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# 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 mortality [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.

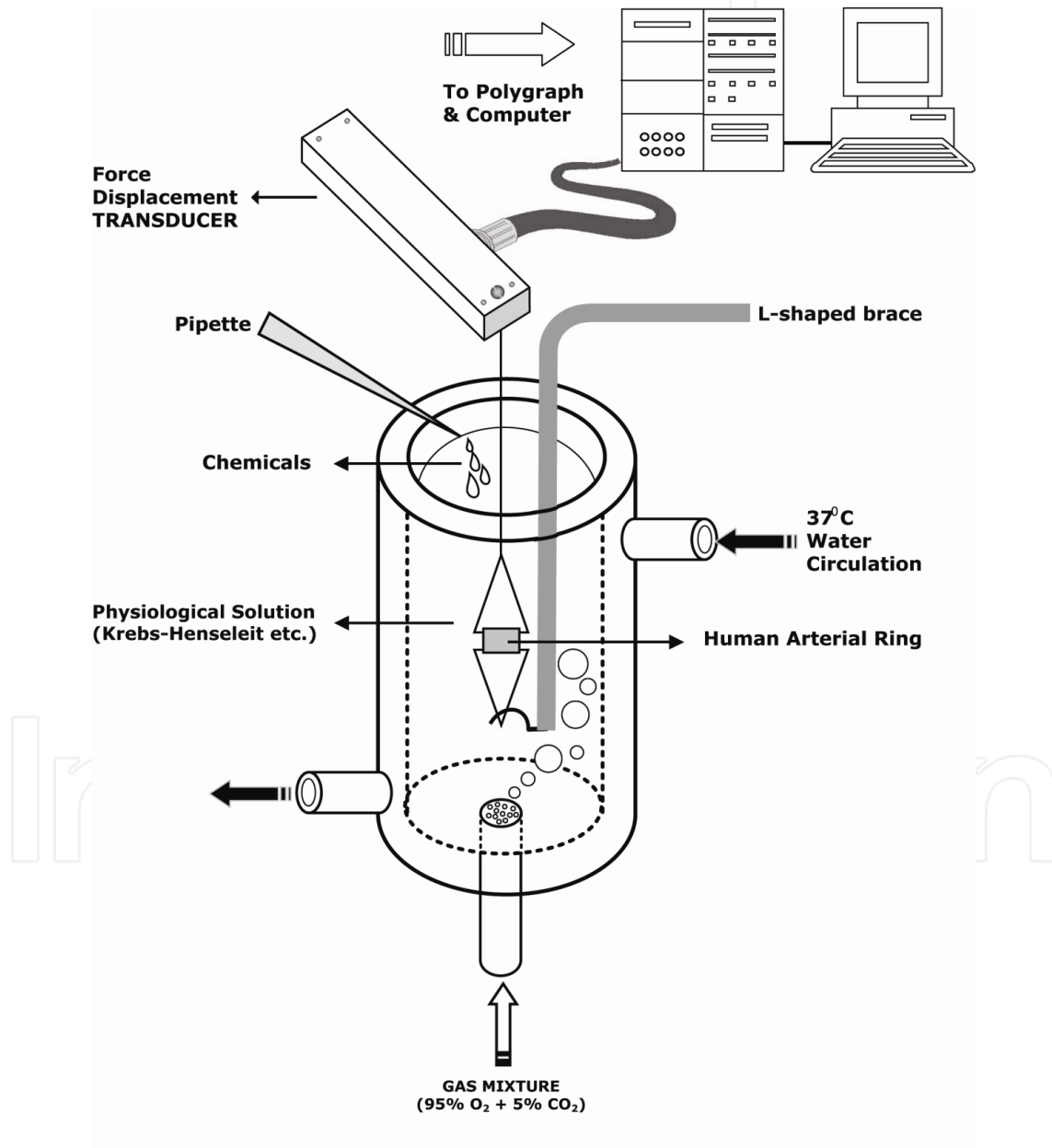
Several vasodilators have been tested and various antispastic methods have been suggested to prevent graft spasm; including papaverine, phenoxybenzamine, calcium antagonists and nitrates etc. Choice of a pharmacological agent to overcome the vasospasm encountered in the arterial grafts must be on the 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

for tension measurement along the former circumferential axis. The solution is gassed with % 95 O<sub>2</sub> and % 5 CO<sub>2</sub> at 37 °C. 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<sub>2α</sub> or potassium chloride (KCl) to test the viability of the vessel. After an additional 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 continuously 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  $\alpha$ -adrenergic receptors on the vascular smooth muscle. Consequently, a selective  $\alpha$  -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 ( $K^+$ ).

<b>Vasoconstrictors</b>	Vascular Smooth Muscle Contraction	Endothelium Relaxation
<b>EDCFs</b>		
Endothelin	ET <sub>A</sub> , ET <sub>B</sub>	ET <sub>B</sub>
<b>α-Adrenoceptor agonists</b>		
Norepinephrine	α <sub>1</sub> , α <sub>2</sub>	α <sub>2</sub>
Methoxamine	α <sub>1</sub>	...
Phenylephrine	α <sub>1</sub>	...
Dopamine	α <sub>1</sub> ***	...
<b>Platelet-derived substances</b>		
5-HT	5-HT <sub>2</sub>	5-HT <sub>1D</sub>
TxA <sub>2</sub> *	TP	TP(?)**
<b>Prostanoids</b>		
TxA <sub>2</sub> *	TP	TP(?)**
PGF <sub>2α</sub>	FP	FP(?)**
<b>Substances released from mast cells and basophils</b>		
Histamine	H (H <sub>1</sub> , H <sub>2</sub> )	H <sub>1</sub>
<b>Muscarinic receptor agonists</b>		
Acetylcholine	M <sub>3?</sub>	M <sub>2</sub>
<b>Renin-angiotensin system</b>		
Angiotensin II	All	All
Vasopressin (ADH)	V <sub>1</sub> ****	...
<b>Depolarizing agent</b>		
Potassium		...

