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Review Article

Pathobiology of Saphenous Vein Grafts

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Abstract. The long saphenous vein graft is the commonest conduit used for coronary artery bypass surgery. The short and long term success of the procedure depends on the patency of these bypass grafts. Vein graft disease can be divided into early (in the first 30 days), intermediate (1 month to 1 year) and late (over 1 year). Early graft failure is usually caused by graft thrombosis and may be related to the surgical procedure, intermediate graft disease results from intimal hyperplasia while late graft pathology is a consequence of atherosclerosis. The etiology and pathological processes leading to these damaging effects on saphenous vein grafts are tackled in this review. The loss of endothelial integrity, the phenotypic changes in vascular smooth muscle cells and involvement of adventitial cells with collaboration of blood borne factors lead to occlusive pathology of saphenous vein grafts. The accelerated intimal hyperplasia and atherosclerosis are characteristic pathobiological features of these vein grafts. Inflammatory and immunological changes and graft thrombosis are mediated through the secretion and up regulation of growth factors, pro coagulant substances and other proteins arising from the vein wall cells and the blood flowing through them.

Keywords: saphenous vein grafts, vein graft failure, CABG surgery, intimal hyperplasia, graft atherosclerosis, graft thrombosis

1 Introduction

The treatment of coronary artery disease includes a surgical procedure whereby diseased sections of coronary arteries are bypassed using autologous blood vessels or grafts. This technique restores the supply of oxygen and nutrients to match the demands of the myocardium by improving coronary blood flow. This procedure is aptly named coronary artery bypass graft (CABG) surgery. Segments of the long saphenous vein are harvested and then joined to the coronary artery beyond the stenotic lesions [coronary artery-saphenous vein graft (SVG) anastomosis] and to the aorta (aorto-SVG anastomosis) both in an end to side manner (Fig. 1). The success of this bypass depends on the size of the coronary artery, the run-off of blood distal to the graft insertion, the rheology of the blood it contains and the biological characteristics of the conduit itself. Apart from the long saphenous vein, the internal thoracic artery, radial arteries and occasionally the gastroepiploic artery, the short saphenous vein and the arm veins are used to provide the conduit. However, the long saphenous vein graft is still the commonest conduit used in coronary artery bypass graft surgery and the bypass operation for peripheral vascular disease (Allen et al., 2005).

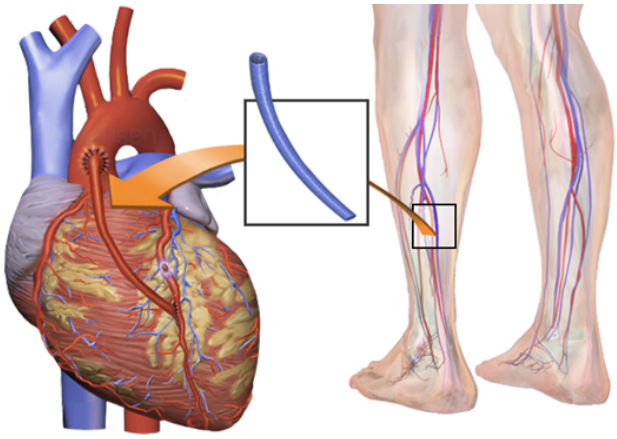

Figure 1: A diagram showing a saphenous vein graft (SVG) anastomosed end to side to the left anterior descending artery (LAD) and to the aorta to bypass a lesion in the proximal segment of the LAD. (Modified from Wikipedia)

Graft failure results from reduction of graft patency and studies have shown that this patency is directly re-

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lated to the clinical and prognostic outcome of the patients (Halabi et al., 2005; Lopes et al., 2012). Various pathophysiological processes lead to early, intermediate and late SVG disease with consequent stenosis or occlusion of the conduit. Early graft failure, occurring in the first 30 days following operation, happens in 8–18% of vein grafts, usually results from technical problems related to the surgery and is mainly caused by graft thrombosis (Fig. 2) (G. M. Fitzgibbon et al., 1996; Chesebro et al., 1982). Intermediate graft failure takes place from 1 month to 12 months after CABG, has an incidence of 10% and is the result of SVG intimal hyperplasia (Bourassa, Campeau, Lesperance & Grondin, 1982; Sharma, Khuri & Folland, 1982; S. Goldman et al., 2004). Late graft failure (Fig. 3) occurs after 1 year and is the result of ensuing graft atherosclerosis. 25% to 35% of graft would have failed at 5 years (Hess et al., 2014; Campeau et al., 1983) and over 50% at 10 years (Kim, Marhefka, Ruggiero, Adams & Whellan, 2013; C. M. Grondin & Thornton, 1995; Campeau et al., 1983; G. M. Fitzgibbon et al., 1996; S. Goldman et al., 2004).

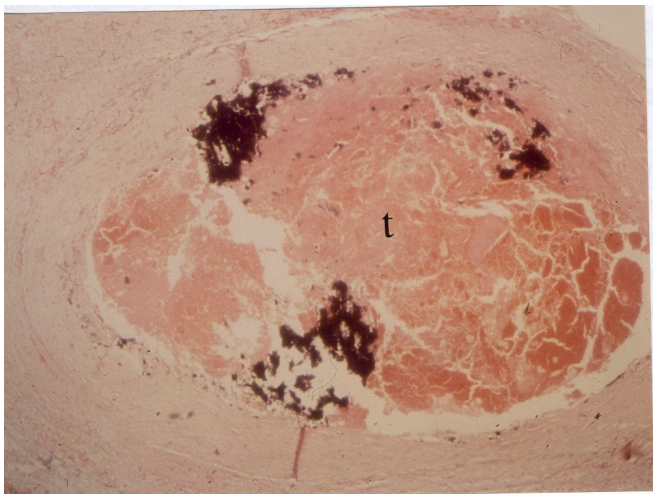

Figure 2: Early graft failure in saphenous vein graft occluded by thrombus (t) in its lumen. (H&E; X12.5 magnification).

