Intraoperative Vein Graft Preservation: What Is the Solution?

Lavinia C. Woodward, BA, Charalambos Antoniades, MD, PhD, and David P. Taggart, MD (Hons), PhD

Christ Church, University of Oxford, Oxford; Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford; and Department of Cardiac Surgery, Oxford University Hospitals Trust, Oxford, United Kingdom

Saphenous vein graft (SVG) disease and subsequent vein graft failure remain a major problem after coronary artery bypass graft operations. In an effort to mitigate loss of endothelial viability, the vein is stored, intraoperatively, in a preservation solution. However, human SVG samples demonstrate endothelial denudation and dysfunction after such storage, the severity of which varies, depending on the medium. The paucity of clinical data evaluating preservation solutions is illustrated by the absence of optimal procedural protocol. This review evaluates the potential efficacy of different storage solutions in preserving vein grafts, in relation to a mechanistic understanding of SVG pathophysiology.

(Ann Thorac Surg 2016;■:■–■)

Coronary artery disease is the leading cause of death worldwide [1], and the single largest contributor to the global burden of disease [2]. Importantly, coronary artery bypass graft (CABG) operation is an effective approach for improving prognosis, symptoms, or both in selected patients with advanced coronary artery disease [3]. However, the long-term efficacy of CABG operations is hampered by vein graft failure (VGF), defined as complete graft occlusion, greater than 70% stenosis, or extensive conduit narrowing on angiography [4]. Indeed, 10% to 15% of saphenous vein grafts (SVGs) occlude within 1 year of operation, and almost one-half of the conduits fail at 10 years [4, 5], increasing the patients' risk of major adverse cardiac-related events [6] and often necessitating repeat revascularization. Correspondingly, vein graft disease is temporally correlated with reoperation and mortality [7]. As such, there is a critical need for strategies that improve long-term vein graft patency and clinical outcomes in patients undergoing CABG operation.

VGF is largely attributable to three temporally distinct processes, with interlinked underlying pathophysiology: acute thrombosis, subacute intimal hyperplasia, and long-term atherosclerosis [4]. Pharmacologic interventions, lifestyle modifications, and molecular therapies have been extensively investigated for the prevention of VGF [4]. However, it is clear that intraoperative measures are crucial in avoiding graft failure. These include use of a no-touch technique, minimizing graft trauma, avoidance of distension [8], and, more recently, use of expandable external vein graft supports [9]. Notwithstanding these important advances, much controversy remains as to the ideal preservation solution for short-term intraoperative storage of the SVG after harvesting. Indeed, evidence from ex vivo studies and animal models is contradictory [10–30], and there is a severe lack of clinical studies investigating graft storage solutions. Accordingly, considerable variation exists in the preservation solutions currently used, and which preservation solution depends largely on surgeon choice, rather than any firm evidence basis.

In this review, we use current understanding of the mechanisms underlying VGF, together with critical appraisal of available evidence, as a rational framework for discussing the characteristics of an optimal preservation solution.

Mechanisms of VGF

Thrombosis is a major cause of early VGF [31], with up to 12% of SVGs occluding within the first month after CABG operation [7]. Vein graft thrombosis results from a failure of local hemostatic balance, through a combination of vessel wall damage, hypercoagulability, and altered flow dynamics, classically defined in Virchow's triad. In short, focal endothelial disruption, a universal feature of SVG harvesting, results in loss of protective antithrombotic pathways, exposure of the thrombogenic basement membrane, and the expression of procoagulant and inflammatory mediators [31]. Subsequent local fibrin accumulation and platelet adherence can lead to thrombus formation and occlusion of the venous conduit.

Although thrombosis is the principle cause of VGF in the first 30 days after CABG operation, intimal hyperplasia, the accumulation of smooth muscle cells (SMCs), and extracellular matrix in the vein intima, are major contributors to SVG disease 1 month to 1 year after

Address correspondence to Lavinia C. Woodward, Christ Church, St. Aldates, Oxford, OX1 1DP, United Kingdom; email: lavinia.woodward@chch.ox.ac.uk.

Professor Taggart discloses a financial relationship with Somahlutions.