\* TxA<sub>2</sub> 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<sub>1</sub> and α<sub>2</sub> 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 spontaneous 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<sub>2</sub> (TxA<sub>2</sub>) 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<sub>2</sub>) [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<sub>2</sub> and PGF<sub>2α</sub>) and α<sub>1</sub>-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

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].  $\text{TxA}_2$  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  $\text{TxA}_2$  [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  $\alpha_1$ -adrenoceptor-dominant artery with little  $\alpha_2$ - or  $\beta$ -function [30,31]. Other receptors functionally demonstrated in IMA are  $\text{ET}_A$ ,  $\text{ET}_B$  [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<sub>2</sub> receptors [40] and relaxes blood vessels through endothelial NO release, mediated by 5-HT<sub>1D</sub> 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  $\text{TxA}_2$ ) 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  $\text{PGI}_2$  [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].

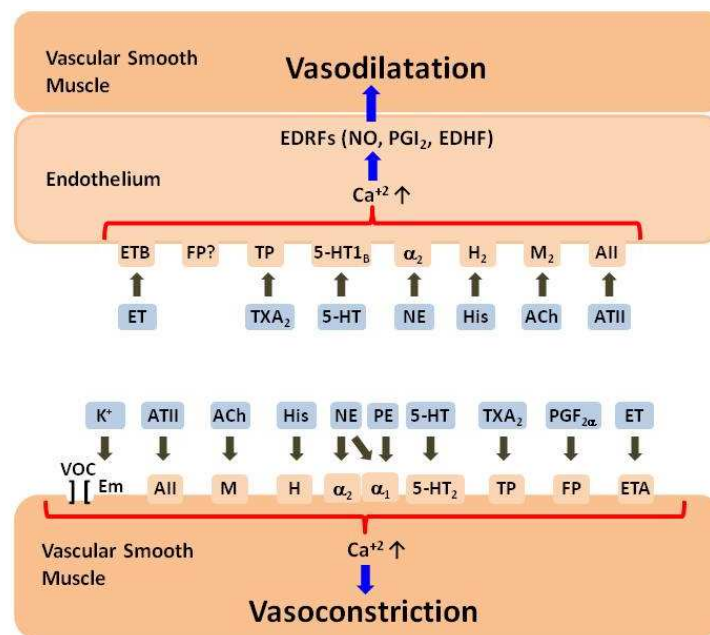
In addition, receptors, for common stimuli of EDRF such as acetylcholine, bradykinin, and substance P are present in the endothelium of arterial grafts [15,48,49]. The vascular endothelial growth factor (VEGF)-induced, endothelium-dependent relaxation, mediated by both NO and prostacyclin in the IMA, has been shown mainly through the KDR (kinase insert domain) receptors, rather than Flt-1 (fms-like tyrosine kinase-1) receptors [45]. Most recently, corticotropin-releasing factor (CRF) receptors  $\text{CRF}_1$ ,  $\text{CRF}_{2\alpha}$  and  $\text{CRF}_{2\beta}$  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 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; All, angiotensin II receptors; ACh, acetylcholine; EDHF, endothelium-derived hyperpolarizing factor; ET, endothelin; FP, PGF<sub>2α</sub> receptors; H (H<sub>2</sub>), histamine receptors; His, histamine; K, potassium; M (M<sub>2</sub>), muscarinic receptors; NE, norepinephrine; PE, phenylephrine; PGI<sub>2</sub>, prostacyclin; 5-HT, 5-hydroxytryptamine (serotonin); TP, thromboxane-prostanoid receptors; VOC, voltage operated channels; α, adrenergic receptors

### 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 plasma-lyte 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<sub>2</sub> receptors,  $\alpha$ -adrenoceptors, or ET receptors) or depolarizing agent (K<sup>+</sup>)- 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  $\alpha$ -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. Inamrinone (previously called amrinone) 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 the 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 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 addition, 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].

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  $TxA_2$ ,  $\alpha$ -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 antivasoconstrictor and vasorelaxant actions, that is, they reduce or prevent cellular response to excitatory stimuli, repolarize or hyperpolarize the cell membrane, overcome a contraction once it has developed, and strengthen 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.

### **$\alpha$ -Adrenoceptor antagonists**

IMA is an  $\alpha_1$ -adrenoceptor-dominant artery with little  $\alpha_2$ - or  $\beta$ -function [30,31,103]. Theoretically, a selective  $\alpha$ -receptor antagonist may be a highly effective antispastic agent because the site of interaction is same. Herewith, the use of  $\alpha$ -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,  $\alpha$ -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  $\alpha_1$ -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<sub>2</sub> -mediated mechanisms [44,45]. However, VEGF has potent hypotensive effect due to systemic vasodilation [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 demonstrated that use of β-adrenoceptor agonists is unlikely to 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<sub>1</sub>-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<sub>2</sub> antagonists**

TxA<sub>2</sub> is one of 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<sub>2</sub> antagonists may be useful in the antispastic therapy of IMA. Accordingly, specific TxA<sub>2</sub> antagonist GR30191 is a potent vasodilator for TxA<sub>2</sub>-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-HT<sub>1D</sub> and 5-HT<sub>2</sub> 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<sub>2</sub> released from platelets during thrombus formation, and 5-HT receptor mediated contractions may be unmasked or amplified [33,108-110]. 5-HT<sub>2A</sub> 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-

response to testosterone may occur in via large-conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  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 botulinum toxin**

It has been demonstrated that botulinum toxin may prevent arterial spasm in vitro [120]. Iloprost, a  $\text{PGI}_2$  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  $\text{TxA}_2$  [13]. Furthermore, it has been reported that IMAs produce substantial amounts of both  $\text{PGI}_2$  and  $\text{TxA}_2$  [128]; nonetheless, the  $\text{TxA}_2$  to  $\text{PGI}_2$  ratio was significantly higher in the RA than in the IMA. Because  $\text{PGI}_2$  antagonizes the actions of  $\text{TxA}_2$ , the higher  $\text{TxA}_2$  to  $\text{PGI}_2$  ratio implies that  $\text{TxA}_2$  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<sub>2</sub> 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<sup>+</sup>, 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 vasodilators 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].

