Introduction

Since the early days of coronary artery bypass grafting (CABG), the biological characteristics and the differences between venous and arterial grafts had already attracted research interest. There is a large body of literature, including our own work, which have demonstrated differences between venous and arterial grafts. For example, the use of the internal mammary artery (IMA) has proven to provide superior long-term results than standard saphenous vein grafts (1,2). Some of the differences between the two types of conduits, which may account for the variations in the long-term patency rate, include:

(I) Veins are more susceptible to vasoactive substances than arteries (3);
(II) The venous wall is supplied by the vasa vasorum whereas the arterial wall may be supplied through the lumen in addition to the vasa vasorum (4);

(III) The endothelium of arteries may secrete more endothelium-derived relaxing factor (EDRF) (5) and may release more nitric oxide (NO) (6,7) and endothelium-derived hyperpolarizing factor (EDHF) (6,7);

(IV) The structure of the vein is subject to low pressure whereas that of the artery is subject to high pressure. After grafting to the aorta-coronary system, venous grafts have to adapt to the higher pressure.

We will describe the biological characteristics of arterial and venous grafts, clinical classification, and scientific considerations for clinical choice of arterial grafts and pharmacological management with antispasm protocols for conduits.

Arterial grafts

Based on the superior long-term results of the IMA, other arteries have been used for CABG (8-14). These conduits include the radial artery (RA) (8), the gastro-epiploic artery (GEA) (9), the inferior epigastric artery (IEA) (10,11), the splenic artery (12), the subscapular artery (13), the inferior mesenteric artery (14), the descending branch of lateral femoral circumflex artery (15), and the ulnar artery (16). In addition, the intercostal artery (17) has also been suggested for use as a graft.

The long-term patency rates for IMA are well established. Similarly, long-term patency for RA (18-23) and GEA (24-27) are also now well recognized, supplementing early reports (28-30). Other arterial conduits are expected to exhibit similar long-term results as the IMA, as it is hypothesized that all arterial conduits have similar biological characteristics such as contractility, relaxing characteristics, endothelial function, and anatomical structure.

However, histological studies have revealed that there are major variations between various grafts in terms of the structure of smooth muscle, such as elastic lamellae (4,31), while comparative functional studies have demonstrated that there are differences with regard to contractility and endothelial function (32-36). Our previous studies have demonstrated that the endothelium of the IMA releases more NO and EDHF than the RA at both the basal and stimulated level (37) and we have recently further shown that the expression and function of endothelial nitric oxide synthase messenger RNA and protein are higher in the IMA than in the RA (38).

These anatomical and physiological dissimilarities form the basis for the divergent clinical manifestations, postoperative functions, and long-term patency rates for the various grafts. Furthermore, it has been observed that the tendency for differing arterial grafts to develop spasms during surgical dissection and perioperative period differs. It is the experience of many surgeons that the GEA has a higher tendency to spasm than the IMA (39). Similarly, in the early adoption of RA grafts in the 1970s, spasm of the RA was a sufficiently serious problem that, together with a low patency rate, led to the abandonment of this arterial graft for clinical use (25). Only after the development of a method to overcome spasm of this arterial graft was it then used again (40,41).

Biological characteristics

A common feature of arterial grafts is that removal of these arteries would not usually affect the blood supply to the organ, as these are conductance arteries and will only be a concern under extreme circumstances. However, there may be differences in the function of these arteries due to different flow and capacitance requirements of their native organ. The differences among these arteries can be described from anatomical, physiological, pharmacological, and embryological perspectives at the organ, tissue, or cellular/molecular level.

Anatomy

The differences in the gross anatomy of the arterial grafts are obvious since they are at different locations in the body and supply different organs. In addition to evidence showing the divergent structure of arteries (4,31), another structural difference is that some arteries such as GEA, IEA and RA contain more smooth muscle cells in their wall and therefore are less elastic. In contrast, other arteries such as IMA may be more elastic and contain higher levels of elastic laminae. These structural variations may account for the differences in the physiological and pharmacological reactivity of the conduits.

