Curr Treat Options Cardio Med (2019) 21: 12
DOI 10.1007/s11936-019-0714-7

Coronary Artery Disease (D Feldman and V Voudris, Section Editors)

Management of Saphenous Vein Graft Disease in Patients with Prior Coronary Artery Bypass Surgery

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Published online: 28 February 2019

This article is part of the Topical Collection on *Coronary Artery Disease*

Keywords Saphenous vein graft · Percutaneous coronary intervention · Coronary artery bypass graft surgery

Abstract

Purpose of review In this review, we summarize the pathogenesis of saphenous venous graft (SVG) failure in patients following coronary artery bypass graft (CABG) surgery. We also provide an update on various aspects of prevention and management of SVG failure.

Recent findings Application of perioperative measures and medical therapies to promote SVG patency is crucial to optimize clinical outcomes in patients following CABG. Percutaneous coronary intervention (PCI) of SVG disease is fraught with complications, with the highest risk being no-reflow and periprocedural myocardial infarction due to distal embolization of microemboli. Minimizing this risk with use of distal embolic protection when feasible and understanding the role of adjunctive pharmacotherapies is critical in reducing the risk of adverse cardiac events.

Summary The long-term patency of SVGs remains a contemporary challenge and is adversely affected by thrombotic occlusion, intimal fibrosis, and accelerated atherosclerosis. Prevention of SVG failure is multifactorial. Use of perioperative measures, medical therapies, and PCI techniques to promote SVG patency is vital to optimize outcomes in patients following CABG. Further prospective trials are needed to define the optimal medical and surgical therapy to maintain short- and long term SVG patency.

Introduction

Coronary artery bypass graft (CABG) surgery has remained the standard of care for patients with significant multivessel and/or left main coronary atherosclerosis and has been well established to improve survival, enhance quality of life, and provide anginal relief [1]. The saphenous vein graft (SVG) is the most common conduit used during CABG to bypass diseased native vessels. Despite advances in surgical techniques and medications, long-term patency of SVGs remains a contemporary challenge and is adversely affected by thrombotic occlusion, intimal fibrosis, and accelerated atherosclerosis. Within 1 year of CABG, 10 to 15% of SVGs occlude and almost half of SVGs fail at 10 years [2–4]. Percutaneous coronary intervention (PCI) of diseased SVGs is performed in nearly 40% of patient with prior CABG undergoing PCI and carries a higher risk, including increased intraprocedural complications, transfusion requirements, risk of no-reflow, and higher mortality [5]. This review discusses the pathogenesis and risk factors for SVG failure as well as medical management and PCI strategies for SVG disease.

SVG failure

Failure of SVGs, which may present angiographically as a complete occlusion, high-grade stenosis, or extensive narrowing, is associated with considerable morbidity and mortality [4, 6]. The Coronary Artery Surgery Study (CASS) described SVG patency rates of 90% within 60 days, 82% at 18 months, and 82% at 5 years [7]. Other studies have corroborated these patency rates, describing early (within 1 month) and intermediate (within 1 year) occlusion rates of 3–8% and 11–13% respectively [8, 9]. Late SVG occlusion rates of 20 and 41% have been noted at 5 and 10 years respectively [8].

Causes of SVG failure vary and include vein trauma during harvest, mechanical complications with the anastomotic site, and subsequent vein degeneration secondary to atherosclerotic disease. SVG failure can be classified into three time phases: early, intermediate, and late. Early (acute) SVG failure (occurring within 1 month of CABG) is primarily attributed to acute thrombosis or technical failure, generally at the site of anastomosis [10]. Numerous precipitating factors can trigger early failure. Factors associated with high risk of graft thrombosis include a small size of the target epicardial vessel resulting in poor distal runoff, size mismatch between the graft and the target vessel creating turbulent flow, graft ischemia, and disruption of the endothelial layer as a result of mechanical trauma and manual distention during surgery. Initial vein harvesting disrupts the vasa vasorum and adventitia, leading to tissue hypoxia in the vessel wall, resulting in release of inflammatory cytokines, which in turn promote thrombosis and intimal hyperplasia [11, 12]. Following harvesting of the SVG, perioperative assessment of graft integrity via high-pressure distension to check for leak can further contribute to endothelial damage [13–15]. Intermediate (subacute) SVG failure (occurring within 1–12 months post-CABG) occurs mainly due to progressive intimal hyperplasia. During this period, the graft adapts to higher arterial pressures by smooth muscle cell proliferation, resulting in intimal hyperplasia [16]. Finally, late SVG failure (occurring more than 12 months after CABG), is primarily due to progressive atherosclerosis, which occurs over the already injured endothelium.