### 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<sup>+</sup>, 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<sub>2</sub> 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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## References

- [1] Sarabu MR, McClung JA, Fass A, Reed GE. Early postoperative spasm in left internal mammary artery bypass grafts. *Ann Thorac Surg.* 1987;44(2):199-200.
- [2] Houghton JL, Callaghan WE, Frank MJ. Disappearance of high-grade left anterior descending stenosis after revascularization. *Cathet Cardiovasc Diagn.* 1988;14(3):169-171.
- [3] McCormick JR, Kaneko M, Baue AE, Geha AS. Blood flow and vasoactive drug effects in internal mammary and venous bypass grafts. *Circulation.* 1975;52(2):72-80.
- [4] Jett GK, Arcidi JM Jr, Dorsey LM, Hatcher CR Jr, Guyton RA. Vasoactive drug effects on blood flow in internal mammary artery and saphenous vein grafts. *J Thorac Cardiovasc Surg.* 1987;94(1):2-11.
- [5] Kawasuji M, Tedoriya T, Takemura H, Sakakibara N, Taki J, Watanabe Y. Flow capacities of arterial grafts for coronary artery bypass grafting. *Ann Thorac Surg.* 1993;56(4):957-962.
- [6] Loop FD, Thomas JD. Hypoperfusion after arterial bypass grafting. *Ann Thorac Surg.* 1993;56(4):812-813.
- [7] Suma H. Spasm of the gastroepiploic artery graft. *Ann Thorac Surg.* 1990;49(1):168-169.
- [8] Fisk RL, Brooks CH, Callaghan JC, Dvorkin J. Experience with the radial artery graft for coronary artery bypass. *Ann Thorac Surg.* 1976;21(6):513-518.
- [9] Mills NL, Bringaze WL 3rd. Preparation of the internal mammary artery graft. Which is the best method? *J Thorac Cardiovasc Surg.* 1989;98(1):73-77.
- [10] He GW, Angus JA, Rosenfeldt FL. Reactivity of the canine isolated internal mammary artery, saphenous vein, and coronary artery to constrictor and dilator substances: relevance to coronary bypass graft surgery. *J Cardiovasc Pharmacol.* 1988;12(1):12-22.
- [11] Rosenfeldt FL, He GW, Buxton BF, Angus JA. Pharmacology of coronary artery bypass grafts. *Ann Thorac Surg.* 1999;67(3):878-888. Review.

- [12] He GW, Yang CQ. Pharmacological studies and guidelines for the use of vasodilators for arterial grafts. In He GW (ed.) Arterial grafting for coronary artery bypass surgery. Springer; 2006. p38-47.
- [13] He GW, Yang CQ, Starr A. Overview of the nature of vasoconstriction in arterial grafts for coronary operations. *Ann Thorac Surg.* 1995;59(3):676-683
- [14] Angus JA, Cocks TM, Satoh K. Alpha 2-adrenoceptors and endothelium-dependent relaxation in canine large arteries. *Br J Pharmacol.* 1986;88(4):767-777.
- [15] Dignan RJ, Yeh T Jr, Dyke CM, Lee KF, Lutz HA 3rd, Ding M, Wechsler AS. Reactivity of gastroepiploic and internal mammary arteries. Relevance to coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 1992;103(1):116-122.
- [16] Chardigny C, Jebara VA, Acar C, Descombes JJ, Verbeuren TJ, Carpentier A, Fabiani JN. Vasoreactivity of the radial artery. Comparison with the internal mammary and gastroepiploic arteries with implications for coronary artery surgery. *Circulation.* 1993;88:115-127.
- [17] He G-W, Yang C-Q, Acuff TE, Ryan WH, Mack MJ. Endothelium-derived hyperpolarizing factor (EDHF) plays a role in human coronary bypass grafts through Na<sup>+</sup>-K<sup>+</sup> pump mechanism [Abstract]. *Circulation* 1994;90:242.
- [18] Henry PJ, Drummer OH, Horowitz JD. S-nitrosothiols as vasodilators: implications regarding tolerance to nitric oxide-containing vasodilators. *Br J Pharmacol.* 1989;98(3):757-766.
- [19] Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci USA.* 1987;84(24):9265-9269.
- [20] Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature.* 1987;327(6122):524-526.
- [21] Moncada S, Korb R, Bunting S, Vane JR. Prostacyclin is a circulating hormone. *Nature.* 1978;273(5665):767-768.
- [22] Feletou M, Vanhoutte PM. Endothelium-dependent hyperpolarization of canine coronary smooth muscle. *Br J Pharmacol.* 1988;93(3):515-524.
- [23] Chen G, Suzuki H, Weston AH. Acetylcholine releases endothelium-derived hyperpolarizing factor and EDRF from rat blood vessels. *Br J Pharmacol.* 1988;95(4):1165-1174.
- [24] He GW, Yang CQ, Graier WF, Yang JA. Hyperkalemia alters EDHF-mediated hyperpolarization and relaxation in coronary arteries. *Am J Physiol.* 1996;271:H760-767.
- [25] Ge ZD, Zhang XH, Fung PC, He GW. Endothelium-dependent hyperpolarization and relaxation resistance to N(G)-nitro-L-arginine and indomethacin in coronary circulation. *Cardiovasc Res.* 2000;46(3):547-556.

