5]	39%[8]
LIMA-LAD graft	3.4%[7]	11.9%[7]	11.9%[7]

[1]Drug eluting stent occlusion was measured by rates of target lesion revascularization; [2]saphenous vein graft patency was measured by angiographic evidence of vessel occlusion; [3]1-year data from a meta-analysis comparing 1st generation DES (PES and SES) to 2nd generation DES (EES)[57]; [4]5-year data from a meta-analysis comparing 1st generation DES (PES) to 2nd generation DES (EES)[16]; [5]1-year and 5-year data from a meta-analysis comparing saphenous vein *vs.* arterial conduits[42]. It should be noted that definitions of graft failure varied between the different studies; [6]10-year data from a multicenter European randomized trial, which used pre-planned repeat angiography to reassess in-stent restenosis[86]; [7,8]rates of SVG and LIMA-LAD were determined via angiography in their respective studies[15,87]

As an attempt to reduce ischemic time and practical considerations of immediate revascularization after a diagnostic angiogram, PCI has become the most frequent revascularization strategy[64]. There is a scarcity of data directly comparing DES with CABG in the setting of ACS, which mostly consists of subgroup analysis of larger PCI *vs.* CABG studies. A recent meta-analysis of these subgroups found reduced myocardial infarction (MI) incidence with CABG (3.8%) when compared to DES (7.5%) after non-ST elevation MI (NSTEMI), with similar rates of mortality (8.7% *vs.* 10.8%, $P = 0.248$) and stroke (2.6% *vs.* 2.8%, $P = 0.788$)[65].

Recent PCI mortality data have favored immediate complete revascularization (the coronary intervention of both culprit and non-culprit obstructive stenoses) rather than culprit-lesion only PCI followed by staged-PCI of non-critical stenosis[66,67]. When compared to culprit-only PCI, complete revascularization has shown similar rates of contrast-induced nephropathy[68].

In summary, revascularization methods in the setting of acute coronary syndrome skew toward PCI in part due mortality benefit from decreased ischemic time. However, in head-to-head analysis there is a modest reduced subsequent MI benefit for CABG.

CONVENTIONAL HCR

HCR consists of 2 separate procedures: surgical CABG surgery with a LIMA graft to the LAD and PCI with implantation of 2nd generation DES to diseased non-LAD coronary arteries. The 2 procedures can be performed back to back in a 1-stage approach or on different days in a 2-stage approach [Table 2 and Figure 1].

The 1-stage approach is generally performed in a hybrid operating room (OR) with the LIMA graft being first anastomosed to the LAD followed by PCI with endovascular implantation of 2nd generation DES in non-LAD arteries[19,69-71]. The surgical LIMA to LAD surgical anastomosis is commonly performed through an anterolateral thoracotomy at the level of the 4-5th intercostal space. The thoracotomy approach has the advantage of shorter ventilation time and post-operative length of stay over a conventional CABG sternotomy[72-75]. However, thoracotomy may be associated with increased pain levels in the immediate post-operative period[70,76]. The use of cardiopulmonary bypass is commonly left to operator preference. Percutaneous endovascular revascularization of diseased non-LAD arteries is performed after administration of loading dose of anti-platelet agents[20]. The advantage of the 1-stage approach is the verification and possible repair of a defective LIMA-LAD anastomosis before initiation of anti-platelet therapy. Its disadvantage is the need for a hybrid OR.

The 2-stage approach encompasses an interval of 1-2 days between surgical and endovascular CAR[71]. It allows for control of bleeding in the post-operative period before initiation of anti-platelet therapy and does

Table 2. 1-Stage *vs.* 2-stage hybrid coronary revascularization

	1-stage	2-stage
Advantages	Gives option for off-pump LIMA-LAD bypass, can avoid a median sternotomy by using thoracotomy with minimally invasive/endoscopic/robotic techniques, shorter ventilation and hospital time, verification and correction of LIMA-LAD grafts prior to antiplatelet therapy induction	Does not require hybrid operating room, increased time for prevention of post-operative bleeding, decreased inflammatory response to bypass surgery that may cause in-stent thrombosis, provide option for PCI-first of non-LAD lesions to avoid ischemia or infarction in those territories during LIMA-LAD surgery
Disadvantages	High cost, long operating time, requirement of hybrid operating room, increased coordination requirement between interventional cardiologist and cardiothoracic surgeon, thoracotomy option has increased pain	Increased inpatient admission time, no option for immediate repair of defective LIMA-LAD anastomosis, increased bleeding risk for PCI-first approach

