Chapter 15

Pharmacology of Arterial Grafts for Coronary Artery Bypass Surgery

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Additional information is available at the end of the chapter

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1. Introduction

Interest has increased in the use of arterial conduits for CABG significantly in most major cardiac surgery centers around the world, because the number of patients receiving arterial grafts and our knowledge about the biologic characteristics of arterial grafts have increased. In addition, more advanced clinical protocols for the use of grafts have been developed and midterm results with alternative arterial grafts are encouraging.

The internal mammary artery (IMA) has been shown to have greater long-term patency for coronary artery bypass grafting when compared with the saphenous vein graft. Because of the superior long-term results of the IMA, other arterial grafts which have recently been advocated include the radial artery (RA), the gastroepiploic artery (GEA), the inferior epigastric artery (IEA), the splenic artery, the subscapular artery, the inferior mesenteric artery, the descending branch of lateral femoral circumflex artery, the intercostal artery and the ulnar artery. One of the various manifestations clinically observed among these arterial grafts is a different tendency to develop spasm during surgical dissection and during the perioperative period which could be the cause of perioperative morbidity and mortalitiy [1-8]. For example, there are reports of vasoactive drugs altering IMA graft flow [3,4]. Moreover, there is accumulating evidence that blood flow in arterial grafts is insufficient in some circumstances [6,7]. Many vasoconstrictors (spasmogens) may cause arterial grafts spasm. Accordingly, antispastic therapy is important in the development of arterial grafts and the nature of constrictor substances that cause arterial graft spasm needs to be determined. In recent years, the problem of graft spasm has become more frequent with the increasing use of new arterial grafts. Therefore, it is essential for surgeons to understand the causes of vascular graft spasm, to improve patency rates and to use the optimal vasodilator in the most appropriate way to counteract vasospasm.

Surgeons have studied graft pharmacology by measuring the effects of vasodilators on blood flow through arterial grafts before they were attached to the heart [9]. Pharmacologists have also joined the study of graft pharmacology by evaluating endothelial and smooth muscle function of bypass grafts using their standard in vitro method, the isolated vessel ring preparation in the organ bath. However, results from these in vitro studies need to be carefully extrapolated to the clinical situations, where the conditions of the arterial grafts are complicated. Even so, the organ bath method can provide very useful information about the effects of vasoactive substances in the arterial grafts.

Several vasodilators have been tested and various antispastic methods have been suggested to prevent graft spasm; including papaverine, phenoxybenzamine, calcium antagonists and nitrates etc. Choice of a pharmacological agent to overcome the vasospasm encountered in the arterial grafts must be on the basis of pharmacological studies. Accordingly, current state of knowledge based on experiments to study the pharmacological effect of a number of vasoconstrictor and vasodilator substances and the practical application of this knowledge can be outlined as following sections:

2. *In Vitro* pharmacology of blood vessels

Pharmacology of isolated blood vessel allows the researcher to investigate the mechanisms of effect of spasmogens or vasodilatory substances. Most studies use the isolated vessel ring preparation in the organ bath, studying removed segments from the grafts during surgery. This technique only requires basic pharmacological equipment, i.e. isolated organ baths, transducers, recorder system etc. An important advantage of this method is that the vessel segment is studied in the organ bath and concentration-response curves for each vasoactive substances to be obtained under controlled conditions without extrinsic neural factors, circulating hormones interacting, blood flow or shear stress. Therefore, dose and response relationships to drugs, either vasoconstrictor or vasodilator substances, can be assessed more readily and accurately than is possible than in vivo experiments. This methodology also enabled agents to be compared with each other, and combinations of vasoactive drugs to be tested [10,11-13]. In vitro measurement of response of vascular preparations may help to researcher to predict what can happen, not what does actually happen in integrative and complicated in vivo conditions. However, isolated organ bath methods cannot identify the actual cause of in vivo spasm. The next challenge is to determine in the body what combination of factors, i.e. extrinsic neural factors, circulating hormones interacting, blood flow or shear stress, influencing passive distension from arterial wall are present the vessel with spasm.

Isolated organ bath technique is a standard research approach which requires basic pharmacological equipment (Figure 1). Segments of human arteries obtained from patients undergoing CABG surgery are placed in oxygenated physiological solution, i.e. Krebs-Henseleit solution etc., at room temperature and transferred immediately to the laboratory. The arteries are dissected from adhering fat and connective tissue then cut into 3-4 mm length rings. The strips are mounted in an organ bath, containing physiological solution, on a L-shaped brace

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for tension measurement along the former circumferential axis. The solution is gassed with % 95 O_2 and % 5 CO_2 at 37 ºC. Changes in arterial tensions are recorded isometrically by a force-displacement transducer by using a recording system, preferably a computer software. The segments are allowed to equilibrate under final resting force of 1-2 g for at least 1 to 1.5 h and they were washed every 10-20 minutes. After the equilibration period, arterial strips were challenged with a vasoconstrictor, i.e. phenylephrine, prostaglandin $F_{2\alpha}$ or potassium chloride (KCl) to test the viability of the vessel. After an additonal 30 min of equilibration period with repeated washing every 10 min, the tissues are challenged with increasing cumulative concentrations of the vasoconstrictor substance to be tested and responses are recorded.