- [26] Schoeffter P, Dion R, Godfraind T. Modulatory role of the vascular endothelium in the contractility of human isolated internal mammary artery. *Br J Pharmacol* 1988;95:531-543.
- [27] Acar C, Jebara VA, Portoghese M, Beyssen B, Pagny JY, Grare P, Chachques JC, Fabiani JN, Deloche A, Guermontprez JL. Revival of the radial artery for coronary artery bypass grafting. *Ann Thorac Surg*. 1992;54(4):652-659.
- [28] van Zwienen JCW, van der Linden CJ, Cimbrere JSF, Lacquet LK, Booij LHDJ, Hendriks T. Endothelin release during coronary artery bypass grafting [Abstract]. *Chest* 1993;103:176S
- [29] Davies GC, Sobel M, Salzman EW. Elevated plasma fibrinopeptide A and thromboxane B<sub>2</sub> levels during cardiopulmonary bypass. *Circulation*. 1980;61(4):808-814.
- [30] He GW, Shaw J, Hughes CF, Yang CQ, Thomson DS, McCaughan B, Hendle PN, Baird DK. Predominant alpha 1-adrenoceptor-mediated contraction in the human internal mammary artery. *J Cardiovasc Pharmacol*. 1993;21(2):256-263.
- [31] He GW, Buxton B, Rosenfeldt FL, Wilson AC, Angus JA. Weak beta-adrenoceptor-mediated relaxation in the human internal mammary artery. *J Thorac Cardiovasc Surg*. 1989;97(2):259-266.
- [32] Seo B, Oemar BS, Siebenmann R, von Segesser L, Lüscher TF. Both ET<sub>A</sub> and ET<sub>B</sub> receptors mediate contraction to endothelin-1 in human blood vessels. *Circulation*. 1994;89(3):1203-1208.
- [33] Yildiz O, Çiçek S, Ay I, Tatar H, Tuncer M. 5-HT<sub>1</sub>-like receptor-mediated contraction in the human internal mammary artery. *J Cardiovasc Pharmacol*. 1996;28(1):6-10.
- [34] He GW, Yang CQ. Comparison of nitroprusside and nitroglycerin in inhibition of angiotensin II and other vasoconstrictor-mediated contraction in human coronary bypass conduits. *Br J Clin Pharmacol*. 1997;44(4):361-367.
- [35] He GW, Yang CQ. Effect of thromboxane A<sub>2</sub> antagonist GR32191B on prostanoid and nonprostanoid receptors in the human internal mammary artery. *J Cardiovasc Pharmacol*. 1995;26(1):13-19.
- [36] He GW, Yang Q, Yang CQ. Smooth muscle and endothelial function of arterial grafts for coronary artery bypass surgery. *Clin Exp Pharmacol Physiol*. 2002;29(8):717-720. Review.
- [37] Liu JJ, Phillips PA, Burrell LM, Buxton BB, Johnston CI. Human internal mammary artery responses to non-peptide vasopressin antagonists. *Clin Exp Pharmacol Physiol*. 1994;21(2):121-124.
- [38] Luu TN, Dashwood MR, Chester AH, Tadjkarimi S, Yacoub MH. Action of vasoactive intestinal peptide and distribution of its binding sites in vessels used for coronary artery bypass grafts. *Am J Cardiol*. 1993;71(15):1278-1282.



- [39] Myers ML, Li GH, Yaghi A, McCormack D. Human internal thoracic artery reactivity to dopaminergic agents. *Circulation*. 1993;88[Part 2]:110-114.
- [40] Cocks TM, Angus JA. Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin. *Nature*. 1983;305(5935):627-630.
- [41] Schoeffter P, Hoyer D. 5-Hydroxytryptamine (5-HT)-induced endothelium-dependent relaxation of pig coronary arteries is mediated by 5-HT receptors similar to the 5-HT<sub>1D</sub> receptor subtype. *J Pharmacol Exp Ther*. 1990;252(1):387-395.
- [42] He GW, Yang CQ. "Vasoactivators"--a new concept for naturally secreted vasoconstrictor substances. *Angiology*. 1994;45(4):265-271.
- [43] Luscher TF, Diederich D, Siebenmann R, Lehmann K, Stulz P, von Segesser L, Yang ZH, Turina M, Grädel E, Weber E. Difference between endothelium-dependent relaxation in arterial and in venous coronary bypass grafts. *N Engl J Med*. 1988;319(8):462-467
- [44] Liu MH, Jin H, Floten HS, Ren Z, Yim AP, He GW. Vascular endothelial growth factor-mediated, endothelium-dependent relaxation in human internal mammary artery. *Ann Thorac Surg*. 2002;73(3):819-824.
- [45] Wei W, Jin H, Chen ZW, Zioncheck TF, Yim AP, He GW. Vascular endothelial growth factor-induced nitric oxide- and PGI<sub>2</sub>-dependent relaxation in human internal mammary arteries: a comparative study with KDR and Flt-1 selective mutants. *J Cardiovasc Pharmacol*. 2004;44(5):615-621.
- [46] Liu ZG, Ge ZD, He GW. Difference in endothelium-derived hyperpolarizing factor-mediated hyperpolarization and nitric oxide release between human internal mammary artery and saphenous vein. *Circulation*. 2000;102(19 Suppl 3):296-301.
- [47] He GW, Liu ZG. Comparison of nitric oxide release and endothelium-derived hyperpolarizing factor-mediated hyperpolarization between human radial and internal mammary arteries. *Circulation*. 2001;104(12 Suppl 1):344-349.
- [48] He GW, Acuff TE, Ryan WH, Yang CQ, Mack MJ. Functional comparison between the human inferior epigastric artery and internal mammary artery. Similarities and differences. *J Thorac Cardiovasc Surg*. 1995;109(1):13-20.
- [49] He GW, Yang CQ. Radial artery has higher receptor-mediated contractility but similar endothelial function compared with mammary artery. *Ann Thorac Surg*. 1997;63(5):1346-1352.
- [50] Chen ZW, Huang Y, Yang Q, Li X, Wei W, He GW. Urocortin-induced relaxation in the human internal mammary artery. *Cardiovasc Res*. 2005;65(4):913-920.
- [51] von Segesser L, Simonet F, Meier 8, Finci L, Faidutti B. Inadequate flow after internal mammaryx coronary artery anastomoses. *Thorac Cardiovasc Surg* 1987;35:352-354.
- [52] von Segesser LK, Lehmann K, Turina M. Deleterious effects of shock in internal mammary artery anastomoses. *Ann Thorac Surg*. 1989;47(4):575-579.