Contractility and incidence of spasm

While the true cause of vasospasm remains unclear, vasospasm is presumed to be the extreme form of vasoconstriction responses to stimuli (spasmogens). These stimuli may be physical (such as mechanical stimulation or temperature changes) or pharmacological (such as nerve
stimulation or vasoconstrictor substances) (35,42-57).

We have suggested (35) that there are two types of vasoconstrictor that are important spasmogens for arterial grafts. Type I [endothelin, prostanooids (TxA2 and PGF2α) and α1-adrenoceptor agonists] are the most potent vasoconstrictors which strongly contract arterial grafts even when the endothelium is intact, while Type II vasoconstrictors (such as 5-HT) only induce a weak vasoconstriction when the endothelium is intact. However, these vasoconstrictors probably play an important role in the spasm of arterial grafts if the endothelium is lost due to surgical handling or from diseases such as diabetes.

Although all arterial grafts react to the vasoconstrictors listed above, there is a general trend that some arteries react to vasoconstrictors in a stronger manner than others (33,34,39,41,48). Despite these variations, there are groups of arteries, including IMA and IEA, that are similar in their contractility response to vasoconstrictors such as endothelin, U46619, or K+ (34,36).

We have also compared the pharmacological reactivity of the human coronary artery from the explanted heart transplant with the bypass grafts in vitro (34). When the large coronary artery has atherosclerotic disease, it may be less reactive to vasoconstrictors compared to arterial grafts, even though the reactivity of the micro-coronary artery may remain high.

Receptors in smooth muscle

Most vasoconstrictors, except potassium ions, contract arterial grafts by activating a specific receptor. For example, the IMA is an α1-adrenoceptor-dominant artery with little α2- or β-function (49,58), in contrast to the RA which has both α1- and α2-function but weak β-function (50).

ETA, ETB (51), 5-HT (52), angiotensin (53), thromboxane-prostanoid (TP) (54), vasopressin V1 receptors (44,55), and vasoactive intestinal peptide (45) receptors have been demonstrated to be functional in the IMA. However, there have been fewer reports on the receptors in other arterial grafts (34,45,48). Moreover, we have recently discovered that the human urotensin II receptor (hUT receptor) exists in the human IMA (46,47) and RA (46).

Receptors in endothelium and endothelial function

Receptors are also located in the cellular membrane of the endothelial cell in the arterial grafts. For example, common stimuli for EDRF such as acetylcholine, bradykinin, and substance P are present in the endothelium of arterial grafts (32,36,48). The vascular endothelial growth factor (VEGF)-induced, endothelium-dependent relaxation, mediated by both NO and prostacyclin in the IMA, has been shown mainly through the KDR receptors, rather than Flt-1 receptors (59). Most recently, we have shown that corticotropin-releasing factor (CRF) receptors CRF1, CRF2α, and CRF2β are present in the human IMA (60). The CRF urocortin-induced endothelium-dependent relaxation in the IMA is likely to be mediated through CRF receptors situated in the endothelium of the IMA (60).

In our recent studies comparing endothelial function among arterial grafts, it was found that IMA has more endothelium-dependent relaxation than the IEA in response to acetylcholine and calcium ionophore A23187 (36), although it is still uncertain whether this is due to intrinsic physiological differences or due to the higher incidence of atherosclerosis in the IEA (31,36). In addition, others also found differences in endothelial function among arterial grafts (56,57).

Most importantly, we have previously demonstrated that the IMA releases more NO and has greater EDHF-mediated hyperpolarisation compared to the saphenous vein (6) and the RA (37). NO and EDHF are the two major EDRFs in arteries (61,62). The higher expression of endothelial NO synthase (eNOS) in the IMA relative to the RA may explain the higher release of NO in IMA (38). These direct and quantitative studies reveal that the IMA has superior endothelial function due to its intrinsic characteristics and this is closely related to its excellent long-term patency.