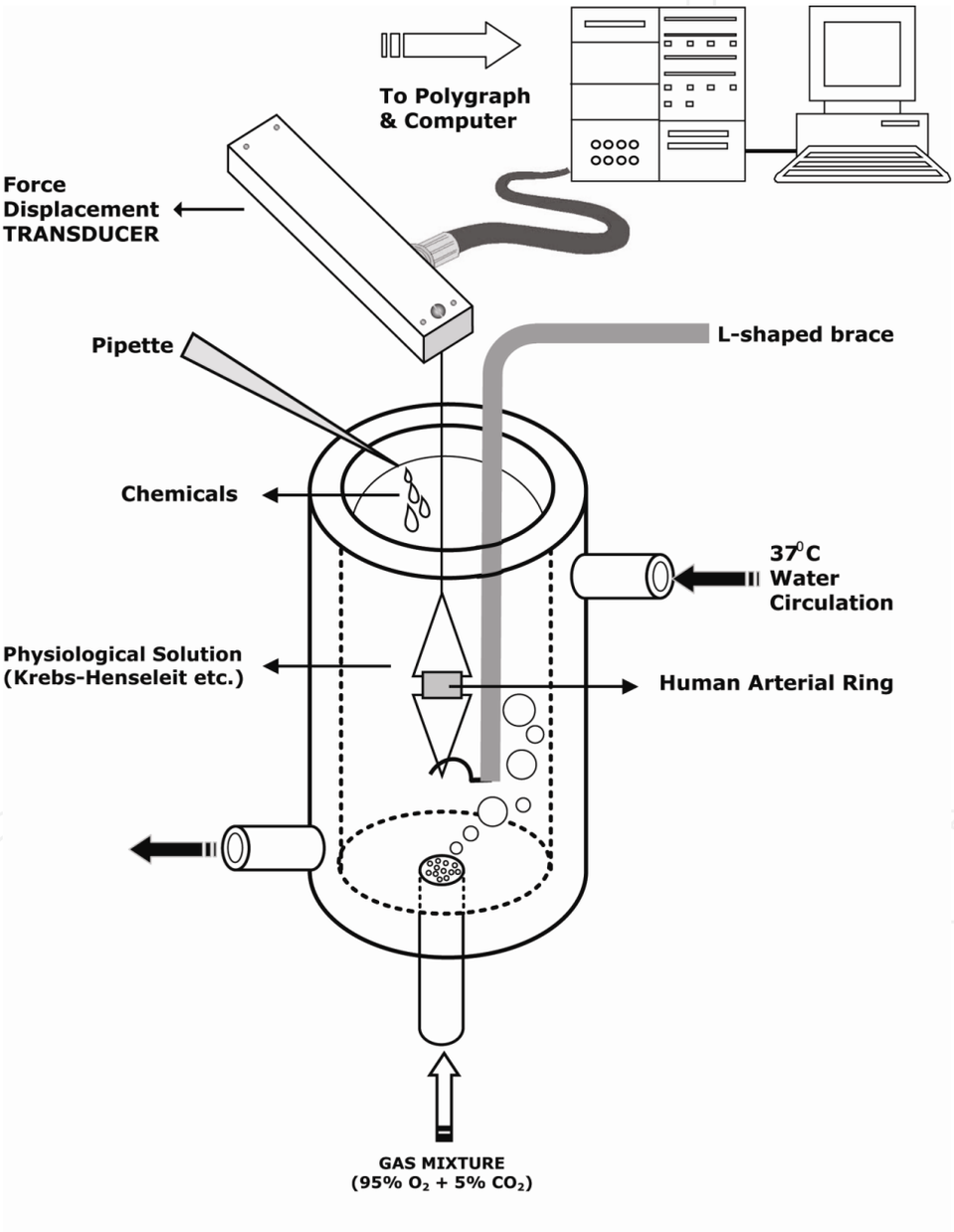

Figure 1. A schematic diagram of a human arterial ring preparation in an organ bath.

Each cumulative concentration is applied after the relaxation to previous concentration reached to a plateau. Vasoconstrictor substance -evoked responses are usually expressed as percentage of the maximum response in each corresponding tissue. Vasodilator agents are studied by establishing concentration-relaxation curves after precontracting the segments with a vasoconstrictor, i.e. phenylephrine, prostaglandin $F_{2\alpha}$ or potassium chloride (KCl). The relaxation is usually expressed as a percentage of the precontracting force. Potency, ie, sensitivity of the vessel to a drug is calculated as EC_{50} values (the concentrations of vasoconstrictor required to produce 50 % of the calculated maximum response). EC_{50} value is used to determine pEC_{50} value (negative $\log_{10}$ of the EC_{50} value). This value can differ considerably with the nature of the agent used for precontraction of the vessel and the amount of contraction that a particular concentration of vasoconstrictor substance will develop. The degree of relaxant effect of a dilator on a vessel precontracted by a particular vasoconstrictor agent, namely functional antagonism, is reflected by pEC_{50} value. Another important value is the maximal efficacy (E_{max}) which reflects the range of maximal response to the drug at high concentration.

A special method that measures the individual length-tension relationship curve for each vessel segment, cut to a precise length, has been developed [10]. This method, called as normalization technique, sets passive distension of the vessel segment to correspond with that caused transmural pressure experienced in vivo. The principal is to establish individual length-tension exponential curves for each vessel by relating the isometric tension, obtained from strain gauge transducers, with the corresponding diameter. This technique has been continously used by several researchers for studying CABG pharmacology [10,14-16].