Risk factors for SVG failure

SVGs have a significantly higher rate of angiographic failure compared with arterial conduits due to their innate properties [17]. Risk factors for SVG failure can be classified into patient-related, graft-related, and surgery-related risk factors. Patient-related factors including age, gender, left ventricular dysfunction, kidney function, aspirin use, serum cholesterol and triglycerides, and Canadian Cardiovascular Society functional class can affect the short and the long-term patency rate of an SVG in a patient [9, 18–21]. The association between traditional atherosclerotic risk factors, like cigarette smoking and diabetes mellitus, and SVG failure has yielded conflicting results [9, 22, 23]. Hypertension, known to be a risk factor for graft intimal hyperplasia, has not been correlated with SVG failure [9, 22]. The best long-term predictors of SVG graft patency were shown to be grafting into the left anterior descending artery and grafting into a vessel that is greater than 2.0 mm in diameter [9, 24]. SVGs to the right coronary artery are least likely to have long-term patency [24]. Surgical factors that predispose patients to SVG failure include poor distal runoff, small target vessel diameter, and size mismatch between the graft and artery.

Prevention of SVG failure

Perioperative measures

Several surgical techniques have been shown to decrease the rate of SVG failure. For instance, harvesting the SVG with the perivascular tissue to avoid manual disruption and distension of the vein improves short- and long-term graft patency compared to conventional technique [25–27]. This "no touch" techniques results in less perioperative smooth muscle cell activation, with lower likelihood of neointimal hyperplasia development [28]. The use of buffered intraoperative storage solution for harvested veins also seems to offer superior structural and functional preservation [29].

The influence of the vein-graft harvesting technique on long-term clinical outcomes had also been studied. Endoscopic vein harvesting has been independently associated with higher rates of SVG failure and adverse outcomes compared to open vein harvesting in observational studies and substudies of randomized controlled studies [30, 31]. However, in the recent Randomized Trial of Endoscopic or Open Vein-Graft Harvesting for Coronary Artery Bypass (REGROUP) study, 1150 patients undergoing CABG were randomly assigned to open or endoscopic vein-graft harvesting [32]. Rates of major adverse cardiac events, a composite of all-cause mortality, nonfatal myocardial infarction, and repeat revascularization, were similar in both arms.

The off-pump technique for CABG without cardioplegia has been associated with poorer graft patency rates compared to on-pump surgery [33, 34]. The relative platelet dysfunction and coagulopathy induced by cardiopulmonary bypass can explain the superior SVG patency rates seen with on-pump surgery. A recent large randomized trial suggested that the off-pump group had poorer graft patency [35] and lower rates of 5-year survival and event-free survival than on-pump CABG (34). However, two recent large randomized controlled trials

showed no difference in clinical outcome between on- and off-pump CABG [36, 37].

Sequential grafting of the saphenous vein allows for revascularization of more than one target vessel. However, in patients undergoing their first CABG, the use of SVG conduits with multiple distal anastomoses was associated with a significantly higher rate of SVG failure at 1 year and a trend toward a higher rate of the composite of death, myocardial infarction, or revascularization at 5 years [38]. A systematic review and meta-analysis of 12 cohort studies, however, showed that the risk of SVG failure was lower in sequential grafts than single SVGs [39].

External venous stents have also been introduced as a means to theoretically reduce the size mismatch between larger saphenous veins and smaller coronary vessels at the distal anastomosis so as to reduce endothelial damage [40]. A large body of preclinical evidence demonstrated a favorable result with these external venous supports in animal models. The use of external stents, however, has still not yet found a role in clinical practice.

Medical management

Currently, antiplatelet and statin therapies are the only treatment options recommended for SVG failure.