2 Early Changes in Saphenous Vein Grafts

Changes in the saphenous vein begin at the time of harvesting, surgical preparation of the vessel and its transplantation into the arterial system. Studies on vein grafts recovered early following bypass graft surgery show that polymorphonuclear (PMN) infiltration into the intima, media and adventitia occurs in the first hours after surgery. This infiltration is an early phenomenon and by 7 to 10 days after bypass graft surgery PMN are virtually absent from the vein graft (Kockx, Cambier, Bortier, De Meyer & Van Cauwelaert, 1992). By 24 hours, most endothelial cells have been denuded

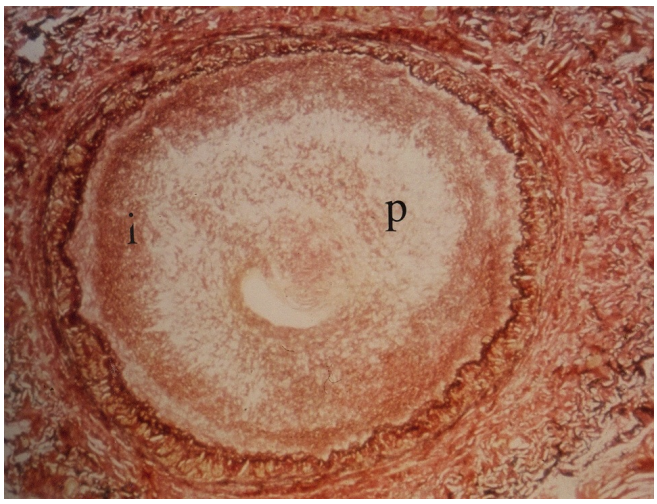

Figure 3: Late graft failure in saphenous vein graft showing intimal hyperplasia (i) and plaque (p) with severe narrowing of the graft lumen (l). (H&E; X 12.5 magnification).

or sloughed (Kockx et al., 1992). Endothelial cell loss may be partly related to injury during surgical preparation of the SV (Gurkan et al., 2014; Angelini, Passani, Breckenridge & Newby, 1987; Angelini, Christie, Bryan & Lewis, 1989). Kockx et al. (1992) suggest that the cause of endothelial denudation is the PMN infiltration however this infiltration could well be the result of chemotactic factors released by damaged endothelium (C. M. Grondin & Thornton, 1995). A recent study by Schlitt et al. (2006) showed that thrombin and mechanical or pharmacological dilatation of human saphenous vein grafts led to increased selectin-mediated PMN adhesion on vascular endothelium with subsequent endothelial dysfunction. Also Chello et al. (2003) showed that substantial distention pressure leads to the expression of endothelial adhesion molecules in human saphenous vein and these in turn cause adhesion of PMNs to the vein wall. High distension pressure leads to endothelial cell separation, causes disruption of the smooth muscle cells in the media (Brindle, 1993) and as soon as there is blood flow the endothelial cells easily wash away leading to possible vasoconstriction. The denuded sections will then be covered with new endothelium 1 to 2 weeks after implantation (Hausmann, Merker & Hetzer, 1996). The denudation of endothelium may induce a cascade mechanism for intimal formation and thickening and this is supported by studies showing that early re-endothelialisation inhibits subsequent intimal thickening in vein grafts (Shiokawa, Rahman, Ishii & Sueishi, 1989; Krijnen et al., 2012). In this acute phase there is also intimal oedema, with deposition of fibrin and platelets onto the endothelium (C. M. Grondin & Thornton, 1995; Chiu & Chien, 2011). Muscle necrosis occurs in the media, which is more marked in its inner circular

smooth muscle layer (Kockx et al., 1992; O'Brien et al., 1998; Cristian et al., 2016). It is suggested that this may occur from medial ischaemia following interruption of the venous vasa vasorum (Brody, Angell & Kosek, 1972) and from direct surgical trauma to the media with induction of an inflammatory response and cell necrosis (Hoch, Stark & Turnispeed, 1995; Mannion et al., 1998; Cristian et al., 2016). Programmed cell death (apoptosis) has also been noted after arterial injury and vein grafting (Kockx et al., 1994; Pearlman, Maillard, Krasinski & Walsh, 1997; O'Brien et al., 1998). The remaining smooth muscle cells in the graft media are of the synthetic phenotype (Kockx et al., 1992) in which state they would respond to various mitogens in contrast to the contractile phenotype, which do not (Thyberg & Fredholm, 1987; Brody, Kosek & Angell, 1972). Growth factors released by the damaged endothelium or injured smooth muscle cells promote platelet aggregation, hyperplasia and the migration of the synthetic smooth muscle cells to the intima resulting into intimal thickening (Brody, Kosek & Angell, 1972; Groves, Kinlough-Rathbone, Richardson, Moore & Mustard, 1979; Packham & Mustard, 1986). PMN, monocytes, lymphocytes and platelets attach to the freely accessible collagen or elastic fibres in the basement membrane (Reidy, 1985). Surgical dissection has been shown to activate adventitial fibroblasts (O'Brien et al., 1997), which in turn migrate through the media to take part in neointimal formation in vein grafts (Shi, O'Brien, Ala-Kokko et al., 1997). This active role of fibroblasts in vascular remodelling is also supported by evidence that extracellular matrix production of the injured adventitia occurs at the same time as neointimal formation (Shi, O'Brien, Mannion et al., 1997).