2.1. Vasoconstrictor and vasodilator agents

Exogenous and endogenous vasoconstrictors are particularly important for vasoconstriction and its extreme form—vasospasm (Figure 2). Table 1 lists vasoconstrictor substances that are generally considered spasmogens for blood vessels and the receptors located on the cellular membrane of vascular smooth muscle, and of endothelium, which mediates vasodilatation. Most of these vasoconstrictor substances contract blood vessels through receptor-mediated mechanisms, i.e. internally secreted epinephrine and norepinephrine cause blood vessels to contract by stimulating α-adrenergic receptors on the vascular smooth muscle. Consequently, a selective α -receptor antagonist will be highly effective because the site of interaction is same. The contraction caused by epinephrine and norepinephrine is partly caused by depolarization of the tissue through voltage-operated calcium (Ca^{2+}) channels (VOCC) and partly caused by calcium release from intracellular sources. Thus, this mechanism would be more resistant to functional antagonist nifedipine. On the other hand, increased extracellular K^+ depolarizes smooth muscle membrane by closing of the hyperpolarizing K^+ channels. This effect allows VOCC to open and intracellular [Ca^{2+}] to rise, resulting in smooth muscle contraction. Therefore, a VOCC antagonist such as nifedipine would readily relax a tissue precontracted by potassium (K^+).

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Vasoconstrictors	Vascular Smooth Muscle Contraction	Endothelium Relaxation
EDCFs		
Endothelin	ET_A, ET_B	ET_B
α-Adrenoceptor agonists		
Norepinephrine	α_1, α_2	α_2
Methoxamine	α_1	…
Phenylephrine	α_1	…
Dopamine	α_1***	…
Platelet-derived substances		
5-HT	5-HT_2	5-HT_{1D}
TxA_2 *	TP	TP (?)**
Prostanoids		
TxA_2 *	TP	TP (?)**
$PGF_{2\alpha}$	FP	FP (?)**
Substances released from mast cells and basophils		
Histamine	H (H_1, H_2)	H_1
Muscarinic receptor agonists		
Acetylcholine	$M_{3?}$	M_2
Renin-angiotensin system		
Angiotensin II	AII	AII
Vasopressin (ADH)	V_1****	…
Depolarizing agent		
Potassium		…

* TxA_2 is also considered as one of the endothelium-derived contracting factors; it is also derived from platelets.

** TP and FP receptors in endothelial cells to be clarified.

*** Dopamine also affects α_1 and α_2 receptors, exist in cardiac and bronchial cells respectively, it causes vasoconstriction at high dose.

**** Mainly effective in renal medulla, it also enhances sympathetic constriction,

EDCFs = Endothelium-derived contracting factors, ADH = antidiuretic hormone.

Table 1. Vasoconstrictors and their Receptors Involved in Vascular Smooth Muscle; Vasodilators in which Mediate Relaxation via Endothelium.

As stated above, vasodilator agents are usually studied by precontracting the vessel. The level of precontraction force should be chosen in the range of 60% to 80% of the maximum contraction of that agent. The precontractile tone should reach to a plateau and remain stable during the experimental period. The precontraction may dissipate in a time-dependent manner. This may lead researcher to ascribe decreased tone due to added drug instead of spontenaous relaxation. Therefore, a parallel time control is necessary to show that the precontraction is stable [11,17,18].

2.2. Influence of endothelial functions on contractility of arterial grafts

It has been well known that vascular endothelium plays an important role in maintaining vascular tone. Endothelium derives a number of vasoconstrictor as well as vasodilator substances. Vascular tone is maintained on the balance between vasoconstriction and vasodilatation caused by these substances. Endothelial cell produces endothelium- derived contracting factors (EDCFs) such as endothelin (ET) and thromboxane A_2 (TxA_2) that cause an increase in the intracellular calcium concentration and mediate contraction of the smooth muscle. Endothelium-dependent relaxation is known to be the effect of a variety of different endothelium-derived relaxing factors (EDRFs). These are endothelium-derived nitric oxide (NO) [19,20], prostacyclin (PGI_2) [21], and endothelium-derived hyperpolarizing factor (EDHF) [22-25]. These relaxing factors induce vasodilatation through different mechanisms by reducing the intracellular calcium concentration in the smooth muscle cell and cause relaxation. Spontaneous (basal) release of EDRF (NO) also depresses the contraction to some extent. As in other vessels, endothelium plays a modulatory role in contractility in CABGs [26]. Studies on endothelial function of CABGs have indicated that arterial endothelium has more ability to produce NO than venous endothelium (11-13, 26). EDHF also plays a role in arterial grafts [17].

Endothelin, prostanoids (TxA_2 and $PGF_{2\alpha}$) and α_1-adrenoceptor agonists are the most potent vasoconstrictors and they strongly contract arterial grafts even when endothelium is intact. On the other hand, some vasoconstrictors, i.e. serotonin (Serotonin (5-hydroxytryptamine, 5-HT)), have been demonstrated as being vasorelaxant agents through the mechanism of EDRF (NO). They induce contraction by their direct contractile effect on smooth muscle, and vasodilatation, induced by EDRF (NO) or EDRFs release due to its stimulation to endothelium. Therefore, these vasoconstrictors do not strongly contract the vessels in endothelium-intact blood vessels. However, when endothelium is damaged or denuded, they evoke a strong contraction.