Aspirin and other antiplatelets

In general, most surgeons no longer discontinue aspirin before CABG and recommend continuing with aspirin throughout the perioperative period. However, randomized and observational studies have had inconsistent results on improving SVG patency and increased risk of bleeding with initiating aspirin preoperatively [41–44]. In a recent randomized trial of patients who were scheduled to undergo CABG, the administration of 100 mg of aspirin preoperatively resulted in neither a lower risk of death or thrombotic complications nor a higher risk of bleeding than that with placebo at 30 days [45]. Long-term use of aspirin, however, has been shown to reduce the incidence of adverse cardiovascular outcomes and improve SVG patency after CABG [46], regardless of low dose versus higher doses of aspirin [47]. Consequently, the initiation (or continuation) of low-dose aspirin is recommended for patients undergoing CABG in both the European Society of Cardiology and the American Heart Association (AHA) guidelines [48••, 49].

Unlike aspirin, it is generally preferred to discontinue or to refrain from perioperative initiation of platelet P2Y12 receptor inhibitors in the elective CABG setting due to an increased risk of bleeding. However, there is evidence suggesting dual antiplatelet therapy (DAPT) perioperatively may be overall beneficial [50]. A meta-analysis of 34 studies suggested patients with acute coronary syndromes requiring urgent CABG should proceed with surgery without delay for a clopidogrel-free period [51]. The addition of a platelet P2Y12 receptor inhibitor agent to aspirin following CABG has been proposed to improve graft survival, primarily in observational studies and subgroup analyses of randomized controlled trials. For instance, the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial suggested among patients undergoing CABG, only the subgroup of patients with ACS benefited from the addition of clopidogrel [50]. The Clopidogrel After Surgery for Coronary Artery

Disease (CASCADE) Study demonstrated that compared with aspirin monotherapy, the combination of aspirin plus clopidogrel did not significantly reduce the process of SVG intimal hyperplasia 1 year following CABG [52]. With regard to ticagrelor, investigators from China recently randomized 500 patients undergoing CABG to receive aspirin alone, ticagrelor alone, or DAPT (ticagrelor plus aspirin) within 24 h of surgery for 12 months. The DAPT arm was superior to aspirin alone in maintaining SVG patency for up to 1 year after elective CABG surgery. The study was not able to evaluate the risk of bleeding due to low number of bleeding events [53•]. The ticagrelor in CABG (TiCAB) trial randomized patients undergoing CABG to ticagrelor monotherapy versus aspirin monotherapy and demonstrated similar rates of major adverse cardiac events and bleeding between both arms [54].

The 2015 AHA Scientific Statement on Secondary Prevention after CABG Surgery recommended the addition of clopidogrel to aspirin for 1 year in patients who receive off-pump surgery and the joint American College of Cardiology/AHA 2016 focused guideline update on duration of DAPT recommended that in patients with ACS who undergo CABG, P2Y12 inhibitor therapy should be resumed after CABG to complete 12 months of DAPT [48••, 55••]. The benefits of routine DAPT, however, have not been well established.

Statins

Hypercholesterolemia is associated with SVG failure, and aggressive lipid-lowering therapy with statins has been associated with improvement in prevention of neointimal hyperplasia, improved SVG patency, and significant reduction in repeat revascularization and adverse cardiovascular events in patients with CABG [19, 20, 56]. Statin therapy slows the progression of venous graft atherosclerotic disease and lowers the risk of cardiovascular death. A recent meta-analysis of eight studies of patients post-CABG demonstrated that long-term aggressive statin therapy, compared to moderate statin therapy, was associated with decreased atherosclerotic progression of SVGs and reduced risk of repeat myocardial infarction and repeat coronary revascularization [57]. Hence, lipid-lowering therapy with statin is recommended in all CABG patients unless contraindicated [57].

Lifestyle modifications

Cigarette smoking has been associated with SVG disease, with higher over twofold rates of angina, MI, requirement for reoperation, and cardiac mortality compared to nonsmokers [58]. The long-term benefit of glycemic control for preventing SVG failure has not been well studied.

Percutaneous coronary intervention for SVG failure

Data from the National Cardiovascular Data Registry (NCDR) noted that 18% of all PCIs were done in patients with prior CABG and nearly 40% of these interventions were performed on diseased SVGs [59]. In 85% of patients presenting with an acute coronary syndrome at least 5 years following CABG, SVF failure was identified as the culprit [60]. Percutaneous intervention on SVG as the culprit vessel in the setting of ACS is usually feasible with acceptable

short-term angiographic results. However, when compared to the results for patients undergoing primary PCI of a native coronary artery in the setting of ACS, the long-term patency and the clinical prognosis are far inferior in patients undergoing PCI to SVG [61, 62]. SVG intervention in the setting of ACS is associated with higher risk of distal embolization due to high thrombus burden and use of embolic protection devices has been recommended.

