Chapter 1

Introduction and objectives
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Vascular grafting is a surgical procedure performed to repair a blocked or damaged artery and during microvascular tissue transfer or replantation of amputated part. Vascular grafts can be classified as either biological (autograft or cadaveric) or synthetic (polyester or polytetrafluoroethylene) (Leon and Greisler, 2003; Chung and Li, 2004). Biological graft material may be veins or arteries. Vein graft is commonly favored but has poor patency rate as compared to the arterial graft (He and Cooley, 2006). Arterial grafting procedures are most commonly performed on the arteries of the heart (coronary arterial bypass graft), legs, kidneys, and intestines, or on the abdominal aorta. Arterial diseases caused by intimal hyperplasia/atherosclerosis, such as coronary artery disease, peripheral vascular disease, and aortic aneurysm, are conditions that commonly require this procedure (Green et al., 1968; Schwartz et al., 1993; Johnston et al., 1995; Hiatt, 2001; Stillaert et al., 2003; Leon and Greisler, 2003; Fuster, 2007).

The first operations on the aorta took place in the early 1800s and were for aneurysmal disease, invariably due to syphilis, in young to middle-aged men. In 1817, Sir Astley Cooper, a student of John Hunter, ligated the aortic bifurcation in a 38-year-old man who had suffered a ruptured iliac artery aneurysm (Brock, 1969). The patient died soon after the operation. Keen, Tillaux, Morris, and Halstead reported similar attempts to ligate aortic and iliac artery aneurysms without patient survival in the 100 years following Cooper’s initial report (Friedman, 1989).

During the same period, vascular reconstruction of the peripheral arteries was developing rapidly. The first attempts to place venous autografts into the peripheral circulation were described by Alfred Exner in Austria and Alexis Carrel in France at the beginning of the twentieth century (Friedman, 1989). Separately, these two individuals pioneered the vascular anastomosis. Exner used techniques with Erwin Payr’s magnesium tubes, while Carrel used segments of vein. Carrel and Charles Guthrie developed the model of the arterial anastomosis in dogs at the Hull Physiological Laboratory in Chicago (Carrel and Guthrie, 1906). In 1912, Carrel was awarded the Nobel Prize in Physiology and Medicine in “recognition of his work on
vascular suture and the transplantation of blood vessels and organs.”

Synthetic vascular grafting have been successful for large diameter arteries (aorta/iliac arteries), they have shown minimal success in arteries with smaller diameter (<6mm). This is because most synthetic materials more prone to infection, bacterial colonization and induce thrombus formation which, within a few months of implantation, causes failure of the vascular graft due to occlusion (Wagner et al, 1994; Chester, 2002). Therefore, biologic vascular grafts are to be used preferentially in small diameter and medium sized arterial reconstruction because of their resistance to bacterial colonization and lipid uptake.

Studies have demonstrated that arterial grafts are preferred over the venous grafts because of long term patency results. There are differences in biological characteristics between the arterial and venous grafts (Kanellaki-Kyparissi et al., 2005; He and Cooley, 2006). These differences are:

1. The veins are more susceptible to vasoactive substances than arteries.
2. Venous wall is supplied by the vasa vasorum whereas the arterial wall may be supplied through the lumen in addition to the vasa vasorum.
3. Pathological changes (thickening of intima and media, and aneurysm) in the wall of venous grafts are more severe than those in the wall of arterial grafts.
4. Endothelium of the arteries may secrete more endothelium-derived relaxing factor and may release more nitric oxide.
5. The structure of the vein is subjected to the low pressure whereas structure of the arteries is subject to high pressure. Therefore, in a high pressure system after bypass surgery, venous grafts have to adapt to the high pressure whereas arterial grafts are used to it.

Medium sized arteries are frequently used as ideal arterial grafts in myocardial revascularization and reconstructive plastic surgeries. Vineberg in 1946 used internal thoracic artery (ITA) for an indirect myocardial revascularization. About two decades later, Kolessov (1967) performed the first ITA-LAD (left anterior descending artery) direct anastomosis on the beating heart as a method of treatment for angina pectoris.
Excellent long-term results of the internal thoracic artery as a graft for coronary artery bypass surgery have encouraged a search for other reliable arterial conduits for total arterial revascularization. Such conduits include the radial artery, gastroepiploic artery, inferior epigastric artery, splenic artery, subscapular artery and posterior intercostal artery (Carpentier et al., 1973; Curtis et al., 1975; Van son et al., 1990, 1993; Suma et al., 1990; Acar et al., 1992; da Costa et al., 1996).

Superficial temporal artery (STA) has been used as a graft for STA-MCA (middle cerebral artery) bypass and for the cranio-facial and scalp reconstruction for several reasons, including its accessibility and proximity to the cerebro-vasculature in distance and in caliber. The first STA-MCA bypass was performed in a human by Yasargil, (1999) on a patient with complete occlusion of the MCA (Yasargil, 1999; Hansen et al., 2007; Halvorson et al., 2009). The study of Ustün et al. (2004) suggests that the middle meningeal artery (MMA) would be suitable for a bypass with the petrous internal carotid artery (ICA).