3. Pharmacology of internal mammary artery

Vasoconstriction may be evoked by various stimuli such as vasoconstrictor substances, nerve stimulation and mechanical trauma. Clinically, although all arterial grafts may develop vasospasm, it develops less frequently in IMA and IEA than in GEA and RA [7,27]. Comparative functional studies have demonstrated that there are differences in arterial grafts with

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regard to contractility and endothelial function. These differences, together with histological and anatomical diversity, may account for possible differences in the perioperative spasm.

The contractility of IMA to vasoconstrictors has been studied extensively [10,13]. TxA_2 is one of the several EDCFs, but it is also derived from platelets. Endothelin is also considered as one of the EDCFs. These two substances are two of the most potent vasoconstrictors known and they are very potent in IMA as well. Elevated plasma concentrations of ET [28] or TXA_2 [29] have been found during cardiopulmonary bypass. Therefore,.these vasoconstrictors are prime candidates as spasmogens for arterial grafts during CABG surgery.

Some receptors on the smooth muscle of IMA have been characterized. For example, IMA is an α_1-adrenoceptor-dominant artery with little α_2- or β -function [30,31]. Other receptors functionally demonstrated in IMA are ET_A, ET_B [32], 5-HT [33], angiotensin [34],TP (thromboxane-prostanoid) [35], vasopressin V_1 receptors [36,37], and vasoactive intestinal peptide [38] receptors. Dopaminergic receptors have also been demonstrated in the IMA [39]. The agonists for these receptors may also be spasmogenic agents for the IMA.

As stated above, some vasoconstrictors have been demonstrated as being vasorelaxant agents. 5-HT is an example of this type of vasoconstrictors and it directly contracts vascular smooth muscle through 5-HT_2 receptors [40] and relaxes blood vessels through endothelial NO release, mediated by 5-HT_{1D} receptors, [41] located in the endothelium. When endothelium is lost, perhaps also when it is damaged, platelets aggregate in the area where endothelium is denuded and release substances such as 5- HT (also TxA_2) that strongly contract smooth muscle. Accordingly, studies have shown 5-HT does not strongly contract IMA with intact endothelium [13,42]. However, its contracting effect is unmasked when endothelium is denuded [13,42].

The endothelium-dependent relaxation exists in IMA [43]. It has also been demonstrated that vascular endothelial growth factor may induce endothelium-dependent relaxation in the human IMA [44]; the relaxation has recently been demonstrated to be mediated by both NO and PGI_2 [45]. Further, physiological substances such as CRF induce both endothelium-dependent and -independent relaxation in the human IMA [46]. IMA releases both NO and EDHF [47]. Recent studies have demonstrated that the endothelium of the IMA releases more NO than the RA at both basal and stimulated levels [47]. Further, the IMA has a greater hyperpolarizing effect on bradykinin-stimulated release of EDHF than the RA does [47].

In addition, receptors, for common stimuli of EDRF such as acetylcholine, bradykinin, and substance P are present in the endothelium of arterial grafts [15,48,49]. 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 (kinase insert domain) receptors, rather than Flt-1 (fms-like thyrosine kinase-1) receptors [45]. Most recently, corticortropin-releasing factor (CRF) receptors CRF_1, $CRF_{2\alpha}$, and $CRF_{2\beta}$ have been shown to be present in the IMA [45]. The CRF urocortin- induced endothelium-dependent relaxation in the IMA is likely through CRF receptors allocated in the endothelium of the IMA [50].

3.1. Spasm of internal mammary artery

Compared to saphenous grafts, IMA is more resistant to ischaemic changes due to high content of elastin with a low metabolic rate. Occasionally, there is severe contraction (spasm), which may be visible or be inferred by minimal free flow. Spasm of IMA can cause inadequate blood flow, which may be detrimental during periods of increased nutritional demand such as weaning from cardiopulmonary bypass [51] or postoperative hypovolemia [52]. In addition, IMAs with poor perioperative flow rates are more likely to occlude [53]. Severe spasm may lead to graft malfunction and even mortality [11,54]. It is essential to to determine whether the IMA should be discarded or alternatively relegated to graft a minor vessel. Thus, a dilator drug, preferably a fast-acting one suitable for intraluminal injection, should be used for maximal pharmacologic dilation of the IMA, which allows the surgeon to evaluate the flow-carrying capacity of the IMA and provides a relaxed, dilated distal vessel that facilitates a precise anastomosis. Vasodilation of the IMA pedicle during CABG surgery may also unmask small bleeding points, improve hemostasis and facilitate placement of anastomotic sutures [9].

Vasoconstriction (or spasm) of IMA may be caused by multiple mechanisms. In addition, vasodilators relax vascular smooth muscle through a specific mechanism or mechanisms. Several vasodilators have been suggested to prevent graft spasm; including papaverine, phenoxybenzamine, calcium antagonists and nitrates. However, there is no "perfect" vasodilator which is effective for every situation.