The first step in planning for diagnostic angiography and possible PCI on grafts is to obtain CABG operative report details or previous angiography reports if available. Currently, femoral artery remains the default access site of choice for PCI in patients with previous CABG [63–65]. SVG angiography via radial artery is thought to be technically more difficult and is associated with greater contrast use, longer procedure time, and greater access crossover and operator radiation exposure compared with transfemoral approach. However, a recent meta-analysis of one randomized and eight nonrandomized studies of patients with previous CABG undergoing PCI demonstrated similar procedure times, contrast volumes, and success rates between radial and femoral access [66].

Optimal guide catheter support is essential for a successful SVG PCI. The aortic size, the position and angle of the grafts, and the operators' preference determine the type and size of guide catheter [67]. For left-sided graft engagement, a Judkins right (JR), Amplatz left (AL), or Amplatz right (AR) are often used. These guide catheters may also be used for right-sided graft engagement. If the graft has an inferior take-off with narrow angle, the multipurpose guide catheter should be considered. Other available catheters include the left bypass, hockey stick, and Ikari left guide catheters. Left coronary grafts are best viewed in a right anterior oblique projection, while right coronary grafts are best imaged in a left anterior oblique projection.

Direct stenting can decrease distal embolization of debris compared with a pre-dilation technique and is associated with reduction in major adverse cardiac events in SVG PCI [68]. Overdilating should be avoided because of the risk of distal embolization due to excessive plaque extrusion. To improve the SVG revascularization outcomes, it is imperative to carefully consider stent type, embolic protection devices (EPDs), and the choice of pharmacotherapy.

Stent type

The superiority of stenting with bare-metal stents (BMS) over plain old balloon angioplasty (POBA) in the management of SVG occlusion was demonstrated over 20 years ago [5, 69]. Drug-eluting stents have been associated with decreased rates of target vessel revascularization (TVR) and target lesion revascularization (TLR) [5, 70–73] and superior mortality has been suggested with DES in several studies [74]. No significant differences in myocardial infarction or stent thrombosis have been noted in DES versus BMS in SVG PCI studies [75]. Two other meta-analyses using pooled data from both observational and randomized trials concluded that DES was associated with improved mortality as well as a reduction in the rate of repeat revascularization [76, 77]. A more recent RCT of DES versus BMS in SVG lesions with larger sample size, which was not included in the above meta-analyses, again demonstrated the superiority of DES in reducing TLR rates but failed to demonstrate any benefit with respect to all-cause mortality, myocardial infarction, or stent thrombosis between DES and BMS [78].

Studies comparing first versus second generation DES in SVG PCI have yielded inconsistent results with some studies demonstrating similar long-term results between each generation DES [79, 80] and others suggesting improved rates of composite all-cause mortality, myocardial infarction, and TVR with second-generation everolimus-eluting stents compared to first-generation DES [81].

Covered stents, which consist of a stainless steel slotted tube covered by an expandable polytetrafluoroethylene (PTFE) membrane, were thought to theoretically reduce periprocedural MI by trapping potentially embolic degenerated atherosclerotic plaque particles behind the PTFE membrane and decrease restenosis by serving as a barrier isolating the lumen from smooth muscle cell proliferation, migration, and extracellular matrix production arising from the media [82]. Outcomes of covered stents versus BMS for SVG intervention were not comparable to BMS [83, 84], despite mandatory high-pressure balloon inflation and long-term dual antiplatelet therapy with covered stents [85]. For the two newer covered stents, long-term randomized comparison studies with BMS are awaited [86, 87].

Embolic protection devices

Embolic protection devices (EPD) prevent distal embolization of debris and plaque particles during SVG intervention. Distal embolization can lead to "no-reflow" phenomenon as well as periprocedural MI and, thus, will adversely affect the outcomes of the SVG intervention. Currently, the most commonly used EPDs utilized in the USA are the distal embolic filters—SpiderFx (Medtronic Inc., Minneapolis, MN) and FilterWireEZ (Boston Scientific, Marlborough, MA). Distal embolic filters use a small net or "basket" with small pores supported by an expandable umbrella frame attached to the distal portion of a 0.014-in. guidewire with a delivery sheath. The basket is deployed distal to the target lesion to trap dislodged debris that embolizes during the intervention. At the end of the procedure, the filter containing the debris is captured in a retrieval sheath and removed from the patient's body. Distal embolic filters allow contrast opacification and continuous distal perfusion during the procedure, but their use is associated with risk of distal embolization during the wiring and device-crossing phases, debris embolization during filter retrieval, and inability to completely contain particles smaller than the basket pore size. Moreover, a disease-free distal landing zone is required for successful application of distal embolic filters [67].