3 Intermediate and late changes in saphenous vein grafts

3.1 Changes occurring four weeks to one year

The endothelium regenerates after 2 weeks to cover a much thicker intima (Fuchs, Mitchener & Hagen, 1978; Hausmann et al., 1996). Fibrointimal hyperplasia describes the more chronic effects of intimal thickening commencing 1 month after grafting (Barboriak, Pintar & Korns, 1974; Unni et al., 1974; Bulkley & Hutchins, 1977; Kalan & Roberts, 1990). This represents regeneration of the intimal layer, which consists of a thick layer of matrix rich in mucopolysaccharides containing fibroblasts, smooth muscle cells and occasional foam cells (Unni et al., 1974). There is loss of smooth muscle cells from the media and some fibrosis rendering the vein graft rigid (Barboriak et al., 1974; O'Brien et al., 1998). The lumen of the graft becomes narrower angiographically (C. Grondin et al., 1974) and by 1 year its length shortens by about 10% during the first year causing radiological 'tenting' of the distal anastomosis (C. M. Grondin & Thornton, 1995).

3.2 Changes after one year

After the first postoperative year and up to the fourth year, histological changes in the vein graft are small and the lumen to wall thickness ratio stabilises although the graft media and intima may become more fibrous with more matrix and fewer nuclei. However during this period an increase in lipid content and number of foam cells in the vein wall become evident (Kalan & Roberts, 1990). It is believed that lipid deposition, foam cell presence and intimal thickening are the precursors or early signs of atherosclerosis (Bulkley & Hutchins, 1977; Kalan & Roberts, 1990; Vlodaver & Edwards, 1973). Although these histological features may appear as early as 3 months postoperatively (Bulkley & Hutchins, 1977) and at 1 year angiographically (G. Fitzgibbon, Leach, Keon, Burton & Kafka, 1986), clinical manifestations of graft disease appear after 3 years following surgery. The changes are indistinguishable histologically from arterial atherosclerosis (Unni et al., 1974; Bulkley & Hutchins, 1977) but in contrast to atherosclerosis in arteries which has got a life history lasting decades, the disease process in saphenous vein coronary grafts is accelerated and unstable leading to sudden pathological events (Killen et al., 1998; Lytle et al., 1992).

4 Aetiology of vein graft disease

Early graft occlusion occurs within 30 days of coronary artery surgery. It has been shown in experimental and clinical studies that early occlusion is mainly thrombotic in nature (Badimon, Ip, Badimon & Fuster, 1990) while late occlusion usually results from intimal hyperplasia with or without thrombus superimposition and atherosclerosis. Thrombosis, intimal hyperplasia and atherosclerosis seem to occur at different times but they are pathophysiologically interlinked in the evolution of vein graft disease.

4.1 Early vein graft disease and occlusion

The saphenous vein can be damaged during harvesting, surgical preparation and implantation onto the coronary arteries and aorta. The initial damage to the vein endothelium and adventitia occurs during harvesting from the leg and this occurs despite using a 'no-touch' technique and very careful dissection (Gottlob, 1977; Roubos, Rosenfeldt, Richards, Conyers & Davis, 1995; Kim et al., 2013). Vein dissection, handling of the vein with surgical instruments and adventitial stripping are all potentially traumatic. Spasm occurs while the vein is being excised leading to endothelial damage (Baumann, Catinella, Cunningham & Spencer, 1981; Raja & Sarang, 2013). Spasm causes endothelial disruption by reducing the luminal surface area upon which the

endothelial layer lies and by causing smooth muscle cell herniation into the endothelial layer or lumen in a pseudopod-like fashion with subsequent protrusion or sloughing of endothelial cells. Surgical distension of the vein with fluid (e.g. heparinised blood or saline) under pressure to check for any leakages from side branches is known to injure both endothelial and medial cell layers as demonstrated in several quantitative morphological and biochemical studies (Lo Gerfo, Quist, Cantelmo & Haudenschild, 1983; Angelini, Breckenridge, Butchard, Armistead & Middleton, 1985; Roubos et al., 1995; Galea et al., 1999; Khaleel et al., 2012). Endothelial damage leads to decreased production of tissue plasminogen activator (tPA) (Nachman & Silverstein, 1993), fibrin accumulation and adherence (Boerboom et al., 1980), platelet aggregation, neutrophil activation and circulating growth modulation (Reidy, 1992; Verrier & Boyle, 1996; Schlitt et al., 2006), which may result in thrombosis and may subsequently contribute to intimal hyperplasia. Exposure of the prothrombotic basement membrane and other subendothelial tissues occurs following endothelial damage with the release of tissue factor (Verrier & Boyle, 1996) and the activation of the extrinsic pathway of coagulation and subsequent graft thrombosis. Medial damage leads to local inflammation with monocyte infiltration. Adherent monocytes that will have entered the vessel wall change into resident macrophages, which secrete smooth muscle cell mitogens and may accumulate lipid deposits thus contributing to vein graft atheroma. Endothelial injury occurs during distension either as a result of direct mechanical trauma or wall tension (Gottlob, 1977; Angelini, Passani et al., 1987; Lo Gerfo, Quist, Crawshaw & Haudenschild, 1981; Stigler et al., 2012; Dong Li et al., 2014). Vein distension induces phosphorylation of p38 mitogen-activated protein kinase (Cornelissen, Armstrong & Holt, 2004). The acute loss of endothelial-independent function that occurs in de-endothelized saphenous veins with direct effect on the VSMC, may be due to the p38 mitogen-activated protein kinase–mediated degradation of the α-actin filament in venous smooth muscle (J. Goldman, Zhong & Liu, 2003). The smooth muscle cells of the vein graft dedifferentiate from their contractile activity with consequent increases in matrix metalloprotease activity and expression of cytoskeleton-associated proteins, enabling migration and proliferation of the smooth muscle cells (J. L. Johnson, van Eys, Angelini & George, 2001). The storage of the vein in a solution of low oncotic pressure (e.g. normal saline, Hartmann's solution, heparinized saline solution) also causes endothelial injury (Zerkowski et al., 1993; Osgood et al., 2014; Wise et al., 2015). The damage to the endothelium reduces the production of prostacyclin (Angelini, Breckenridge, Psaila et al., 1987) and endothelium-derived relaxing factor (Angelini et al., 1989) both of which normally oppose platelet activation (Radomski, Palmer & Moncada, 1987). Angelini and others showed reduction of short-term patency with endothelial damage and promotion of platelet and leukocyte adhesion in a pig arteriovenous bypass graft model (Angelini, Bryan, Williams, Morgan & Newby, 1990). Other causes for early occlusion of vein grafts include kinking, technical error in proximal and distal anastomosis and sudden exposure of vein graft to high-pressure pulsatile arterial system. Technical errors during suturing may result in obliteration, narrowing, artery wall dissection and tearing of the coronary artery leading to thrombosis and early graft occlusion at the site of the distal anastomosis. Early occlusion from thrombosis is more likely following endarterectomy of the coronary artery where the intima and inner portion of the media are shelled out to increase the diameter of the lumen rendering the distal anastomosis possible. This procedure denudes the endothelium and parts of the media leaving behind a highly thrombogenic surface which is known to promote early graft thrombosis (Walley, Byard & Keon W.J., 1991; Poston et al., 2006). Atherosclerotic disease at the anastomotic site and poor run-off of blood in the coronary artery distal to the anastomosis also predispose to early graft occlusion (Rasmussen et al., 1997).