LIMA: left internal mammary artery; LAD: left anterior descending; PCI: percutaneous coronary intervention

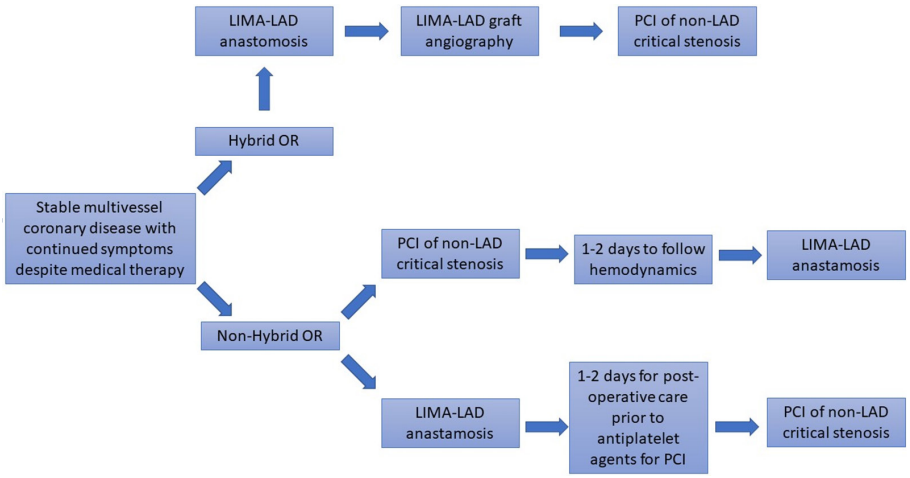

Figure 1. Hybrid Coronary Revascularization process flow-chart. This flow-chart details the steps of Hybrid Coronary Revascularization for both hybrid OR and non-hybrid OR settings. In LIMA-LAD anastomosis can be through mini-thoracotamy or sternotomy. In the hybrid-OR 1-step approcach, LIMA-LAD graft can be immediately visualized with angiography. OR: operating room; LIMA: left internal mammary artery; LAD: left anterior descending; PCI: percutaneous coronary intervention

not require a hybrid OR. When patients have critical lesions of non-LAD arteries, PCI with endovascular implantation of 2nd generation DES in diseased non-LAD arteries can be first performed to avoid complications (hypotension and hemodynamic compromise) at the times of thoracotomy and the LIMA graft to the LAD[77]. The PCI endovascular revascularization first approach increases the risk of bleeding as CABG surgery is then performed in patients who are receiving dual anti-platelet therapy[77].

HCR IN CLINICAL PRACTICE

Given the complex multi-disciplinary nature of HCR and its pre-procedural planning, its clinical utility would be in the treatment of stable ischemic heart disease with refractory angina [Figure 2]. Coronary physiologic assessments such as fractional flow reserve[78] have shown benefit in selecting a subset of patients who may benefit from PCI when compared to medical management. At this time there is no current data for potential use in acute coronary syndrome, but that may change over time with the increasing number of hybrid ORs and multi-disciplinary heart teams. HCR allows for a less invasive approach than traditional CABG, while providing added mortality/graft patency benefit of the LIMA-LAD over the multi-vessel PCI with DES[79-81].