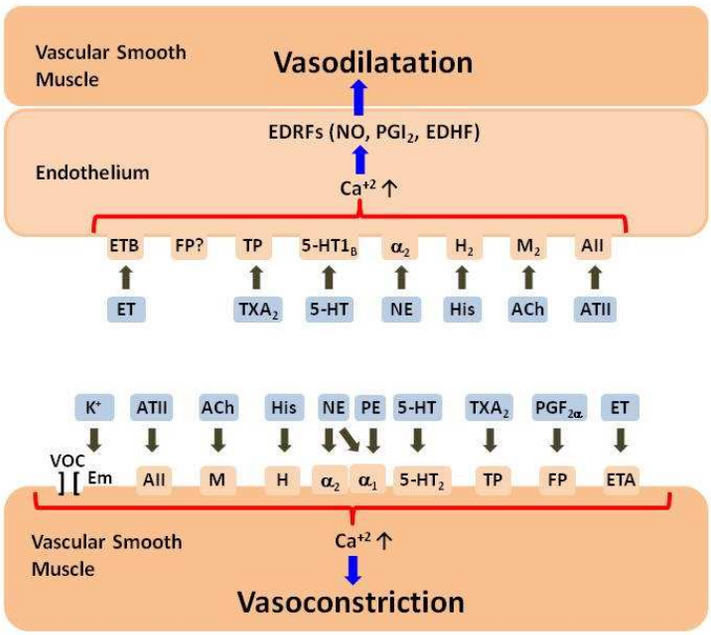

Figure 2. Endothelium-derived relaxing factor (EDRF) is produced and released by the endothelium to promote smooth muscle relaxation. NO, nitric oxide; AII, angiotensin II receptors; ACh, acetylcholine; EDHF, endothelium-derived hyperpolarizing factor; ET, endothelin; FP, $PGF_{2\alpha}$ receptors; H (H_2), histamine receptors; His, histamine; K, potassium; M (M_2), muscarinic receptors; NE, norepinephrine; PE, phenylephrine; PGI_2, prostacyclin; 5-HT, 5-hydroxytryptamine (serotonin); TP, thromboxane-prostanoid receptors; VOC, voltage operated channels; α, adrenergic receptors

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3.2. Effect of vasodilator substances on IMA

To promote dilation of the IMA, some vasodilating substances have been applied to the outside of the pedicle [55-58] or injected intraluminally with or without hydrostatic dilation [9,55,56,58,59]. The vasodilator substances available are as follows:

Papaverine

The traditional topical vasodilator papaverine was first recommended by George Green, the pioneer IMA surgeon, in early days of IMA grafting to overcome spasm [60]. It is still widely used due to its satisfactory vasorelaxant effect in arterial grafts [61,62]. Papaverine is a non specific vasodilator substance which relaxes vessels via multiple mechanisms such as inhibition of phosphodiesterase [63], which increases cyclic guanosine monophosphate (cGMP) level in smooth muscle cells, decreasing calcium influx [64,65] or inhibition of release of intracellularly stored calcium [66]. Although hydrostatic dilation with papaverine dissolved in saline solution provides good dilation at high concentrations, it carries a potential risk of mechanical damage to the media and intima caused by cannulation and overstretching and by chemical damage as a result of the acidity of the solution [67-70]. The problem of acidity of papaverine solutions may be overcome by mixing the solutions with blood or albumin before its use [71]. However, the pharmacological action is uncertain in such a mixture. Additionally, papaverine has a slower onset of the vasodilating effect when compared to other vasodilators such as nitroglycerin (NTG) and verapamil [10,62,72]. However, once its effect reaches a plateau, it is sustained [10,62,72]. Papaverine hydrochloride is relatively unstable in non-acidic solutions and a white precipitate is sometimes formed when papaverine is added to the plasmalyte solution (pH approximately 7.4) [73]. In light of these points, papaverine is still an effective vasodilator for IMA. Its topical spray on the adventitia of the IMA may be effective but it is not recommended for systemic use.

Nitrovasodilators

Nitrovasodilators (organic nitrates), NTG, glyceryl trinitrate (GTN) and sodium nitroprusside (SNP), are a diverse group of pharmacological agents that produce vascular relaxation by releasing NO, which activates guanylate cyclase, resulting in an accumulation of cyclic GMP in the smooth muscle cell. This in turn reduces intracellular calcium concentrations and leads to vasodilatation. These drugs are effective against a range of constrictor stimuli and they are widely used in CABG patients. Nitrovasodilators have been shown to be potent vasodilators in the human IMA [55,61,74-79]. It has been demonstrated that NTG is compares favorably with diltiazem in the prevention of IMA spasm [80] and it is effective for either topical, intraluminal, or systemic use [78,81,82]. Although, nitrates are slightly more effective in blocking receptor operated channels, they are effective in treating established vascular spasm, regardless of the nature of contraction, i.e., either receptor mediated (TxA_2 receptors, α-adrenoceptors, or ET receptors) or depolarizing agent (K^+)- mediated contraction [10,54]. However, rapid tolerance (tachyphylaxis) of vessels develops to nitrovasodilators. Therefore, they are less potent in the prevention of vasospasm [54,74,75,83]. NTG is more potent in its

vasorelaxing effect when it is compared to SNP. However, SNP is more effective in inhibition ANGII and α-adrenoceptor-mediated contraction in the IMA [34].