4.1.1 Graft thrombosis

Vein graft thrombosis follows the pathological process of Virchow's triad namely changes in blood flow, alterations in blood rheology and changes in the vessel wall. Decrease of blood flow occurs at kink sites of vein grafts, or narrowed parts of vein from tight ligatures or distorted anastomoses to the coronaries and the aorta. Early thrombotic occlusion of vein grafts occurs most commonly at these sites. Thrombosis also occurs on vein lumen denuded from endothelium during surgical preparation, leaving the blood in contact with subendothelial collagen, binding and initiating platelet activation (Baumgartner, Muggli, Tschopp & Turitto, 1976). Cardiopulmonary bypass and major surgery alter blood rheology, which may predispose to thombogenicity (Lowe, 1987; Hsu, 1997; Galea, Rebuck, Finn, Manchè & Moat, 1998). CABG surgery alters circulating levels of the coagulation factors with a marked perioperative elevation of plasma fibrinogen favouring a prothrombotic response (Moor et al., 1994; Mannucci et al., 1995).

4.2 The endothelium and graft thrombosis

The vascular endothelium is a key participant in several processes such as coagulation, fibrinolysis, membrane permeability regulation, lipid transport, vasomotor tone, inflammation and the sustenance or alteration of vessel wall structure. The endothelium pro-