Multiple studies examined the association between EPD use and outcomes and yielded conflicting results. Use of EPD in SVG PCI has been associated with over 40% relative reduction in 30-day all-cause mortality, myocardial infarction, emergency CABG, or TLR, primarily driven by reduced rates of myocardial infarction and no-reflow [88]. While some investigations revealed improved outcomes including post-procedural TIMI flow following routine use of EPDs [89, 90], others failed to find any benefit with EPD use [91]. A recent systematic review and meta-analysis of eight studies failed to show any benefit from the routine use of EPDs in SVG PCI with regard to all-cause mortality, major adverse cardiovascular events, myocardial infarction, or TVR. One study even

noted a higher rate of periprocedural MI with EPD use [92]. The use of EPD is currently deemed a class I recommendation by the American College of Cardiology Foundation/American Heart Association/ Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) Guidelines for PCI during SVG intervention when feasible to decrease the risk of periprocedural MI, distal embolization, and no-reflow [93]. Despite the class I recommendation, EPDs are often underutilized in clinical practice for SVG intervention [59]. Deployment of distal protection filters can be technically challenging in the presence of complex anatomy [94] and use of EPDs was shown to prolong the procedural time.

Adjunctive pharmacotherapy

Several analyses have suggested a lack of benefit of glycoprotein IIb/IIIa (GP IIb–IIIa) inhibitors in SVG intervention. A pooled analysis of five randomized clinical trials (EPIC, EPILOG, EPISTENT, IMPACT II, and PURSUIT) demonstrated no benefit from adjunctive GP IIb–IIIa inhibition in SVG intervention [95]. In particular, among patients undergoing graft PCI, the incidence of the composite end point of death, myocardial infarction, or revascularization at 30 days was 16.5% in the platelet GP IIb–IIIa inhibitor group and 12.6% in the placebo group (odds ratio, 1.38; 95% CI, 0.85 to 2.24; $P = 0.18$). At 6 months, 39.4% of patients randomized to GP IIb–IIIa inhibitors and 32.7% of patients allocated to placebo had an ischemic event (hazard ratio, 1.29; 95% CI, 0.97 to 1.72; $P = 0.07$). The use of GPIIb–IIIa inhibition is currently not recommended and deemed a class III recommendation by the ACCF/AHA/SCAI Guidelines for PCI [93].

While use of an anticoagulant is recommended during SVG intervention, no agent has been shown to be superior to others and, hence, both heparin and bivalirudin are commonly used for anticoagulation. Intragraft vasodilators are often prophylactically administered before SVG PCI, but also after PCI if slow flow or no-reflow occurs. Adenosine, nitroprusside, nicardipine, and verapamil can all be utilized to improve flow in the setting of no-reflow and prophylactically to decrease the likelihood of impaired flow post-stenting [96–98].

Conclusions

The long-term patency of SVGs remains a contemporary challenge and is adversely affected by thrombotic occlusion, intimal fibrosis, and accelerated atherosclerosis. Prevention of SVG failure is multifactorial. Application of perioperative measures and medical therapies to promote SVG patency is crucial to optimize clinical outcomes in patients following CABG. PCI of SVG disease is fraught with complications, with the highest risk being no-reflow and periprocedural myocardial infarction due to distal embolization of microemboli. Minimizing this risk with the use of distal embolic protection when feasible and understanding the role of adjunctive pharmacotherapies is critical in reducing the risk of adverse cardiac events. Further prospective trials are needed to define the optimal medical and surgical therapy to maintain short- and long-term SVG patency.

Compliance with Ethical Standards

Conflict of Interest
Neda Dianati Maleki and Arash Ehteshami Afshar each declare no potential conflicts of interest.
Puja B. Parikh serves on the scientific advisory board of AstraZeneca.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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- •• Of major importance

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