One of the complications seen after bypass surgery is vasospasm of the arterial grafts this may be caused by sympathetic nerves (Barry et al., 2003). Vasospasm may be caused by various factors, such as mechanical handling of the recipient artery, drugs or perioperative trauma (Penttilä et al., 2001). Arterial diameter and arterial blood flow is regulated by neural and endothelial factors. The potential cause of the vasospasm shortly after surgery may be due to increased levels of catecholamines in the graft wall, which may cause pathologically enhanced constriction of vascular grafts (Penttilä et al., 2001, 2004). Hence, the ideal grafts for replacing or bypassing medium sized arteries should have sparsely innervated with sympathetic nerves (Heikki et al, 2004).

Medium sized arteries that are innervated with sympathetic nerves are well known to clinicians for certain diseases allegedly caused by the involvement of sympathetic nervous system i.e. Migraine - superficial temporal and middle meningeal arteries (Peroutka, 2004); Ischemic acute renal failure – Renal artery (Fujii et al., 2003; Neumann et al., 2004); irritable bowel syndrome – mesenteric/marginal artery (Birch...
et al., 2008). Sympathetic nerves exert vasoconstrictor tone in most blood vessels, utilizing noradrenaline (NA), adenosine 5α-triphosphate (ATP) and neuropeptide Y (NPY). Antibodies to tyrosine hydroxylase (TH), a rate-limiting enzyme involved in the synthesis of catecholamines (Figure 1), can be used as a marker for sympathetic nerves.

![Enzymatic pathway of catecholamine synthesis](image)

**Figure 1: Enzymatic pathway of catecholamine synthesis**

Medium (Muscular) sized arteries have tunica intima with a prominent internal elastic membrane and a tunica media with a prominent smooth cell component (Figure 2). The muscular arteries may control the affluence of blood to the organs by contracting or relaxing the smooth muscles of the Tm. Certain arteries types are more prone to age related pathological changes, while other artery types are remain free from the age related pathological changes (Vink et al., 2002). With advancing age, modifications of the cardiovascular system occur. Ageing is associated with alterations in a number of structural and functional properties of arteries, including diameter, wall thickness, wall stiffness, and endothelial function. In rodent and nonhuman primate models of ageing, diffuse intimal thickening has been observed with advancing age, even though these animals do not develop atherosclerosis. The diffusely thickened ageing intima contains matrix proteins, collagen, glycosaminoglycans, vascular smooth muscle cells
that are thought to have migrated from the media (Li et al., 1999; Asai et al., 2000; Najjar et al., 2005).

**Figure 2: Microstructure of the medium sized artery**

An adaptive thickening of the intima can be observed within the human arterial system. Adaptive intimal thickening could be considered as a physiological adaptation of the intima to variations in flow, wall tension or both (Stary et al., 1992). When atherosclerosis develops, atherosclerotic lesions develop in regions with adaptive intimal thickening. Rupture of a vulnerable atherosclerotic lesion may lead to acute thrombus formation and subsequent occlusion of the artery, causing clinical syndromes like myocardial infarction. Although the development of atherosclerosis is influenced by systemic risk factors like hypercholesterolaemia and hypertension, certain types of arteries are more prone to develop clinically manifest atherosclerosis than other artery types (Stary et al., 1992). Atherosclerosis/intimal hyperplasia being the main cause for the renal artery stenosis, leads to reduced renal perfusion and manifested as hypertension, progressive renal failure and recurrent pulmonary edema (Mann et al., 1992; Xenos et al., 2003). Previous studies have shown that the characteristic features/structure of the arterial wall influences the occurrence of the age related pathological changes (Barry et al., 2003, 2007).

Hence, it will be advisable to select arteries which show resistance to age related pathological changes, for arterial grafting.
Hence, the present study aims to ascertain the characteristics of arterial wall and histomorphometry of the selected human medium sized arteries for different age groups and also, to assess the effect of ageing on these arteries in order assess their suitability as arterial bypass-grafts.

We also intend to obtain insight into the sympathetic innervation of the medium sized arteries as they provide anatomical evidence in better understating of the sympathetic nervous system disorders that affect medium sized arteries. It is well known to the surgeons that due sympathetic over activity while handling during surgery, arteries may go in spasm and thrombosis may set in.

To the best of our knowledge, there is a still lack of data on the histomorphometry, effect of ageing and sympathetic innervation of the human medium sized arteries. Therefore, in the present study we selected internal thoracic, posterior intercostal, middle meningeal, superficial temporal, right coronary, left anterior descending, renal and mesenteric segments of marginal arteries from the human body. The reason for selecting these arteries as they used as arterial grafts (internal thoracic, posterior intercostal, superficial temporal artery, middle meningeal) or prone to stenosis (coronary, renal and mesenteric arteries) or associated with sympathetic nervous system disorders (Migraine - superficial temporal artery; middle meningeal artery; Ischemic acute renal failure – Renal artery, angina pectoris-coronary arteries and irritable bowel syndrome-marginal artery).

All above arteries were processed for Hematoxylin - Eosin (H&E) and Verhoeff - Van Gieson (VVG) staining for histological and morphometric studies. Same arteries were also processed for TH immunohistochemical staining for sympathetic innervation.

**Objectives of the study**

- To study the detailed microanatomy and histomorphometry of the medium sized arterial wall and compare with that of arteries from different sites.
- To study the effect of ageing on the medium sized arteries.
- To study the sympathetic innervation of the medium sized arteries.