Smooth muscle relaxation

No major differences have been observed among arterial grafts in the endothelium-independent relaxation (such as to nitroglycerine) (32,36) although there may be some differences in response to vasodilator substances with regard to sensitivity (45).

Embryological considerations

Commonly used arterial grafts belong to different groups of arteries in various locations of the body and can be divided into somatic arteries and splanchnic arteries (63). Somatic arteries supply the body wall and include the IMA, the IEA, the subscapular artery and the intercostal artery, while splanchnic arteries supply visceral organs and include the GEA and the splenic artery. Embryonic studies (63) have
shown that somatic arteries develop from intersegmental branches to the body wall whereas splanchnic arteries develop from segmental branches of primitive dorsal aorta to supply the digestive tube.

Arteries that supply extremities and limb arteries belong to a special type. Upper limb arteries are developed from somatic arteries whereas lower limb arteries develop from the dorsal root of the umbilical artery.

Physiological considerations

Arterial grafts for coronary surgery are conduit arteries which function to carry blood flow to organs. Since the arterial grafts supply organs with different physiological functions, these arteries have differences in structure and reactivity in order to adapt to the need for blood supply to those individual organs. This explains why some of them are more readily spastic (more reactive to vasoconstrictors) than others.

Segmental difference

The reactivity of the grafts varies along the length of conduit arteries, as evident in the IMA where the mid portion is less reactive compared to the distal and the proximal portions (64,65). The major muscular components are located at the two ends of the artery (muscular regulator), which may also be true for other arterial grafts (66). In particular, the distal end is more efficient as the physiological regulator for flow because this region contains relatively more smooth muscle cells and is smaller in diameter, characteristics which are important for regulating distribution of blood flow. Paradoxically, these characteristics may also be detrimental when such arteries are used as bypass grafts. In terms of preventing vasospasm of the arterial grafts, trimming off the small and highly reactive distal end of the grafts may be important and clinically feasible (64).

Incidence of atherosclerosis

In general, the incidence of atherosclerosis in the four major arterial grafts is low compared with the left anterior descending artery (LAD) (4). Particularly, early studies demonstrated low incidence of atherosclerosis in the IMA (67) through angiograms, which also frequently show that a patent IMA exists with a stenotic vertebral artery. In contrast, the incidence of atherosclerosis at the proximal end of the IEA may be high as seen in a small group of patients (31,36). This may be related to the high incidence of atherosclerosis in the lower limb than the upper limb arteries and that the IEA is the first branch of the external iliac artery (36). The incidence of atherosclerosis is low in the GEA (31,68). In the IMA grafts (1,2), the incidence of atherosclerosis is still low (69) even 15 to 21 years later. There is evidence showing that it could be also low in the RA (70).

Pharmacology of vasoactive substances in arterial grafts

Arterial grafts are conductance arteries which react with vasoactive substances such as vasoconstrictor substances and vasodilator substances. Since this is a large topic it is impossible to include in this article, the reader may find more details in reference 71 that cover this issue. Our original studies on this topic are also recommended for reading (42-44,46-50,53,54,59,71-113).

Clinical classification and selection

The variations of arterial grafts’ biological characteristics should be taken into account when selecting appropriate use of such grafts. To better understand the biological behavior of the grafts, their common features and the differences, a clinical classification may be useful for the practicing surgeon.

Clinical classification

Based on experimental studies on their vasoreactivity, taken together with the anatomical, physiological, and embryological considerations described above, we have proposed a functional classification for arterial grafts that may be useful clinically (34,114) (Figure 1).

Our classification suggests that there are three types of arterial grafts as follows:

- Type I, somatic arteries;
- Type II, splanchnic arteries;
- Type III, limb arteries.

