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Comments on Vasa Vasorum in Human Great Saphenous Vein

Andrzej Loesch

Centre for Rheumatology, Division of Medicine, University College London, Royal Free Campus, Rowland Hill Street, London NW3 2PF, UK; a.loesch@ucl.ac.uk; Tel.: +44(0)20-7794-0500 (ext. 33247)
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In a recently published review article in *iCirculation*, Michael R. Dashwood [1] discusses the morpho-functional aspects of the human great saphenous vein (SV), focusing on the vasa vasorum, coronary artery bypass grafting (CABG), blood flow, and graft patency. The role and fate of the vasa vasorum in the SV as a coronary graft are of particular interest. Preservation of the vasa vasorum during SV graft harvesting for CABG allows a substantial quantity of oxygenated blood to be delivered to the graft wall; thus, the vasa vasorum contribute to an anti-ischaemic effect. This has been elegantly demonstrated in no-touch SV grafts during CABG [2], in which vein stripping of the pedicle and vein distension are avoided during harvesting [3].

The question arises as to the role of the vasa vasorum and blood circulation within the SV graft wall once the graft is implanted into the coronary circulation. It has been suggested that the vasa vasorum open into the vein lumen, which may play a physiological role, for example, in the maintenance of graft patency [4]. However, no such luminal terminations of the vasa vasorum have been demonstrated in detailed examinations of corrosion casts of human SVs, which provide some of the best descriptions of the complex three-dimensional arrangement of the vasa vasorum within the human SV wall [5–7].

More recently, several papers have discussed the possible role of the vasa vasorum in human SV used as a coronary graft; however, no clear picture of their physiology in the graft has yet emerged [1,2,8,9]. Regardless of the various hypotheses and points of view on the subject, the intention here is to comment on some of the data presented in the article by Dashwood [1].

Figure 4 in Dashwood's paper [1] schematically illustrates a hypothetical density and distribution of the vasa vasorum, as well as potential blood flow within the vasa vasorum of no-touch SV grafts after CABG. Interestingly, in 2018, Stingl et al. [10] described a histological study of the time-dependent spread of the vasa vasorum in aorto-coronary venous grafts (presumed to have been harvested conventionally). Their findings showed a progressive extension of the vasa vasorum from the adventitia into the media and, at later stages (24 months after graft implantation), into the hyperplastic and atherosclerotic intima and plaques. Notably, no vasa vasorum terminating in the intima or lumen were observed in control samples or early graft explants [10]. In agreement with this work, structures that may appear as blood vessels projecting into the SV lumen, as observed at the light microscopic level in no-touch SV graft preparations (e.g., the middle panel in Figure 1 in [1]), are most likely formed by intimal folds and endothelial projections of the original venous lumen [10]. The prominence of these structures may depend on the plane of section or the degree of distension of the SV lumen. Therefore, these projections do not represent terminations of the vasa vasorum within the SV lumen; this interpretation has also been discussed previously [9]. As an illustration, Figure 1A–C presents laser confocal microscopy (LCM) images of intimal immunoreactivity for inducible nitric oxide synthase (iNOS) in no-touch (Figure 1A) and conventional (Figure 1B) SV graft material. Notably, no continuity is observed between the iNOS-positive intima of the SV lumen and the adventitial vasa vasorum (Figure 1C).

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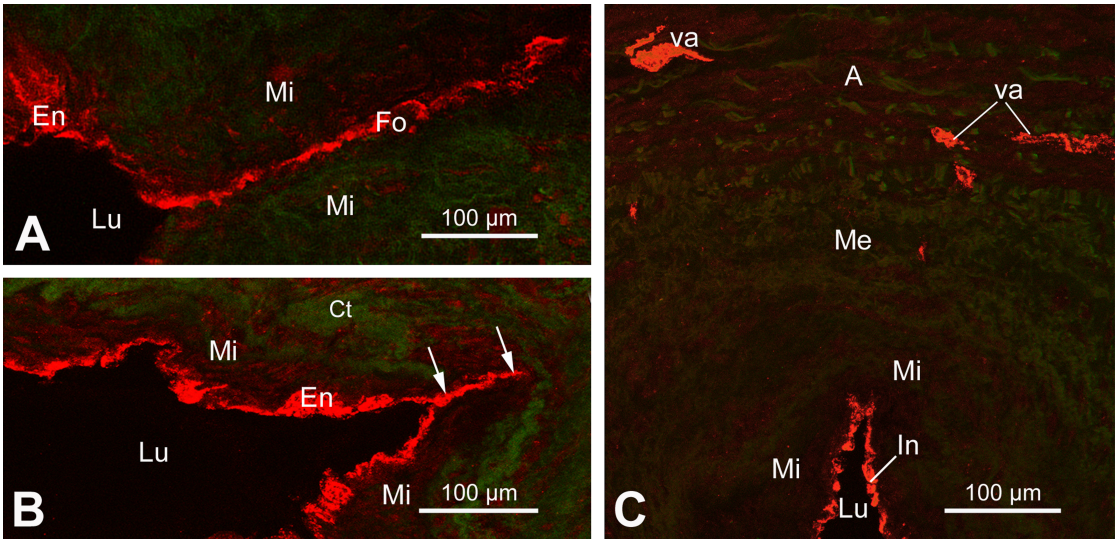


Figure 1. The laser confocal microscopy of transverse sections of proximal segments of human great SV harvested for CABG and immunolabelled (red stain) for inducible nitric oxide synthase (iNOS). (**A**) Note in no-touch SV showing iNOS-positive endothelium (En) of luminal folds (Fo) giving a false impression of a blood vessel being there; Lu—lumen, Mi—internal layer of the media. (**B**) Section of conventional SV shows iNOS-positive endothelium in the partially distended luminal fold; a non-distended part of the fold might resemble a blood vessel (two arrows); Ct—connective tissue. (**C**) Section of no-touch SV shows no connectivity between iNOS-positive vasa vasorum (va) and the iNOS-positive luminal intima (In); A—adventitia, Me—external layer of the media. It is acknowledged that (**A**–**C**) images are from [9] with permission.