duces and secretes proteins which regulate these processes; increases or decreases vascular tone, promotes coagulation or fibrinolysis, enhances or inhibits platelet and leucocyte adhesion or causes structural changes in the vessel wall through the release of growth factors and matrix proteins (Lüscher, Tanner, Tschundi & Noll, 1993; Crossman, Carr, Tuddenham, Pearson & McVey, 1990; Harlan, 1985). The intact endothelium is anti-thrombotic and anti-coagulant under basal conditions and this is achieved through various processes to inhibit coagulation and promote fibrinolysis most markedly NO secretion and the expression of eNOS (Lüscher, Landmesser, von Eckardstein & Fogelman, 2014). The endothelial cells contribute several components of the coagulation cascade. The saphenous vein graft endothelium can be affected by local injurious stimuli (shear stress, surgical injury, hypoxia and cytokines) or by systemic inflammatory processes such as endotoxins and cytokines produced by cardiopulmonary bypass and ischaemia-reperfusion injury (Verrier & Boyle, 1996). Firstly, the endothelial cell does not constitutively express tissue factor (Drake, Morrissey & Edgington, 1989; Crossman et al., 1990). Tissue factor is a 47-kDa membrane bound glycoprotein co-factor which in conjunction with factor VIIa causes the activation of the extrinsic pathway of coagulation (Nemerson, 1988) permitting activation of factors IX and X. Most other cells in the subendothelial layers constitutively express tissue factor therefore exposure of these layers following endothelial injury leads to clot formation at the site of endothelial denudation (Edgington, Ruf, Rehemtulla & Mackman, 1991). Also injurious stimuli to the endothelium lead to up-regulation of tissue factor by the endothelial cells initiating coagulation and there is evidence to suggest that the endothelium supports the coagulation process, whether initiated by the extrinsic or the intrinsic pathways. Endothelial cells carry high-affinity receptors for factors IX and X (Heimark & Schwartz, 1983) and in these cells, IXa binding was potentiated in the presence of factors VIII and X indicating the facilitatory role of the endothelium in the coagulation process (Stern, Nawroth, Kisiel, Vehar & Esmon, 1985). The second endothelial-derived anticoagulant mechanism involves thrombomodulin. Thrombomudulin is a membrane bound anti-thrombotic regulatory protein synthesised by endothelial cells and is expressed on the cellular membrane, where it forms a 1:1 complex with thrombin (Dittman & Majerus, 1990; Esmon & Owen, 1981). This complex activates circulating protein C, which in the presence of its co-factor protein S, causes inactivation of factors VIIIa and Va (Esmon, 1987), destroying their pro-coagulant co-factor activity. The harvesting and preparation of the saphenous vein attenuates the activity of thrombomodulin by up to 30%, further increasing the procoagulant effect (Cook et al., 1991). The overall coagulant status of the cell will then depend upon the relative balances of tissue factor and thrombomodulin activity and the endothelium has developed a complex mechanism that allows it to down-regulate thrombomodulin while up-regulating tissue factor expression at the same time in response to surgical injury, cytokines, endotoxin, hypoxia, shear stress and other stimuli (Nawroth, Handley, Esmon & Stern, 1986; Bevilacqua et al., 1986; Conway & Rosenberg, 1988; Moore, Esmon & Esmon, 1989; Conway, Bach, Rosenberg & Konigsberg, 1989; E. M. Boyle, Verrier & Spiess, 1996). Another important anticoagulant process utilises the potential of the endothelium to express heparin on its surface (Marcum, McKenney & Rosenberg, 1984; Colburn & Buonassisi, 1982). Compared to arteries, the vein media and its poorly developed internal elastic lamina expresses less heparan sulphate (Cox, Chiasson & Gotlieb, 1991) leading to a procoagulant situation. The expression of this anticoagulant proteoglycan is mediated by increased release of antithrombin III. Heparin binds to thrombin reducing the cleavage of fibrinogen to fibrin. It has been suggested that the activation of thrombin, which occurs on the platelet membrane also occurs on the surface of endothelial cells (Rodgers & Shuman, 1983). Thrombin was formed when adding factor Xa and prothrombin to endothelial cells and this process was inhibited by anti-factor V antibody. The production of factor V by the endothelium was substantiated by S35 methionine studies (Cerveny, Fass & Mann, 1984) confirming that the abnormal endothelium plays a role in the thrombin formation. If any clot is formed the constitutive endothelial cell expression of tissue plasminogen activator (tPA) bonds with thrombospondin and the complex catalyses the conversion of plasminogen to plasmin promoting local lysis of the clot forms (van Hinsbergh, 1988; Dichek & Quertermous, 1989; Crossman et al., 1990). However, the injured endothelium upregulates plasminogen-activator inhibitor-1 (PAI-1), which also promotes procoagulant effects.

Apoptosis of the endothelial cells may occur in the vein subjected to the surgical technique and implanted in an extraneous part of the circulation. Apoptotic endothelial cells were shown to increase tissue factor procoagulant activity and decrease antigenic thrombomodulin, heparan sulphates and tissue factor pathway inhibitor levels and their activity. Moreover thrombin formation was also increased in the presence of apoptotic endothelial cells. The procoagulant effect in these cells was caused by increased expression of membrane phosphatidylserine and the loss of anticoagulant membrane components (Bombeli, Karsan, Tait & Harlan, 1997). The final endothelial anticoagulant mechanism is the

constant local secretion of soluble vasoactive products such as nitric oxide (Palmer, Ashton & Moncada, 1988; Lüscher et al., 2014), prostacyclin (MacIntyre, Pearson & Gordon, 1978) and adenosine which maintain vasodilation and prevent platelet aggregation and adhesion (Furlong, Henderson, Lewis & Smith, 1987; Radomski et al., 1987). Production of nitric oxide and prostacyclin is lower in veins than in arteries and their production is further reduced by bypass grafting due to endothelial cell loss or metabolic dysfunction (Angelini et al., 1989). Platelet activation stimulates synthesis of thromboxane A2 (Roth, 1986) and release of dense-granule components including serotonin and ATP and α-granule components including platelet-derived growth factor, platelet factor IV, fibrinogen, fibronectin, von Willebrand factor antigen and β-thromboglobulin (Stenberg & Bainton, 1986). These agents together promote vasoconstriction (Lam, Chesebro, Steele, Badimon & Fuster, 1987), further platelet aggregation (Roth 1986) and hence further thrombin and fibrin generation (Shuman & Greenburg, 1986). The low fluid shear stress in grafted saphenous veins as compared to arteries, reduces the shear-dependent release of tPA, NO and prostacyclin (Allaire & Clowes, 1997; Kabirian, Amoabediny, Haghighipour, Salehi-Nik & Zandieh-Doulabi, 2015).

Surgical technical problems that reduce blood flow through the graft may increase the risk of thrombosis. Saphenous veins, especially when denuded of endothelium are very sensitive to circulating vasoconstrictors, including endothelin-1, which is the most potent of endogenous vasoconstrictors (Ganesh et al., 2016). The plasma levels of soluble endothelin-1 increases steeply at the initiation of cardiopulmonary bypass followed by an additional slower rise during its course (te Velthuis et al., 1996). The resulting venoconstriction may attenuate blood flow through the graft and promote stasis. Furthermore thrombin has a vasoconstrictor effect in the saphenous vein (Yang et al., 1997; Gudmundsdóttir et al., 2008).