From anatomical considerations, somatic arteries (Type I) such as the IMA are located in and supply blood to the body wall. Additionally, other somatic arteries such as the IEA, the subscapular artery, or the intercostal artery have similar contractility to the IMA. This has already been demonstrated for the IEA (4), although there are no data available yet for the others. While the IEA was histologically demonstrated as a muscular artery (4), its
pharmacological reactivity (34) as well as embryonic origin is similar to the IMA. Furthermore, the wall of the IEA is thinner than the GEA (46) and therefore we classified this artery as Type I, together with the IMA.

Splanchnic (visceral) arteries (Type II) such as the GEA supply blood to visceral organs. Other splanchnic arteries, including the splenic artery and the inferior mesenteric artery, have similar reactivity to the GEA although this requires experimental confirmation. Type III arteries such as the RA are located in the limb. Other limb arteries such as the ulnar artery and the lateral femoral circumflex artery are also in this group.

As previously mentioned, the Type II artery GEA and the Type III artery RA have higher pharmacological reactivity to vasoconstrictors, a characteristic that may be extended to all Type II and Type III arteries.

Type II arteries are prone to spasm because of the higher contractility of splanchnic arteries, which is also responsible for the tremendous changes to splanchnic artery blood flow under various circumstances to accommodate the function of the alimentary tract. The flow increases after meals and decreases under critical situations. In contrast, Type I arterial grafts (somatic arteries) are less reactive than Type II grafts because they are mainly “less reactive” conduit arteries except at the end of the artery, which functions as a muscular regulator for blood flow, as demonstrated in the human IMA (64-66).

Type III arteries are located in RA of the limbs and have a higher tendency for spasm compared to somatic arteries (Type I). It is a common clinical observation that the extremities of arteries are prone to spasm in either physiological conditions or under pathological conditions, as seen in Raynaud’s disease.

The prevalence of vasospasm in arterial grafts also correlates with their endothelial function. The Type I artery, particularly the IMA, releases more NO and has higher EDHF-mediated relaxation and hyperpolarization than the Type III artery RA (37,38) and may prove to have the best endothelial function among arterial grafts. This certainly contributes to the superior patency of this graft. Importantly, most of the studies comparing the endothelial function of arterial grafts are performed in vascular segments taken from coronary artery bypass grafting patients who are old and have coronary disease; the superior endothelial function of the IMA may merely reflect the fact that this artery is usually free from atherosclerosis whereas other type (Type II and III) arteries are usually more involved with atherosclerotic changes that diminish the endothelial function.

Because Type II and III arteries are prone to spasm due to higher contractility, they require more active pharmacological intervention (34,37,48).

There are clinical implications relating to this classification. Firstly, this clinical classification may be useful when searching for new arterial grafts or predicting the behavior of a graft. Type I arteries may be less spastic than Type II and Type III which posits their advantageous use perioperatively, particularly when their most reactive portion, the distal section, is trimmed off (64,65,115). In fact, in common clinical practice since the 1980s, the IMA has been used as the first choice of arterial grafts and is always used to graft the most important coronary artery, the LAD.

With this classification system, the surgeon is able to predict the behavior of the arterial graft and choose an optimal pharmacological method to overcome vasospasm.
For the Type II or III arteries, more active pharmacological intervention is necessary in order to prevent or treat vasospasm in these arteries.

The most important issue in coronary grafting for anastomosis is the long-term patency of the graft, which is dependent on technical factors and endothelial function. Vasospasm is also related to the long-term patency as seen in the early use of the RA, which encountered a severe problem with spasms reducing the patency of the RA graft (40,41). Even in the largest series from Tatoulis and colleagues who are highly experienced with arterial grafting, the patency for RA was 89% at 4 years, compared to 98% the patency for the left IMA at 5 years (19). Although technical factors, such as target vessels, may be involved in this difference, the aforementioned differences in the endothelial function regarding NO and EDHF between the IMA and RA may play a role.