- [53] Huddleston CB, Stoney WS, Alford WC Jr, Burrus GR, Glassford DM Jr, Lea JW 4th, Petracek MR, Thomas CS Jr. Internal mammary artery grafts: technical factors influencing patency. *Ann Thorac Surg.* 1986;42(5):543-549.
- [54] He GW, Rosenfeldt FL, Buxton BF, Angus JA. Reactivity of human isolated internal mammary artery to constrictor and dilator agents. Implications for treatment of internal mammary artery spasm. *Circulation.* 1989;80(3 Pt 1):1141-150.
- [55] Cooper GJ, Wilkinson GA, Angelini GD. Overcoming perioperative spasm of the internal mammary artery: which is the best vasodilator? *J Thorac Cardiovasc Surg.* 1992;104(2):465-468.
- [56] Dion RA, Verhelst R, Goenen M, Rousseau M, Baele P, Ponlot R, Schoevaerdt JC, Chalant CH. Sequential mammary artery grafts in one hundred and twenty consecutive patients: indications, operative technique, 6 months postoperative functional and angiographic controls. *J Cardiovasc Surg (Torino).* 1989;30(4):635-642.
- [57] Dion R, Verhelst R, Rousseau M, Goenen M, Ponlot R, Kestens-Servaye Y, Chalant CH. Sequential mammary grafting. Clinical, functional, and angiographic assessment 6 months postoperatively in 231 consecutive patients. *J Thorac Cardiovasc Surg.* 1989;98(1):80-88.
- [58] Galbut DL, Traad EA, Dorman MJ, DeWitt PL, Larsen PB, Kurlansky PA, Button JH, Ally JM, Gentsch TO. Seventeen-year experience with bilateral internal mammary artery grafts. *Ann Thorac Surg.* 1990;49(2):195-201.
- [59] Eckel L, Skupin M, Schröder R, Gusic L, Beyersdorf F, Sarai K, Krause E. Adequate flow through the internal mammary artery graft achieved by a dilatation technique. *Thorac Cardiovasc Surg.* 1990;38(3):157-160.
- [60] Green GE. Rate of blood flow from the internal mammary artery. *Surgery.* 1971;70(6):809-813.
- [61] He GW, Rosenfeldt FL, Angus JA. Pharmacological relaxation of the saphenous vein during harvesting for coronary artery bypass grafting. *Ann Thorac Surg.* 1993;55(5):1210-1217.
- [62] He GW, Yang CQ. Use of verapamil and nitroglycerin solution in preparation of radial artery for coronary grafting. *Ann Thorac Surg.* 1996;61(2):610-614.
- [63] Martin W, Furchgott RF, Villani GM, Jothianandan D. Phosphodiesterase inhibitors induce endothelium-dependent relaxation of rat and rabbit aorta by potentiating the effects of spontaneously released endothelium-derived relaxing factor. *J Pharmacol Exp Ther.* 1986;237(2):539-547.
- [64] Huddart H, Saad KH. Papaverine-induced inhibition of electrical and mechanical activity and calcium movements of rat ileal smooth muscle. *J Exp Biol.* 1980;86:99-114.
- [65] Fujioka M. Lack of a causal relationship between the vasodilator effect of papaverine and cyclic AMP production in the dog basilar artery. *Br J Pharmacol.* 1984;83(1):113-124.