4.3 Causes of late graft occlusion

Graft occlusion in the first year after implantation is caused mainly by intimal hyperplasia with superimposed thrombosis (Blaas et al., 2016). Experimental studies suggest that ischaemia, higher intraluminal pressure, and oxygen tension are major causes of fibrous hyperplasia (Brody, Kosek & Angell, 1972). Intimal hyperplasia is believed to represent adaptation of the vein to the trauma of transplantation and although early papers had suggested that intimal hyperplasia may be reduced by aspirin (McCann, Hagen & Fuchs, 1980), this was disproved in later research (Fuster & Chesebro, 1985; Yamaguchi et al., 1991; Landymore, MacAuley & Manku, 1990, 1992) although other anti-platelet therapy may reduce intimal hyperplasia (Göncü et al., 2010; Hermann, Weber & Schror, 2002). Smooth cell proliferation continues after re-endothelialisation occurs and although the endothelium appears morphologically intact there is evidence that it is functionally impaired (Angelini et al., 1989; Komori, Okadome & Sugimachi, 1991). After the first year of implantation, vein occlusion is caused principally by graft atherosclerosis. In 70 to 85% of patients presenting with unstable angina (Chen et al., 1996) and myocardial infarction (Douglas, 1994; Chen et al., 1996) following coronary artery bypass graft the culprit lesion is atherosclerotic vein graft stenosis, often with superimposed thrombosis. The atherosclerosis is rapidly progressive (Yahagi et al., 2016). It has been suggested that this progressive form of atherosclerosis occurring in saphenous vein grafts is either initiated or promoted by intimal injury to the graft (Bulkley & Hutchins, 1977; Smith & Geer, 1983) or by conventional cardiac risk factors particularly hyperlipidaemia with lesser effects from smoking and diabetes (Solymoss, Nadeau, Milette & Campeau, 1988; Neitzel, Barboriak, Pintar & Quresh, 1986).

4.3.1 Accelerated Intimal hyperplasia (AIH)

Intimal hyperplasia is the accumulation of smooth muscle cells and extracellular matrix in the intima and is the major disease phenomenon occurring in the vein graft between one month and one year after implantation that eventually reduces the graft lumen and may have superimposed thrombosis (Zubilewicz, Wronski & Bourriez, 2001). Intimal hyperplasia has been described as a chronic structural change in the graft which process leads to formation of thickened fibrocellular layer between the endothelium and the inner elastic lamina (Dilley, McGeachie & Prendergast, 1988). Various studies have shown that many veins exhibit mild intimal or medial fibrosis before grafting (Thiene et al., 1980) and diffuse intimal hyperplasia develops in all vein grafts and is unavoidable (Campeau, Lesperance & Bourassa, 1984; Fuchs et al., 1978). It is believed to be part of the reparative process that takes place in all vessels after injury (Schwartz, DeBlois & O'Brien, 1995). It can be found as a diffuse layer spread evenly throughout the graft or as a focal lesion found anywhere in the graft (Fuchs et al., 1978) however some studies show a thicker intimal layer at the anastomosis (De Weese & Green, 1980; Madras, Ward, Johnson & Singh, 1981). The process of intimal hyperplasia starts within 24 hours of endothelial injury with medial smooth muscle proliferation in response to a number of cytokines and growth factors released from activated endothelial cells, platelets and macrophages (Holt et al., 1992) with the early involvement of the immediate response gene *c-fos* (Galea et al., 1999). Also, NF-κB mediated signalling is central in gene regulation of numerous cytokines and adhesion molecules involved in AIH (Hu et al., 2002; Miyake, Aoki

& Shiraya, 2006). Indeed, proliferation of intima-bound medial VSMC is pivotal to AIH in vein grafts (Dilley et al., 1988; Schwartz et al., 1995) and in the development of atherosclerosis (Ross, 1986; Stary et al., 1992). Intimal hyperplasia occurs quite quickly in vein grafts, angioplasty and transplantation and is termed accelerated intimal hyperplasia.