Furthermore, arteries of the same type may have different long-term patency due to the presence of atherosclerosis either in the native artery, the graft, or other factors. While the Type I artery IMA has been well established with its superior long-term patency, the IIEA has lower patency than IMA (116,117). Several factors may account for this as: (I) the IIEA is used as a free graft; (II) the IIEA is very small at the distal end which increases technical difficulties (118); (III) the size of the proximal IIEA is less than 2 mm which causes difficulty for the aortic anastomosis (118); and (IV) the IIEA, at least in the proximal part, has a higher incidence of atherosclerosis which may influence patency (4). Therefore, the proposed new technique involves trimming off the very small section of the distal end of the IIEA and the atherosclerotic proximal end so it can be used as a part of a composite graft (118). In this way, use of the IIEA may reach a similar patency rate comparable to the IMA.

The patency rate of Type II and III arteries not well established compared to the IMA. Suma reported that the cumulative patency rate estimated by the Kaplan-Meier method was 96.6% at 1 month, 91.4% at 1 year, 80.5% at 5 years, and 62.5% at 10 years (119). Causes of late occlusion were primary anastomotic stenosis and anastomosis to a less critically stenosed coronary artery. Voutilainers and associates (120) reported that 82.1% (23/26) of GEA grafts were patent at 5 years. From those studies, the patency of the GEA, as a Type II artery, is acceptable but inferior to that of the IMA which was 95% at 10 years and 88% at 15 years (19).

The patency rate of the RA was poorer, with 35% incidence of narrowing or occlusion of the RA (121). With modified technique, avoiding skeletonization and using calcium antagonists, the early patency increased to 93.5% at 9 months (41), 83% at 5 years (122) in Acar’s group and 93.1% to 95.7% in other groups (123,124) at 3-21 months in the early period of the use of RA. In addition, Tatoulis and associates reported that the RA patency at 1 year was 96% and at 4 years it was 89% (19).

These results suggest that Type II and III arteries may have inferior patency to that of the IMA. However, if vasospasm and technical problems can be overcome, and endothelial function is well preserved, then the patency of Type II and III arteries may significantly improve.

In summary, arterial grafts are biologically divergent conduits arteries which can be functionally and clinically classified as three types. Type II (such as GEA) and Type III (such as RA) are more readily spastic than Type I (such as IMA). In order to obtain the best results, antispasm therapy, preservation of endothelial function, and other technical modifications are essential particularly in Type II & III arteries.

Pharmacological management: antispasm protocols for conduits

Pharmacological management in CABG is a complex topic which includes two major aspects. Firstly, systematic administration of pharmacological agents is used in order to maintain cardiac output and graft function during the pre-, intra-, and post-operative period, and secondly, arterial conduits are pharmacologically managed with both systematic and topical methods.

There are a few antispasm protocols available in different units around the world. We present the following protocols used in our practice, which are also used by other cardiac surgeons in various countries.

The GW HE Protocol (modified UHK Protocol) for arterial grafting

Based on the above pharmacological studies, we have developed an antispasm protocol, the GW HE Protocol (modified UHK Protocol) for use in arterial grafting (77,78). While the solution (VG solution) was originally developed for IMA and saphenous vein harvesting and was later expanded to include RA grafting, it should also be useful for arterial grafting using other grafts. The use of VG solution in RA grafting necessitates the inclusion of pre-, intra-, and
post-operative management. The necessity of postoperative calcium antagonists for IMA grafting, however, should be decided by the surgeon and cardiologist according to the patient's condition.

**Preoperative for RA grafting (not necessary for using other grafts)**

(I) Allen Test for both arms;
(II) Doppler flow examination for the ulnar artery during Allen test and for the RA flow to demonstrate its patency.

**Intraoperative**

(I) Use verapamil plus nitroglycerin (VG) solution, which has a concentration of approximately 30 μmol/L of verapamil and NTG in an isotonic solution of pH 7.4. The components include (75-78):
- Verapamil hydrochloride, 5 mg;
- Nitroglycerin (NTG), 2.5 mg;
- Heparin, 500 unit;
- 8.4% NaHCO$_3$, 0.2 mL;
- Ringer’s solution, 300 mL.