- [66] Brading AF, Burdyga TV, Scripnyuk ZD. The effects of papaverine on the electrical and mechanical activity of the guinea-pig ureter. *J Physiol.* 1983;334:79-89.
- [67] Boerboom LE, Olinger GN, Bonchek LI, Gunay II, Kissebah AH, Rodriguez ER, Ferrans VJ. The relative influence of arterial pressure versus intraoperative distention on lipid accumulation in primate vein bypass grafts. *J Thorac Cardiovasc Surg.* 1985;90(5):756-764.
- [68] Malone JM, Kischer CW, Moore WS. Changes in venous endothelial fibrinolytic activity and histology with in vitro venous distention and arterial implantation. *Am J Surg.* 1981;142(2):178-182.
- [69] van Son JA, Tavilla G, Noyez L. Detrimental sequelae on the wall of the internal mammary artery caused by hydrostatic dilation with diluted papaverine solution. *J Thorac Cardiovasc Surg.* 1992;104(4):972-976.
- [70] Constantinides P, Robinson M. Ultrastructural injury of arterial endothelium. 1. Effects of pH, osmolarity, anoxia, and temperature. *Arch Pathol.* 1969;88(2):99-105.
- [71] Roberts AJ, Hay DA, Jawahar LM, et al. Biochemical and ultrastructural integrity of the saphenous vein conduit during CABG: preliminary results of the effect of papaverine. *J Thorac Cardiovasc Surg* 1984;88:39-48.
- [72] He GW, Buxton BF, Rosenfeldt FL, Angus JA, Tatoulis J. Pharmacologic dilatation of the internal mammary artery during coronary bypass grafting. *J Thorac Cardiovasc Surg.* 1994;107(6):1440-1444.
- [73] Cunningham JN Jr. Papaverine hydrochloride preservation of vein grafts. *J Thorac Cardiovasc Surg.* 1982;84(6):933.
- [74] He GW, Yang CQ, Mack MJ, Acuff TE, Ryan WH, Starr A. Interaction between endothelin and vasodilators in the human internal mammary artery. *Br J Clin Pharmacol.* 1994;38(6):505-512.
- [75] He GW, Shaw J, Yang CQ, Hughes C, Thomson D, McCaughan B, Hendle PN, Baird DK. Inhibitory effects of glyceryl trinitrate on alpha-adrenoceptor mediated contraction in the human internal mammary artery. *Br J Clin Pharmacol.* 1992;34(3):236-243.
- [76] He GW, Yang CO, Gately H, Furnary A, Swanson J, Ahmad A, Floten S, Wood J, Starr A. Potential greater than additive vasorelaxant actions of milrinone and nitroglycerin on human conduit arteries. *Br J Clin Pharmacol.* 1996;41(2):101-107.
- [77] He GW, Yang CQ. Comparison of the vasorelaxant effect of nitroprusside and nitroglycerin in the human radial artery in vitro. *Br J Clin Pharmacol.* 1999;48(1):99-104.
- [78] Zabeeda D, Medalion B, Jakobshvilli S, Ezra S, Schachner A, Cohen AJ. Comparison of systemic vasodilators: effects on flow in internal mammary and radial arteries. *Ann Thorac Surg.* 2001;71(1):138-141.

- [79] Shapira OM, Xu A, Vita JA, Aldea GS, Shah N, Shemin RJ, Keaney JF Jr. Nitroglycerin is superior to diltiazem as a coronary bypass conduit vasodilator. *J Thorac Cardiovasc Surg.* 1999;117(5):906-911.
- [80] Shapira OM, Alkon JD, Macron DS, Keaney JF Jr, Vita JA, Aldea GS, Shemin RJ. Nitroglycerin is preferable to diltiazem for prevention of coronary bypass conduit spasm. *Ann Thorac Surg.* 2000;70(3):883-888.
- [81] Chavanon O, Cracowski JL, Hacini R, Stanke F, Durand M, Noirclerc M, Blin D. Effect of topical vasodilators on gastroepiploic artery graft. *Ann Thorac Surg.* 1999;67(5):1295-1298.
- [82] Lobato EB, Janelle GM, Urdaneta F, Martin TD. Comparison of milrinone versus nitroglycerin, alone and in combination, on grafted internal mammary artery flow after cardiopulmonary bypass: effects of alpha-adrenergic stimulation. *J Cardiothorac Vasc Anesth.* 2001;15(6):723-727.
- [83] Cable DG, Caccitolo JA, Pearson PJ, O'Brien T, Mullany CJ, Daly RC, Orszulak TA, Schaff HV. New approaches to prevention and treatment of radial artery graft vasospasm. *Circulation.* 1998;98(19 Suppl):II15-21.
- [84] Beavo JA, Reifsnyder DH. Primary sequence of cyclic nucleotide phosphodiesterase isozymes and the design of selective inhibitors. *Trends Pharmacol Sci.* 1990;11(4):150-155. Review.
- [85] Beavo JA. Multiple isozymes of cyclic nucleotide phosphodiesterase. *Adv Second Messenger Phosphoprotein Res.* 1988;22:1-38. Review.
- [86] He GW, Yang CQ. Inhibition of vasoconstriction by phosphodiesterase III inhibitor milrinone in human conduit arteries used as coronary bypass grafts. *J Cardiovasc Pharmacol.* 1996;28(2):208-214.
- [87] Liu JJ, Doolan LA, Xie B, Chen JR, Buxton BF. Direct vasodilator effect of milrinone, an inotropic drug, on arterial coronary bypass grafts. *J Thorac Cardiovasc Surg.* 1997;113(1):108-113.
- [88] He GW. Effect of milrinone on coronary artery bypass grafts. *J Thorac Cardiovasc Surg.* 1997;114(2):302-304.
- [89] Yildiz O, Nacitarhan C, Seyrek M. Potassium channels in the vasodilating action of levosimendan on the human umbilical artery. *J Soc Gynecol Investig.* 2006;13(4):312-315.
- [90] Yildiz O. Vasodilating mechanisms of levosimendan: involvement of K<sup>+</sup> channels. *J Pharmacol Sci.* 2007;104(1):1-5.
- [91] Yildiz O, Seyrek M, Yildirim V, Demirkilic U, Nacitarhan C. Potassium channel-related relaxation by levosimendan in the human internal mammary artery. *Ann Thorac Surg.* 2006;81(5):1715-1719.