In the intact media of blood vessels, the major function of the smooth muscle cell is maintenance of tension via contraction-relaxation (Stadler, Campbell & Campbell, 1989) and the cells are arranged predominantly in a circular fashion. In keeping with their function, the cell cytoplasm contains numerous myofilament bundles whereas synthetic organelles such as rough endoplasmic reticulum are few in number and located at the perinuclear region (J. H. Chamley-Campbell, Campbell & Ross, 1981). Phenotypic modulation is an important initial event in the pathophysiology of intimal proliferation. In the majority of cases the VSMCs must first modulate from the contractile state into a synthetic phenotype before they become secretory and responsive to mitogenic stimulation (J. H. Chamley-Campbell et al., 1981) and capable of migration (J. Chamley-Campbell, Campbell & Ross, 1979; Thyberg, Palmberg, Ksiazek & Sjölund, 1983). Intimal VSMCs have also been shown to originate from adventitial fibroblasts, from bone marrow progenitor cells, pericytes and pre-existing intimal cells (Shi et al., 1996). The endothelial cell plays a regulatory role in intimal growth through a number of growth-inhibitory mechanisms therefore endothelial cell loss during surgical manipulation of the vein modifies these effects. Once the endothelium is denuded, platelets adhere to the vessel wall, spread and degranulate releasing mitogens such as platelet-derived growth factor (PDGF) that stimulate the smooth muscle cells to migrate to the intima. Injured endothelial and smooth muscle cells secrete other mitogens such as basic fibroblast growth factor that stimulates proliferation of SMCs in the media (Clowes, 1991). Plaques of modified smooth muscle cells have been found in the intima as early as nine and ten days following grafting (Brody, Angell & Kosek, 1972; Barboriak, Pintar, Van Horn, Batayias & Korns, 1978). Immunocytochemical studies in diseased aortocoronary vein bypass grafts have shown that the majority of cells within the fibrous intimal thickening in veins are smooth muscle cells and macrophages were seldom seen as compared to atherosclerotic arterial disease (Tsukada, Tejima, Amano, Suzuki & Numano, 1988). The modulated smooth muscle cells continue to proliferate further in the neointima. Later these activated SMCs synthesise large quantities of elastin, collagen and proteoglycans and Thyberg, Nilsson, Palmberg and Sjölund (1985) demonstrated that they produce four to five times the amount of connective tissue compared to the contractile phenotype with collagen production being the most florid (Ang, Tachas, Campbell, Bateman & Campbell, 1990). This contributes to deposition of the extracellular matrix leading to progressive increase in intimal fibrosis with reduction in cellularity (Allaire & Clowes, 1997). The activated SMCs temporarily produce PDGF-like substance, which stimulates intimal growth in an autocrine manner (Nilsson, 1987). It has been shown recently that Polo like kinase 1 (PLK1), a serine/threonine kinase that regulates cell cycle progression and mitosis and its expression and activity is elevated in tissues and cells with high mitotic index might play a critical role in VSMC mitosis in hyperplastic intima of vein grafts (Sur, Swier, Radwan & Agrawal, 2016). The secretory phenotypic cellular cytoplasm contains large amounts of free ribosomes, rough endoplasmic reticulum and mitochondria but very few myofilaments (Thyberg et al., 1983). There is a corresponding decrease in myosin, tropomyosin and actin (Kallioniemi, Jaakkola, Nikkari & Nikkari, 1984). Actin changes its isoform from being mainly smooth muscle α-actin in the contractile phenotype to β-actin that is not predominantly a muscle actin (Rubbia & Gabbiani, 1989). This type of synthetic smooth muscle cells have been described in vein graft intimal thickening (Unni et al., 1974; Dilley et al., 1988), in atherosclerotic plaques (Campbell, Black & Campbell, 1989) and foetal blood cells (Nikkari, Rantala, Pystynen & Nikkari, 1988). Histologically these modified smooth muscle cells in the intima are oriented parallel to the long axis of the vessel (Spray & Roberts, 1977; McGeachie, Prendergast & Morris, 1983). The extracellular space of the intima contains some collagen fibres, also aligned with the direction of blood flow; some microfibrils, 10 µm in diameter and rarely elastin (Fuchs et al., 1978; Brody, Angell & Kosek, 1972). Synthetic SMCs show an increased ability to bind and ingest lipoproteins in vitro (Campbell, Reardon, Campbell & Nestel, 1985). Also, vein grafts incorporate more total lipids than arteries and normal veins in hyperlipidaemic patients (Lie, Lawrie & Morris, 1977). The intima of a normal vein is made up of a single layer of endothelial cells (Rhodin, 1968) and the presence of intimal smooth muscle cells is regarded as the first step to intimal hyperplasia. At 2 weeks after autologous grafting of a vein patch to the rat carotid artery, the venous intimal smooth muscles cells existed in various stages of differentiation (Cuevas & Gutierrez Diaz, 1982) and at 3 weeks the cells had differentiated to contain many myofilaments, dense bodies, caveolae intracellulares and gap junctions. This apparent maturation of modified smooth muscle cells to form a muscular intima has also been described by Unni et al. (1974). In contrast to arterial injury, vein grafts AIH occur mostly after re-endothelialisation of the vessel (Dilley,

McGeachie & Tennant, 1992). One explanatory mechanism is the transient ischaemia occurring in the vein from the time of harvesting to reperfusion after implantation in the arterial system. These adverse conditions induce the formation and secretion of superoxide radicals, which promote SMC proliferation and at the same time depress the endothelial production of antiproliferative agents such as prostacyclin, NO and adenosine (Holt et al., 1993; Rao & Berk, 1992). Also loss of the vasa vasorum blood supply in the vein may lead to ischaemia and fibrosis. The phenotypic modulation in SMCs appears to be reversible depending on their proliferative state (J. H. Chamley-Campbell et al., 1981; Stadler et al., 1989). Modulation into the synthetic state can be inhibited in vitro by a feeder layer of confluent endothelial or contractile SMCs and by heparin (J. H. Chamley-Campbell et al., 1981). In vein grafts, SMCs forming intimal hyperplasia modulate back into the contractile phenotype about 3 months after grafting (Dilley et al., 1988). The ability of SMCs to change back into their contractile phenotype seems to depend also on the length of time the proliferative stimulus was applied for (J. H. Chamley-Campbell et al., 1981). Cells that have been in the synthetic phenotype for a considerable period of time cannot change back to the contractile phenotype and will remain permanently responsive to mitogens and hence maintain the stimulus of intimal hyperplasia and atherosclerotic plaque formation. When vein grafts are implanted in the arterial circulation the vein wall is subjected to increased wall stress, which is also implicated in the aetiology of AIH. This has been shown in animal models where increased wall stress was shown to up regulate vein graft intimal receptors for VSMC mitogen basic fibroblast growth factor which is released by injured endothelial and smooth muscle cells (Nguyen et al., 1994). Vein distension also increases vein diameter reducing mean blood velocity and decrease in shear stress. This reduction in shear stress upregulates the production of mitogens such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF) and endothelin 1 and downregulates growth inhibitors like transforming growth factor-β and NO, thus inducing smooth muscle cell proliferation and intimal hyperplasia (Cox et al., 1991; Allaire & Clowes, 1997; Mitra, Gangahar & Agrawal, 2006). This increase in growth factor activity in both low and high shear stress conditions leads to the supposition that there is an optimum shear value below and above which AIH occurs (Lemson, Tordoir, Daemen & Kitslaar, 2000). Another mechanism that has been shown to be involved in neointimal formation in a porcine model of saphenous vein involves the role of perivascular fibroblasts. These fibroblasts may infiltrate injured media of arterialised SVGs, differentiate to myofibroblasts, acquiring alpha-smooth muscle actin and take part in neointimal formation. The intima of human saphenous vein grafts, retrieved during repeat coronary artery bypass surgery exhibits the profile of cytoskeletal proteins resembling myofibroblasts seen in porcine vein grafts which suggest that this process is mimicked in the clinical situation (Shi, O'Brien, Mannion et al., 1997).