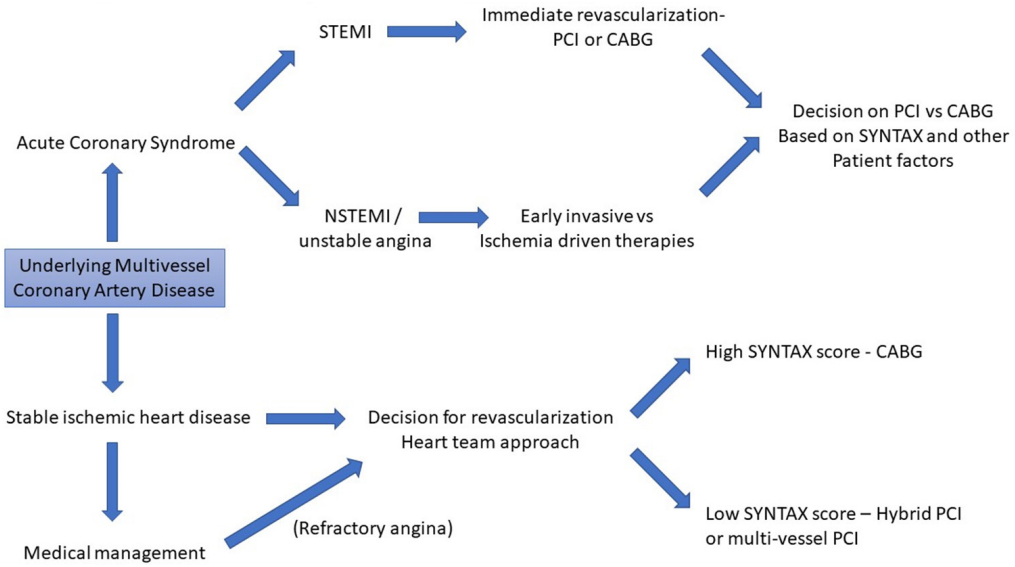

Figure 2. A proposed clinical-decision making flowchart with Hybrid Coronary Revascularization implementation. PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction

PRAGMATIC HCR

The 1-stage approach to conventional HCR requires a hybrid OR that is only available in one third of hospitals in the United States[20]. The 1-stage approach also requires a close collaboration between interventional cardiologists and cardio-thoracic surgeons. Such collaboration is common for a trans-catheter aortic valve implantation procedure but is not common practice for the management of CAD patients[82]. The major aim of HCR is to provide CAD patients with the long-lasting beneficial outcome that LIMA affords and the complete revascularization including attention to chronic total occlusion that endovascular stenting allows[83-85].

HCR is a most suited form of revascularization for patients with mCAD and low to intermediate SYNTAX score. Patients with mCAD and high SYNTAX score are better served by CABG surgery with implantation of multi arterial conduits and when needed SVG[12]. A more pragmatic approach to HCR than that underlined in above-mentioned protocols is likely to facilitate its adoption by interventional cardiologists and cardio-thoracic surgeons. The 2-stage approach to HCR appears to be eminently more practical than the 1-stage approach in most American medical centers. CABG of LIMA to LAD may be conveniently performed through sternotomy as CT surgeons are more familiar with the sternotomy than the thoracotomy approach for CABG. An interval of 2-3 days between surgical and endovascular revascularization allows times for the inflammatory response to surgery to subside and for control of peri-operative bleeding before initiation of dual anti-platelet therapy. The 1-stage approach to HCR and the practice of HCR in patients with critical obstructions of non-LAD arteries will await encouraging results of the 2-stage approach to HCR.

CONCLUSION

In the age of PCI, HCR combines the known benefit of LIMA to LAD grafting with the minimally invasive approach of stenting non-LAD territories. The wide acceptance of HCR by the cardiovascular community will require demonstration of safety and long-lasting benefit on cardiovascular outcomes. A more pragmatic approach than currently outlined may help interventional cardiologists and cardiothoracic surgeons gain experience with dual surgical/endovascular coronary revascularization.

DECLARATIONS

Authors' contributions

Concept and design: Gacad V, Singh T, Motwani A, Samson R, Le Jemtel TH
Data acquisition: Gacad V, Singh T, Motwani A
Data analysis: Gacad V, Singh T, Motwani A
Manuscript preparation: Gacad V, Singh T, Motwani A
Critical revision and finalizing of the manuscript: Gacad V, Singh T, Motwani A, Samson R, Le Jemtel TH

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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