- [92] He GW, Acuff TE, Ryan WH, Yang CQ, Douthit MB, Bowman RT, Mack MJ. Inhibitory effects of calcium antagonists on alpha-adrenoceptor-mediated contraction in the human internal mammary artery. *Br J Clin Pharmacol.* 1994;37(2):173-179.
- [93] Wei W, Floten HS, He GW. Interaction between vasodilators and vasopressin in internal mammary artery and clinical significance. *Ann Thorac Surg.* 2002;73(2):516-522.
- [94] Atwal KS. Pharmacology and structure-activity relationships for  $K_{ATP}$  modulators: tissue-selective  $K_{ATP}$  openers. *J Cardiovasc Pharmacol.* 1994;24 Suppl 4:S12-17. Review.
- [95] Quast U, Guillon JM, Cavero I. Cellular pharmacology of potassium channel openers in vascular smooth muscle. *Cardiovasc Res.* 1994;28(6):805-810. Review.
- [96] Lazdunski M, Allard B, Bernardi H, De Weille J, Fosset M, Heurteaux C, Honoré E. ATP-sensitive  $K^+$  channels. *Ren Physiol Biochem.* 1994;17(3-4):118-120.
- [97] He GW, Yang CQ, Graier WF, Yang JA. Hyperkalemia alters EDHF-mediated hyperpolarization and relaxation in coronary arteries. *Am J Physiol.* 1996;271(2 Pt 2):760-767.
- [98] He GW, Yang CQ. Superiority of hyperpolarizing to depolarizing cardioplegia in protection of coronary endothelial function. *J Thorac Cardiovasc Surg.* 1997;114(4):643-650.
- [99] He GW. Potassium-channel opener in cardioplegia may restore coronary endothelial function. *Ann Thorac Surg.* 1998;66(4):1318-1322.
- [100] Liu MH, Floten HS, Furnary AP, Yim AP, He GW. Effects of potassium channel opener aprikalim on the receptor-mediated vasoconstriction in the human internal mammary artery. *Ann Thorac Surg.* 2001;71(2):636-641.
- [101] Ren Z, Floten S, Furnary A, Liu M, Gately H, Swanson J, Ahmad A, Yim AP, He GW. Effects of potassium channel opener KRN4884 on human conduit arteries used as coronary bypass grafts. *Br J Clin Pharmacol.* 2000;50(2):154-160.
- [102] He GW, Yang CQ. Inhibition of vasoconstriction by potassium channel opener aprikalim in human conduit arteries used as bypass grafts. *Br J Clin Pharmacol.* 1997;44(4):353-359.
- [103] Yan M, Liu DL, Chua YL, Chen C, Lim YL. Tyrosine kinase inhibitors suppress alpha1-adrenoceptor mediated contraction in human radial, internal mammary arteries and saphenous vein. *Neurosci Lett.* 2002;333(3):171-174.
- [104] Conant AR, Shackcloth MJ, Oo AY, Chester MR, Simpson AW, Dihmis WC. Phenoxybenzamine treatment is insufficient to prevent spasm in the radial artery: the effect of other vasodilators. *J Thorac Cardiovasc Surg.* 2003;126(2):448-454.
- [105] Shafiei M, Omrani G, Mahmoudian M. Coexistence of at least three distinct beta-adrenoceptors in human internal mammary artery. *Acta Physiol Hung.* 2000;87(3):275-286.

- [106] Cracowski JL, Stanke-Labesque F, Chavanon O, Blin D, Mallion JM, Bessard G, Devillier P. Vasorelaxant actions of enoximone, dobutamine, and the combination on human arterial coronary bypass grafts. *J Cardiovasc Pharmacol*. 1999;34(5):741-748.
- [107] Katai R, Tsuneyoshi I, Hamasaki J, Onomoto M, Suehiro S, Sakata R, Kanmura Y. The variable effects of dopamine among human isolated arteries commonly used for coronary bypass grafts. *Anesth Analg*. 2004;98(4):915-920, table of contents.
- [108] Yildiz O, Ciçek S, Ay I, Demirkiliç U, Tuncer M. Hypertension increases the contractions to sumatriptan in the human internal mammary artery. *Ann Thorac Surg*. 1996;62(5):1392-1395.
- [109] Yildiz O, Smith JR, Purdy RE. Serotonin and vasoconstrictor synergism. *Life Sci*. 1998;62(19):1723-1732. Review.
- [110] Chen J, Yildiz O, Purdy RE. Phenylephrine precontraction increases the sensitivity of rabbit femoral artery to serotonin by enabling 5-HT<sub>1</sub>-like receptors. *J Cardiovasc Pharmacol*. 2000;35(6):863-870.
- [111] Rego AC, Oliveira CR. Influence of lipid peroxidation on [3H]ketanserin binding to 5-HT<sub>2</sub> prefrontal cortex receptors. *Neurochem Int*. 1995;27(6):489-496.
- [112] Yildiz O, Seyrek M, Gul H, Un I, Yildirim V, Ozal E, Uzun M, Bolu E. Testosterone relaxes human internal mammary artery in vitro. *J Cardiovasc Pharmacol*. 2005;45(6):580-585.
- [113] Yildiz O, Seyrek M, Un I, Gul H, Candemir G, Yildirim V. The relationship between risk factors and testosterone-induced relaxations in human internal mammary artery. *J Cardiovasc Pharmacol*. 2005;45(1):4-7.
- [114] Seyrek M, Yildiz O, Ulusoy HB, Yildirim V. Testosterone relaxes isolated human radial artery by potassium channel opening action. *J Pharmacol Sci*. 2007;103(3):309-316.
- [115] Yildiz O, Seyrek M. Vasodilating mechanisms of testosterone. *Exp Clin Endocrinol Diabetes*. 2007;115(1):1-6. Review.
- [116] Irkilata HC, Yildiz O, Yildirim I, Seyrek M, Basal S, Dayanc M, Ulku C. The vasodilator effect of testosterone on the human internal spermatic vein and its relation to varicocele grade. *J Urol*. 2008;180(2):772-776.
- [117] Seyrek M, Irkilata HC, Vural IM, Yildirim I, Basal S, Yildiz O, Dayanc M. Testosterone relaxes human internal spermatic vein through potassium channel opening action. *Urology*. 2011;78(1): 233.e1-5.
- [118] Yildiz O, Seyrek M, Irkilata HC, Yildirim I, Tahmaz L, Dayanc M. Testosterone might cause relaxation of human corpus cavernosum by potassium channel opening action. *Urology*. 2009;74(1):229-232.
- [119] Yildiz O, Seyrek M. Effects of testosterone on vascular tone. In Chichinadze K (ed.) *Testosterone: Biochemistry, therapeutic uses and physiological effects*. Nova Science Publishers; 2012. p159-183.