4.3.2 Accelerated Graft atherosclerosis

Atherosclerotic plaque is not detected until one year after surgery and is rarely observed before the second or third year after implantation (Atkinson, Forman & Vaughn, 1985; Solymoss et al., 1988; Kalan & Roberts, 1990). Plaques are observed histologically in 21% of grafts at a mean of 5 years after operation. The pathogenesis of atherosclerosis includes impaired lipid metabolism and an improper immune response leading to chronic inflammation of the artery or vein graft (Weber & Noels, 2011). The fundamental process of atherosclerosis is similar in native coronary arteries and SVGs but it is rapidly progressive in the latter that is similar to the accelerated atherosclerosis occurring in chronic transplant rejection. This rapid disease process is possibly closely related to chronic endothelial injury and dysfunction (Dilley et al., 1992; E. M. Boyle, Lille, Allaire, Clowes & Verrier, 1997). The atherosclerotic lesions occurring in vein grafts differ morphologically from lesions arising in arteries. Vein graft atherosclerosis tends to be diffuse, concentric, and friable with a poorly developed or absent fibrous cap and little evidence of calcification, whereas native coronary disease is proximal, focal eccentric and non friable with a well developed fibrous cap and frequent calcification (Lie et al., 1977; Kalan & Roberts, 1990; Ratliff & Myles, 1989). Histologically, vein graft atherosclerosis has the foam cells as the principal or even the only cells in the lesion and they appear to erode the thickened intima. Consequently, graft atherosclerosis resembles experimentally induced atherosclerosis in animal models rather than fatty streaks and plaque lesions in human arteries. The presence of these foam cells and inflammatory cells such as multinucleated giant cells has led some researchers to propose an immunological basis for vein graft atherosclerosis (Ratliff & Myles, 1989). The evidence for this is firstly because this form of atherosclerosis is very similar to that occurring in coronary arteries in patients with underlying immunological vascular diseases (Ansari, Larson & Bates, 1985; Bulkley & Roberts, 1975), in laboratory animals with experimentally induced immunological vascular injury (Wissler & Vesselinovitch, 1983; Alexander, Clarkson & Fulgham, 1985) and in experimental and human cardiac transplantation (Kottke-Marchant & Ratliff, 1988; D. Johnson, Gao, Scroeder & Billingham, 1988). Secondarily, patients undergoing aortocoronary bypass have been shown to be immunologically stimu-

lated in the postoperative period (Baker, Cohen, Head, DeShong & Graeber, 1986; De Scheerder et al., 1986). Thirdly, atherosclerotic saphenous vein grafts has shown increased deposition of immunoglobulin (Fitzmaurice & Ratliff, 1990; Schepers et al., 2006). Lipid metabolism in the saphenous vein is relatively atherogenic with increased lipid synthesis and uptake (Larson, Hagen & Fuchs, 1974) and decreased lipolysis (Shafi, Palinski & Born, 1987). The presence of high levels of LDL cholesterol and diabetes are independent factors in SVG atherosclerosis (Yanagawa et al., 2014). In vivo intravascular ultrasound studies suggest that the focal compensatory enlargement observed in atherosclerotic native coronary arteries does not occur in diseased saphenous vein grafts (Nishioka et al., 1996). Graft atherosclerosis is otherwise indistinguishable from the native disease but because of the thin fibrous cap on a lipid-rich lesion they are more fragile and prone to rapture and thrombosis. Apoptosis plays an important role in the development of the atherosclerotic plaque mainly through smooth muscle cell and macrophage death leading to plaque instability (S. Bjorkerud & Bjorkerud, 1996; Bennett & Boyle, 1998). Oxidised low density lipoproteins have been shown to induce apoptosis of smooth muscle cells and macrophages through the modulation of Fas and bcl-2 protein expression (Li, Yang & Mehta, 1998). Superimposition of thrombosis on atherosclerotic vessels is a common occurrence and may lead to recurrent angina or myocardial infarction after CABG. In one study over two thirds of resected vein grafts during coronary reoperations for recurrent symptoms showed late thrombosis (Solymoss et al., 1988). Thrombosis and instability of the plaque in vein grafts can occur through two mechanisms. Plaque macrophages may release matrix-degrading enzymes that weaken the fibrous cap (Libby et al., 1996; Finn, Nakano, Narula, Kolodgie & Virmani, 2010). Foam cells in the diseased saphenous vein graft possibly release a factor that induces smooth muscle cell apoptosis in the atherosclerotic intima depleting the plaque of SMCs. This depletion could promote plaque rapture and thrombosis (Kockx et al., 1996; Kockx & Herman, 2000; Stoneman & Bennett, 2004; Libby, 2008). Complement factor C5a has been implicated in plaque rapture in grafts (Wezel et al., 2014).

The understanding of the detailed pathology of the different stages of SVG disease offers different possible opportunities for researchers and clinicians to find ways to counteract this pathological process and improve short and long term patency of these conduits thus reducing mortality and morbidity from such a common disorder. Although arterial conduits such as the left internal mammary has shown better long term patency, this vessel is mainly used on the left anterior descending coronary artery which is usually a bigger vessel than the others with consequent better flow capacity therefore comparison is difficult. The long saphenous vein is still the commonest conduit used in coronary bypass surgery therefore improvement in its patency rate is essential because it is here to stay.

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