The claim in [1] that a scanning electron microscopy (SEM) study supports the idea that some blood vessels, or vessel-like profiles, project into the intima of the SV lumen (see the final lines of the third paragraph on page 3 and the second paragraph on page 4 of [1]) is not entirely accurate. The cited study [11] used to support this claim did not identify such projections; rather, the closest vasa vasorum vessels to the SV lumen were located approximately 60–70 μm away. Indeed, an earlier SEM study by Souza et al. [12] presented an image of a longitudinal section through the no-touch SV, showing a visible longitudinal opening that was interpreted as a vasa vasorum. However, given the substantial size of this elongated structure (with a varying diameter of approximately 30–80 μm), it is equally possible that it represents a longitudinally sectioned luminal fold (or a tributary branch), rather than a vasa vasorum. It must be stressed that the vasa vasorum vessels of such calibre are typically first-order or second-order draining veins that penetrate adventitia [5]; therefore, they do not terminate in the SV lumen.

More recent publications have addressed the morphological characteristics of the vasa vasorum in SV graft material used for CABG, and, where appropriate, some interpretations of earlier findings have been revised; these revisions include ultrastructural examinations of the luminal–intimal surface of SV graft material [8,9]. Accordingly, a variety of openings, ranging in size from approximately 5 μm to 20 μm, have been observed in the SV luminal intima [9]. Among these, openings measuring approximately 10–20 μm are considered to represent branches of tributaries rather than terminations of the vasa vasorum, whereas smaller openings (approximately 5–10 μm) are thought to be non-vascular structures, potentially functioning as “channels” involved in subtle intima–subintima communication [9]. Therefore, the statement by Dashwood [1] that the recent review [9] interpreted luminal openings in the range of 5–20 μm as components of blood vessels (e.g., branches of tributaries rather than vasa vasorum terminations) is not entirely accurate, as it does not distinguish between these two categories of openings (vascular and non-vascular) described above [9]. Furthermore, the SV lumen also exhibits a third type of openings, measuring approximately 3 μm by 30 μm, which likely represents entrances to small luminal folds (subfolds) protruding into the inner media [9]. These structures may be mistaken for vascular profiles when viewed at the light microscopic level.

One of the important anatomical findings highly relevant to the phenomenon of retrograde blood flow refilling the wall of the SV graft [2] is the drainage of the venae vasorum into the terminal segments of tributaries in the human SV [6]. It is therefore highly likely that, through this vascular pathway—graft lumen → terminal tributary segment → venae vasorum—substantial quantities of oxygenated aortic blood can enter the vasa vasorum system of the graft upon completion of the proximal anastomosis [9]. Consequently, the direction of blood flow entering the graft wall would be opposite to that in the intact SV, where tributaries normally drain into the SV

lumen. In the SV used as a coronary graft, it is likely that arterial blood enters the graft wall via one or more proximally located tributaries and exits via distally located tributaries, returning to the graft lumen. A broader discussion of the vasa vasorum in the SV as a graft, based on morphological and ultrastructural findings, has been presented elsewhere [8,9].

It is evident that once the SV is dissected from the leg—whether using a no-touch, conventional, or endoscopic harvesting technique—it becomes inevitably disconnected from its original blood supply and nerve network. The latter is particularly well developed, comprising sympathetic nerves that innervate both venous and arterial vessels of the vasa vasorum [13]. Consequently, the newly implanted SV used as a coronary graft is exposed not only to a markedly different haemodynamic environment compared with that of the intact SV, but also to altered or absent physiological control mechanisms, such as sympathetic innervation, at this stage. These new physiological circumstances certainly affect SV grafts, but why some grafts are more patent than others is not always clear.

In conclusion, the study of the structure and physiology of the SV as graft material for CABG will continue to evolve. It is believed that further discoveries are likely, potentially through the application of new approaches, without the need to republish previously established findings. In particular, the potential reconnection of the native vasa vasorum of the SV graft with those of the host coronary artery and the contractile properties and role of pericytes, as well as the possible re-establishment of innervation of the vasa vasorum (e.g., autonomic projections from the host coronary artery to the graft), appear to be of considerable interest in understanding the mechanisms underlying graft adaptation, improvement, or failure. Hence such research would also emphasize that the vasa vasorum and luminal intima of SV grafts play a critical role in contributing to graft patency.

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Conflicts of Interest

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Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

Abbreviations

A	Adventitia
CABG	Coronary artery bypass grafting
Ct	Connective tissue
En	Endothelium
Fo	Luminal folds
In	Intima
iNOS	Inducible nitric oxide synthase
LCM	Laser confocal microscopy
Lu	Lumen
Me	External layer of the media
Mi	Internal layer of the media
SEM	Scanning electron microscopy
SV	Great saphenous vein
Va	Vasa vasorum

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