Published by Elsevier

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.05.097

Abbreviations and Acronyms

AHB = autologous heparinized blood
CABG = coronary artery bypass graft
EDR = endothelial-dependent relaxation
eNOS = endothelial nitric oxide synthase
NO = nitric oxide
NOS = nitric oxide synthase
NS = normal saline
SEM = scanning electron microscopy
SMC = smooth muscle cell
SVG = saphenous vein graft
UWS = University of Wisconsin Solution
VGF = vein graft failure

implantation [31]. Such intimal thickening leads not only to luminal narrowing but also to forming a diffuse atherosclerosis-prone region within the conduit, as also occurs in native arteries [32]. This adverse vascular remodelling of an SVG after surgical manipulation and introduction into the high-pressure arterial circulation is complex and incompletely understood [33]. Nonetheless, as with thrombogenesis, endothelial cell loss is centrally implicated in the pathogenesis of intimal hyperplasia [33, 34]. This is unsurprising, given the key role of endothelial cells in modulating SMC proliferation and ingress and the deposition of extracellular matrix by a number of tonic inhibitory pathways [31]. Moreover, endothelial activation and denudation precipitate the infiltration of inflammatory cells, which secrete cytokines and growth factors, promoting SMC proliferation and chemotaxis [34]. Finally, mitogens, such as platelet-derived growth factor, released from platelets activated at the site of endothelial injury, further stimulate subendothelial fibroproliferation [35]. In addition to endothelial cell loss, transient ischemia followed by reperfusion during vein harvesting and grafting reduces endothelial production of antiproliferative mediators, such as prostacyclin and nitric oxide (NO) [31].

Necropsy studies have identified extensive atherosclerotic lesions in SVGs as early as 1 year after coronary bypass operation [36]. Correspondingly, atherosclerosis is the main cause of VGF beyond the first year of graft implantation [37]. As described above, both inflammatory cell infiltration through the damaged endothelium and intimal hyperplasia contribute to conduit atherogenesis. Hence, loss of endothelial integrity, adhesion molecule expression, reduced prostacyclin and NO formation, and generation of SMC mitogens also contribute to vein graft atherosclerosis [38]. Although conceptually sound, it is important to note that there is no evidence for an advantageous effect of endothelial structural integrity on graft patency or clinical outcomes after CABG operation.

To date, there are no double-blinded, randomized controlled clinical trials assessing the relative efficacy of different intraoperative storage solutions. However, this understanding of the pathophysiology underpinning the three predominant mechanisms of VGF allows for critical evaluation of available evidence from ex vivo studies of human SVGs and animal models (Table 1).

Search Strategy

In March 2015, the PubMed database was searched using the terms "CABG," "saphenous vein graft," "storage solution," and "preservation." Reference lists of identified articles were searched for further articles, and the "similar articles" function was used on all included articles.

Evaluation of the Evidence

Although technical failure and a multitude of factors may contribute to VGF, endothelial damage during vein harvesting and implantation is directly and indirectly implicated in acute, intermediate, and long-term vein graft disease [31, 34, 35, 38]. The structural and functional viability of the SVG endothelium may be impaired through trauma during harvesting, excessive manipulation and distension during preparation for grafting, and through exposure to high arterial pressures and turbulent flow. Nevertheless, the choice of intraoperative storage solution has been shown to significantly influence the preservation of the endothelial structural characteristics [11, 12, 15, 17–20, 22, 23, 25] and vascular function [11–13, 16–19, 23–28, 30]. Thus, the question of "which storage solution best preserves SVGs?" may ultimately be restated as "which solution best preserves endothelial integrity?"

Preservation of Endothelial Structure

Maintenance of a structurally intact endothelial barrier at the luminal surface of SVGs is imperative to graft patency, particularly through avoidance of acute thrombosis. However, ex vivo studies investigating the effect of various intraoperative solutions on endothelial structural integrity have yielded conflicting results.

In 1980, Gundry and colleagues [10] challenged the widespread use of saline for SVG storage after harvesting. With the use of scanning electron microscopy (SEM), the group revealed superior preservation of endothelial structural characteristics in human saphenous vein segments stored in autologous heparinized blood (AHB), compared with storage in normal saline (NS) at the same temperature [10]. Similarly, Lamm and colleagues [22], also using SEM, showed that continuous perfusion with autologous blood minimized endothelial damage, compared with storage in a crystalloid solution. However, these results potentially reflected not only the influence of solution composition but also the effect of continuous graft perfusion versus conventional storage, thereby hampering interpretation of the findings.

In contrast, other studies have failed to consistently substantiate the superiority of storage with autologous blood over crystalloids. Indeed, Catinella and colleagues [11] reported reduced endothelial desquamation and formation of fibrin-platelet aggregates in ex vivo human saphenous vein segments stored in buffered heparinized