Phosphodiesterase inhibitors

Phosphodiesterases (PDE) are a diverse family of enzymes that hydrolyse cyclic nucleotides and thus play a key role in regulating intracellular levels of the second messengers cyclic adenosine monophosphate (cAMP) and cGMP which modulate vascular smooth muscle tone. Concentrations of cAMP and cGMP are controlled through synthesis by cyclases and through hydrolysis by PDEs. Non-selective PDE inhibitors including papaverine have been injected routinely by surgeons, in and around the artery to prevent IMA spasm, but papaverine is not administered systemically. The discovery of eleven types of PDEs [84,85] provides an impetus for the development of isoenzyme selective inhibitors for the treatment of various diseases. Inamirinone (previously called amrirone) and milrinone are bipyridine compounds that inhibit phosphodiesterase (PDE) III, a form found in cardiac and smooth muscle. Therefore, they increase myocardial contractility and vasodilation, and they are called as 'inodilators'. These drugs are useful in postoperative management of patients who undergo open heart surgery, particularly in patients who present ventricular dysfunction and receive arterial grafts for coronary artery bypass surgery. Favorable effects of inamrinone on the IMA [76,86-88] have been reported. In addition, it has been demonstrated that inamrinone has a greater than additive vasodilatory effect when used in combination with NTG [76]. It was also demonstrated that systemically administered milrinone and nitroglycerin dilate the IMA after cardiopulmonary bypass [82]. Levosimendan is a new agent developed for the treatment of acute and decompensated heart failure. It exerts potent positive inotropic action and peripheral vasodilatory effects. The mechanism of vasodilation by levosimendan may involve reduction of Ca^{2+} sensitivity of contractile proteins in vascular smooth muscle, the lowering of intracellular free Ca^{2+}, the potential inhibition of PDE III, and an opening of K^{+} channels [89,90]. We have recently shown that levosimendan effectively and directly decreases the tone of IMA [91]. Therefore, levosimendan may be a cardiovascular protective agent by its relaxing action on IMA.

Calcium antagonists

It has been known since the late 1800s that calcium influx was necessary for he contraction of smooth and cardiac muscle. The discovery of calcium channel in smooth and cardiac muscle was followed by the finding of several different types calcium channels including VOCC (L, T, N and P types) and receptor -operated calcium channels, (ROCC). The discovery of these channels made possible the development of clinically useful new generation calcium antagonists (calcium channel blockers). These drugs are consist of three chemically divergent groups: Dihydropyridine (nifedipine, etc.), phenylalkylamines (verapamil, etc.), and benzothiazepines (diltiazem, etc.). Important differences in vascular selectivity exist among the calcium antagonists. In general, nifedipin is the most potent. In addidion, verapamil is more potent than diltiazem. It has been demonstrated that nifedipine is more potent than diltiazem with regard to the vasorelaxant effect in the human IMA [54].

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The degree of vasodilatory effect of calcium antagonists is dependent on the nature of contraction. Calcium antagonists are less effective in blocking receptor-operated than voltage-operated calcium channels. For example, increased extracellular K^+ depolarizes smooth muscle membrane by closing of the hyperpolarizing K^+ channels. This effect allows VOCC to open and intracellular [Ca^{2+}] to rise, resulting in smooth muscle contraction. Therefore, a VOCC antagonist such as nifedipine would readily relax a tissue precontracted by K^+. On the other hand, the contraction caused by receptor agonists is partly caused by calcium influx and partly caused by calcium release from intracellular sources. Consequently, calcium antagonists are weak in either preventing or treating TxA_2, α-adrenoceptor, or VP_1 receptor-mediated contraction, in comparison to K^+-mediated contraction [54,74,92,93].

Potassium (K^+) channel openers

Drugs that open potassium channels (potassium channel openers, KCOs) can exert antivaso-constrictor and vasorelaxant actions, that is, they reduce or prevent cellular response ro excitatory stimuli, repolarize or hyperpolarize the cell membrane, overcome a contraction once it has developed, and strengten the resting state of the vessel. KCOs are considered to comprise a heterogeneous group of organic compounds [94]. These are apricalim, bimakalim, celikalim, cromakalim, levokromakalim, diazoxide, L-27,152, P 1075, minoxidil sulphate, pinacidil, and nicorandil. KCOs act by stimulating ion flux through a distinct class of potassium channels which are inhibited by intracellular adenosine triphosphate (ATP) and activated by intracellular nucleoside diphosphates. They restrain the opening probability of voltage-dependent L- and T-type calcium-channels and decrease agonist-induced Ca^{2+} release from intracellular sources through inhibition of inositol trisphosphate (IP_3) formation, and lower the efficiency of calcium as an activator of contractile proteins [95]. Additionally, they may accelerate clearance of intracellular free calcium via the Na^+/Ca^{2+} exchange pathway [95]. The functional outcome of these effects is to reduce the membrane excitability and to drive vascular myocytes into a relaxed state. Particularly, vascular smooth muscle is sensitive to KCOs [96-99]. In view of these points, KCOs are of great value as therapeutic agents [98,99,] and aprikalim [100,102] have been studied in the human IMA and found to be potent vasodilators in a number of receptor-mediated contractions. Therefore, this group of drugs may become clinically useful antispastic agents by their relaxing action on IMA.

α-Adrenoceptor antagonists

IMA is an α_1-adrenoceptor-dominant artery with little α_2- or β -function [30,31,103]. Theoretically, a selective α -receptor antagonist may be a highly effective antispastic agent because the site of interaction is same. Herewith, the use of α-adrenoceptor antagonists such as phenoxybenzamine as an antispastic agent has a rationale. However, the nature of vasoconstriction is complex and may involve many other vasoconstrictors (Table 1). It has been demonstrated that, α- adrenoceptor antagonists are not effective in reversing the contraction evoked by other vasoconstrictors such as vasopressin, angiotensin II, endothelin-1, and KCl [104]. From pharmacological point of view, use of phenoxybenzamine is inappropriate as the sole antispastic agent in the arterial grafts. Moreover, a novel α_1-adrenergic receptor blocking substance with calcium antagonist with activity, AJ-2615, has been studied with regard to inhibition of

vasoconstriction in the IMA [44]. Further studies on this kind of substances may provide development of new antispastic protocols.