(II) The RA is removed immediately after dissection from the arm and stored in the VG solution at the room temperature;

(III) Once the harvesting of the RA has initiated, low dose nicardipine (0.5 mg per hour; 5 mg in 100 mL D5W, IV at 10 mL per hour) is given systematically.

**Postoperative**

(I) Nicardipine is infused IV at the same dose until the patient is able to take oral calcium antagonists;

(II) Continuing a low dose of one of the calcium antagonists for at least 6-12 months. This can be nicardipine 20 mg twice a day; or verapamil 120-240 mg per day (A test dose 120 mg is recommended), or diltiazem at an appropriate low dose. The choice of the calcium antagonist (nicardipine/diltiazem/verapamil) is based on availability, the patient’s condition, particularly the heart rate, as well as the preference of the cardiologist. Use of beta-blockers should be cautious when some of the calcium antagonists are given.

During harvesting of the IMA, this solution is sprayed on the pedicle as well as injected into the lumen. The solution was also shown to be effective in intraluminal injection after CABG to reverse spasm of grafts and coronary arteries (110).

### The GW HE antispasm solution No. 2. (NG solution) for arterial grafting

**Design of the nicardipine plus nitroglycerin (NG) cocktail**

Alongside its limited availability, verapamil also has a bradycardiac effect which may prevent the simultaneous use of β-blocker. Additionally, the advent and development of new generations of calcium antagonists have led to decreased use of verapamil. For these reasons, we designed a new cocktail that is composed of a second generation of the dihydropyridine calcium antagonist, nicardipine and nitroglycerin. Following testing, effectiveness of this cocktail was demonstrated on both human IMA and RA (125).

We tested the effect of nicardipine and NTG at the concentration of 30 μmol/L (–4.5 logM) on the human IMA and RA segments in the organ chamber. From previous studies (42,53,71,74-78,81,84,91-93,96,110), this concentration was expected to have maximal or nearly maximal effect.

This cocktail consists of 30 μmol/L (–4.5 logM) nicardipine and 60 μmol/L (–4.3 logM) NTG in an isotonic solution of pH 7.1. The components of the clinical (NG) cocktail include:
- Nicardipine hydrochloride, 5 mg;
- NTG, 5 mg;
- 8.4% NaHCO$_3$, 0.3 mL*;
- Normosol-R solution, 300 mL;
- (heparin, 500 Unit could be added).

*The pH of NG (nicardipine hydrochloride 5 mg and NTG 5 mg) in Normosol-R solution (300 mL) without adding NaHCO$_3$ is 6.6. When a volume greater than 0.3 mL of 8.4% NaHCO$_3$ is added, the solution becomes gradually turbid at pH of 7.1-7.4. This however, does not affect the antispastic effect (125). However, if nicardipine hydrochloride (5 mg) and NTG (5 mg) are added to Multiple Electrolytes Injection (Baxter International Inc, Shanghai, China) with pH of 7.4, the cocktail solution is clear and there is no need to add NaHCO$_3$ (126).

In summary, we have presented two solutions for use as part of an antispasm protocol during arterial grafting. Our experimental studies (75-78,125) have demonstrated that these solutions are effective vasodilator cocktails that relax vasoconstriction caused by all mechanisms, including depolarizing and receptor mechanisms. This is superior compared to other solutions such as α-adrenoceptor antagonists which are only effective at reversing adrenoceptor-mediated spasm, and calcium antagonists...
alone which are only effective at reversing depolarizing agent (K⁺)-mediated spasm. Our clinical trials have demonstrated that these are excellent vasodilators both to reverse or prevent spasm (75,76,110,126). Most recently, we have also demonstrated that the use of antispasm nicardipine and nitroglycerin cocktail solution increases IMA graft flow during off-pump coronary artery bypass grafting (126).

Acknowledgements

Disclosure: The author declares no conflict of interest.

References

23. Nezić DG, Knezević AM, Milojević PS, et al. The fate of


50. He GW, Yang CQ. Characteristics of adrenoceptors in...