- [120] Murakami E, Iwata H, Imaizumi M, Takemura H. Prevention of arterial graft spasm by botulinum toxin: an in-vitro experiment. *Interact Cardiovasc Thorac Surg.* 2009;9(3):395-398.
- [121] Ozdemir C, Ikizler M, Besogul Y, Karakaya A, Sirmagul B. An alternative agent for radial arterial graft spasm: application of topical iloprost. *Scand Cardiovasc J.* 2007;41(3):201-206.
- [122] Mussa S, Choudhary BP, Taggart DP. Radial artery conduits for coronary artery bypass grafting: current perspective. *J Thorac Cardiovasc Surg.* 2005;129(2):250-253. Review.
- [123] [123] Barner HB. The continuing evolution of arterial conduits. *Ann Thorac Surg.* 1999;68(3 Suppl):S1-8.
- [124] Shah PJ, Bui K, Blackmore S, Gordon I, Hare DL, Fuller J, Seevanayagam S, Buxton BF. Has the in situ right internal thoracic artery been overlooked? An angiographic study of the radial artery, internal thoracic arteries and saphenous vein graft patencies in symptomatic patients. *Eur J Cardiothorac Surg.* 2005;27(5):870-875.
- [125] Sahin MA, Guler A, Cingoz F, Yokusoglu M, Demirkol S, Ozal E, Demirkilic U, Arslan M. Mid-term results of radial artery grafts used in coronary bypass surgery. *Gulhane Med J.* 2012; 54(1): 7-13. Turkish.
- [126] Possati G, Gaudino M, Prati F, Alessandrini F, Trani C, Glieca F, Mazzari MA, Luciani N, Schiavoni G. Long-term results of the radial artery used for myocardial revascularization. *Circulation.* 2003;108(11):1350-1354.
- [127] Lockowandt U, Ritchie A, Grossebener M, Franco-Cereceda A. Endothelin and effects of endothelin-receptor activation in the mammary and radial artery. *Scand Cardiovasc J.* 2004;38(4):240-244.
- [128] Gupte SA, Zias EA, Sarabu MR, Wolin MS. Role of prostaglandins in mediating differences in human internal mammary and radial artery relaxation elicited by hypoxia. *J Pharmacol Exp Ther.* 2004;311(2):510-518.
- [129] Attaran S, John L, El-Gamel A. Clinical and potential use of pharmacological agents to reduce radial artery spasm in coronary artery surgery. *Ann Thorac Surg.* 2008;85(4):1483-1489. Review.
- [130] Vuurmans T, Hilton D. Brewing the right cocktail for radial intervention. *Indian Heart J.* 2010;62(3):221-225. Review.
- [131] Suma H. Optimal use of the gastroepiploic artery. *Semin Thorac Cardiovasc Surg.* 1996;8(1):24-28.
- [132] Koike R, Suma H, Kondo K, Oku T, Satoh H, Fukuda S, Takeuchi A. Pharmacological response of internal mammary artery and gastroepiploic artery. *Ann Thorac Surg.* 1990;50(3):384-386.
- [133] Ochiai M, Ohno M, Taguchi J, Hara K, Suma H, Isshiki T, Yamaguchi T, Kurokawa K. Responses of human gastroepiploic arteries to vasoactive substances: comparison with



responses of internal mammary arteries and saphenous veins. *J Thorac Cardiovasc Surg.* 1992;104(2):453-438.

- [134] He GW, Yang CQ. Comparison among arterial grafts and coronary artery. An attempt at functional classification. *J Thorac Cardiovasc Surg.* 1995;109(4):707-715.
- [135] Yang Z, Siebenmann R, Studer M, Egloff L, Lüscher TF. Similar endothelium-dependent relaxation, but enhanced contractility, of the right gastroepiploic artery as compared with the internal mammary artery. *J Thorac Cardiovasc Surg.* 1992;104(2):459-464.
- [136] Ali AT, Montgomery WD, Santamore WP, Spence PA. Preventing gastroepiploic artery spasm: papaverine vs calcium channel blockade. *J Surg Res.* 1997;71(1):41-48.
- [137] Formica F, Ferro O, Brustia M, Corti F, Colagrande L, Bosisio E, Paolini G. Effects of papaverine and glycerylnitrate-verapamil solution as topical and intraluminal vasodilators for internal thoracic artery. *Ann Thorac Surg.* 2006;81(1):120-124.
- [138] Mügge A, Barton MR, Cremer J, Frombach R, Lichtlen PR. Different vascular reactivity of human internal mammary and inferior epigastric arteries in vitro. *Ann Thorac Surg.* 1993;56(5):1085-1089.
- [139] Tadjkarimi S, O'Neil GS, Schyns CJ, Borland JA, Chester AH, Yacoub MH. Vasoconstrictor profile of the inferior epigastric artery. *Ann Thorac Surg.* 1993;56(5):1090-1095.
- [140] Tadjkarimi S, Chester AH, Borland JA, Schyns CJ, O'Neil GS, Yacoub MH. Endothelial function and vasodilator profile of the inferior epigastric artery. *Ann Thorac Surg.* 1994;58(1):207-210.