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) has been studied in the human IMA and found to be a potent vasodilator through KDR receptors and NO -and PGI_2 -mediated mechanisms [44,45]. However, VEGF has potent hypotensive effect due to systemic vasodilaton [44,45]. Therefore, the use of VEGF as a vasorelaxant agent may not be the primary consideration for antispastic therapy in arterial grafts.

β-Adrenoceptor agonists: Dopamine and dobutamine

Albeit at least three distinct beta-adrenoceptors exist in IMA [105], β -receptor function is weak [31]. Consequently, it has been demonsted that use of β -adrenoceptor agonists is unlikely relax the IMA significantly [106]. Same study also indicated that beta-receptor agonist dobutamine exerts weak vasodilator effect in IMA. Dopamine-induced responses are complex and dose-dependent, inasmuch as the complexity of interaction between dopamine and dopamine receptors as well as α_1-adrenoceptors [107]. In IMA, dopamine induced a vasorelaxation on the norepinephrine contraction only at higher concentrations [107]. Similar to VEGF, the use of dopamine and dobutamine may not be the primary consideration for antispastic therapy. On the other hand, vasodilator effect of β-adrenoceptor agonists in IMA at high concentrations should be kept in mind when these agents are used primarily as inotropic agents.

TxA_2 antagonists

TxA_2 is one of the the most potent vasoconstrictors known and it is very potent in IMA as well [10,13]. Inasmuch as its importance in thrombosis together with its elevated plasma concentrations during cardiopulmonary bypass, specific TxA_2 antagonists may be useful in the antispastic therapy of IMA. Accordingly, specific TxA_2 antagonist GR30191 is a potent vasodilator for TxA_2-mediated contraction in IMA [86]. However, to date, no clinical data are available.

5-HT receptor antagonists

Studies on human IMA have shown that 5-HT directly contracts IMA through $5\text{-}HT_{1D}$ and $5\text{-}HT_2$ receptors [33,108-110]. In IMA, 5-HT receptor mediated contractions are unmasked when endothelium is denuded [13,42]. Additionally, studies have shown 5-HT may interact synergistically with other vasoconstrictor substances, such as TxA_2 released from platelets during thrombus formation, and 5-HT receptor mediated contractions may be unmasked or amplified [33,108-110]. $5\text{-}HT_{2A}$ receptor antagonist ketanserin has antihypertensive properties and it's recently used to reduce the severity and frequency of the vasospasm in Raynaud's phenomenon [111]. Therefore, it may have potential to overcome IMA spasm when it's applied topically.

Testosterone

Testosterone may exert vasorelaxant effects on several vascular tissues [112-119]. We have studied effects of testosterone in the human IMA and found that vasorelaxant re-

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sponse to testosterone may occur in via large-conductance Ca^{2+}-activated K^+ channel-opening action [112]. Clinical studies of testosterone therapy in male patients with coronary artery disease raised promising results. Therefore, the use of testosterone, i.e. direct topical administration on adventitia, as a vasorelaxant agent may be considered for antispastic therapy in arterial grafts.

Iloprost and botilinum toxin

It has been demonstrated that botilinum toxin may prevent arterial spasm in vitro [120]. Iloprost, a PGI_2 analogue, may be considered as an alternative antispastic agent in arterial grafts [121].

4. Pharmacology of other arterial grafts

4.1. Radial artery

The use of the RA as a graft for coronary revascularization was already introduced in the 1970s, but shortly thereafter it was abandoned due to high incidence of vasospasm and comparatively poorer short-term and long-term patency rates than IMA [27,122-124]. This was partly due to the inability to recognize RA spasm, but it was also due to lack of proper pharmacological tools to prevent this. It was later noted that radial grafts were indeed patent in patients long after their surgery. Thereafter, the RA was reassessed and its role as an alternative arterial graft was re-established.

Because of the dual blood supply to the hand, RA occlusion is not associated with major clinical sequelae but prevention is important. RA spasm rarely leads to serious vascular complications but can cause patient discomfort and can result in prolonging or failure of the procedure. Several studies now suggest that the vasospastic tendency of RA grafts has been countered in the operating room (immediately after harvest) by treating the artery with papaverine or milrinone, or both, and placing it in a bath of heparinized saline containing NTG or a combination of NTG and a calcium channel blocker to prevent spasms. Similarly, protection from immediate postoperative and postdischarge vasospasm is sought through the use of intravenous or oral combinations of the aforementioned vasodilator drugs. However, clinical studies indicate that such vasodilatory precautions do not provide the expected protection from postoperative vasospasm of RA grafts. Although the patency rate of RA is debatable, mid-term and long-term patency rates may reach 90% and greater, that makes the RA a valuable addition in arterial grafting [125,126].

RA has less active endothelium compared to IMA and is stronger receptor-mediated contractions can be evoked in the RA than in the IMA [49,127], which presumably predisposes it to higher incidences of spasm. Additionally, it was previously reported that RA grafts are more sensitive to TxA_2 [13]. Furthermore, it has been reported that IMAs produce substantial amounts of both PGI_2 and TxA_2 [128]; nonetheless, the TxA_2 to PGI_2 ratio was significantly higher in the RA than in the IMA. Because PGI_2 antagonizes the actions of TxA_2, the higher TxA_2 to PGI_2 ratio implies that TxA_2 would exert greater effects in the RA. Contraction to KCl

in the RA is stronger than in the IMA or the GEA [16]. The RA is more reactive than the IMA to angiotensin II and ET-1, but the endothelial function of the RA is similar to the IMA [49].

Pharmacological and non-pharmacological strategies have been evaluated to prevent RA occlusion and RA spasm. A number of pharmacological 'cocktails' have been successfully tested but there is currently no agreement on the optimal combination of agents. RA studied in vitro was found to relax fully either to GV solution or to papaverine, but the relaxation to GV solution was more rapid in onset and of longer duration than for papaverine [62]. GV (GTN +Verapamil) solution has been found to be satisfactory when is used on the RA to dilate it during harvesting and preparation and it [11,129]. It can be argued that GV solution represents the optimum agent for RA spasm when used in the perioperative period [129]. It has been suggested that a 'cocktail' of agents may be given to counteract RA spasm before transradial coronary angiography or angioplasty [130]. A combination of heparin, NTG and verapamil seems to be associated with the best preventive outcome [130].

4.2. Gastroepiploic artery

Excellent long-term angiographic results have been reported with GEA [131], but its progressive loss of caliber with mobilization and its greater tendency for vasospasm compared with other arterial conduits both in in vitro testing [13] and in clinical practice [7] has limited its widespread use.

Spasm of the GEA is a well-described clinical phenomenon [7] Some studies have suggested that the GEA and the IMA have similar response to NE, phenylephrine, and 5-HT [132,133], and that the IMA is more reactive to the TXA_2 mimetic, U46619. On the other hand, Dignan and associates [15] have found that the GEA has a stronger contractility than the IMA and more reactive to K^+, NE, and 5-HT. He and Yang [13,134] compared the contractility of the GEA, the IMA, and the IEA and found that among arterial grafts the GEA has the highest contractility. Variation of techniques used in the studies may account for diverse results from different groups. Therefore, the above mentioned vasoconstrictors may be the spasmogenic agents for the GEA [15]. Additionally, relaxation of the GEA to SNP [15] or to endothelium-dependent vasodilators [134,135] appears to be similar to the IMA.

Several vasodiators have been studied to counteract GEA spasm [81,136]. It has been demonstrated that papaverine, when given externally on the perivascular fat of the GEA, prevents GEA spasm for up to 2 hr [136]. In contrast, intraluminally applied papaverine does not show graft protection against NE-induced spasm. In addition, nifedipine prevents NE-induced spasm only when given intraluminally. Same study has also shown that verapamil is the most potent and versatile vasodilator with effective graft protection of up to 2 hr whether applied externally or internally and is the preferred agent for protecting against GEA spasm [136]. During intraoperative preparation of the GEA graft, GTN and papaverine to a lesser extent, used as topical vasodilators, appear to be more efficient in external application to increase the free flow of the GEA [81]. GV solution has been suggested to be suitable to treat spasm of GEA [137] GTN has a more rapid onset and verapamil has a longer action than papaverine [11]. That should prevent spasm of conduit in the early postoperative hours [137].

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4.3. Inferior epigastric artery

It has been demonstrated that there is no difference between the IEA and the IMA for some vasoconstrictors, such as ET, NE, K^+, and U46619 [48] However, a previous study showed that IEA contracted less in response to histamine, but relaxed more in response to endothelium-dependent vasodilators, compared with the IMA [138]. Different contractile responses to TXA_2 and NE between the IEA and the IMA have also been reported [139]. In general, it has been argued that the contractile response of the IEA is basically similar to that of the IMA [11].

It has been demonstrated that endothelium dependent relaxation is reduced in the IEA compared with the IMA [140]. Another report has shown that the non–receptor-mediated endothelium dependent relaxation (induced by calcium ionophore A23187) in the IEA is less than in the IMA, although the receptor-mediated endothelium-dependent relaxation induced by acetylcholine is similar [48]. This decreased endothelium-dependent relaxation may be an early sign of arteriosclerosis in the IEA [48], since non– receptor-mediated endothelium-dependent relaxation is impaired.

5. Conclusion

The problem of grafts spasm has become more obvious with the increasing use of new arterial grafts. Arterial spasm is a multifactor phenomenon modulated by different mechanism, such as drugs, temperature, endogenous catecholamine, and mechanical stimuli (surgical trauma), which is the most common cause. Surgical trauma can usually be minimized by harvesting the artery as a pedicle rather than skeletonizing it by careful surgical technique.

Antispastic management is an important part of technical considerations during CABG surgery. There is extensive evidence that the use of appropriate vasodilators during CABG surgery can facilitate the operative procedure as well as improve graft flow and reduce structural damage to the graft conduit. Spasm of arterial graft conduits is best managed by prevention rather than treatment after it has occurred. There are many dilators of arterial grafts that vary in potency, rapidity of onset, and duration of action as shown in organ bath studies. Using these findings to make a rational choice of type of dilator and optimal concentration for clinical use requires an understanding of the reactivity of that particular type of graft to vasoconstrictor and vasodilator agents. In addition, clinical choice of grafts must be based on consideration of many additional factors, including the systemic effects of the agent if it enters the circulation, the effect of the agent and its vehicle on the endothelium, convenience of preparation, and cost.

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