Antispastic Management in Arterial Grafts in Coronary Artery Bypass Grafting Surgery

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Arterial grafts have long-term patency superior to vein grafts but have a tendency to develop spasm that can lead to potentially life-threatening complications. A perfect antispastic protocol should include advanced surgical technique and adequate pharmacologic methods. All pharmacologic vasodilator drugs relax the vessel through specific mechanisms, and therefore, there is no perfect, single best vasodilator to prevent or treat spasm of the arterial graft against all mechanisms of contraction. One of the choices is to use a combination of pharmacologic vasodilators targeting different mechanisms of spasm to obtain the reliable and best effect.

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REVIEW

Despite of the success of coronary artery bypass grafting surgery (CABG) in the past decades that remains the standard treatment particularly for three-vessel disease, in recent reports, spasm in arterial grafts is still a clinical problem, with an incidence of at least 0.43% in all CABG surgery [1]. We have recently reviewed the incidence and possible mechanisms of spasm, clinical manifestations, and management of spasm, as well as principles of prevention of spasm in arterial grafts [1]. The present review serves as the second part of a systematic review of this clinical problem with focus on the antispastic management, and we strongly recommend reading the previous review in *The Annals* [1] and this review together as a series to obtain a complete view on spasm and management of arterial grafts.

Review Criteria

A search for original articles focusing on coronary artery revascularization published between 1950 and 2015 was performed in the MEDLINE and PubMed databases. The search terms used were "arterial grafting antispastic," "coronary artery bypass grafting," and "spasm coronary arterial grafting," alone and in combination. All articles identified were English language, full-text papers. We also searched the reference lists of identified articles for further relevant papers. Owing to the limit on references allowed for this review, we cited only some of the most relevant references.

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Vasodilator Agents Used for Arterial Grafts

Papaverine

Early studies reported a traditional topical vasodilator, papaverine, with satisfactory results [2], and it has been used since in internal mammary artery (IMA) [3] and other arterial grafts [4]. Papaverine is an opioid derivative and a nonspecific vasodilator substance that relaxes blood vessels through several mechanisms, including inhibiting phosphodiesterase (PDE) and decreasing calcium influx or inhibiting release of intracellularly stored calcium [2]. However, papaverine is not recommended for systemic use. The major concern of the topical use of papaverine is its acidic nature, which may damage endothelial function. Indeed, the pH is 4.4 at 2.5 mmol/L and pH 4.8 at 30 μmol/L for papaverine solution [5, 6]. A common clinical protocol to topically use papaverine is to mix papaverine with blood (intraluminal 1% papaverine in blood), which may reduce its acidity owing to the buffering effect of blood. In addition, the onset of the vasodilation effect of papaverine is slower than with other vasodilators [5, 6]. Papaverine was also shown to be inferior to nitroglycerin (NTG) in the gastroepiploic artery (GEA) [7].

Nitrovasodilators

Organic nitrates (nitrovasodilators) such as NTG, namely, glyceryl trinitrate, sodium nitroprusside (SNP), or isosorbide dinitrate are widely used in CABG patients. They release nitric oxide (NO), a powerful stimulant for guanylate cyclase that raises cyclic guanosine monophosphate (cGMP) in the smooth muscle cell [8], subsequently reduces intracellular calcium concentrations, and leads to relaxation.

Nitrovasodilators (NTG or SNP) have been demonstrated to be potent vasodilators in the human

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Abbreviations and Acronyms

ATP = adenosine triphosphate
CABG = coronary artery bypass grafting surgery
cAMP = cyclic adenosine monophosphate
cGMP = cyclic guanosine monophosphate
ET = endothelin-1
GEA = gastroepiploic artery
IMA = internal mammary artery
KCO = potassium-channel openers
NO = nitric oxide
NTG = nitroglycerin
PDE = phosphodiesterase
RA = radial artery
SNP = sodium nitroprusside
TXA_2 = thromboxane A_2

IMA [5, 9–18], radial artery (RA) [5, 12–14, 17–19], GEA [7], and inferior epigastric artery [20]. It was demonstrated that NTG is effective for either topical [7, 13] or systemic [13, 14, 17] use. Nitrates are slightly more effective in blocking receptor-operated channels than blocking depolarizing agent-mediated contraction [9]. Early studies focusing on NTG and nitroprusside showed different effects of these drugs in vitro and in vivo [16].

In general, nitrates are effective in treating established vascular spasm, regardless of the nature of the contraction [9], but less potent in prevention of vasospasm [9, 10, 19]. That is probably related to the tolerance of a vessel to these nitrovasodilators [8, 9, 21], as it was demonstrated later that mitochondrial aldehyde dehydrogenase plays a role in the mechanism of the development of tolerance to nitroglycerin [21]. Compared with each other, NTG is more potent than SNP in the vasorelaxing effect, but SNP is more effective in preventing angiotensin II and α-adrenoceptor–mediated contraction in the IMA [22].

Calcium Antagonists

Classical calcium antagonists were three chemically divergent groups: dihydropyridine (eg, nifedipine), phenylalkylamines (eg, verapamil), and benzothiazepines (eg, diltiazem). The new generations of these drugs, particularly the new dihydropyridines such as nicardipine [23, 24], amlodipine [25], and cilnidipine [26], have been developed in the past decades, and they all express vasodilatory effect in arterial grafts. In addition to the calcium-channel blocking, some of these new generations of calcium antagonists such as amlodipine [25] and cilnidipine [26] may also stimulate the vascular endothelium to release NO, which may further enhance the vasorelaxant effect in arterial grafts. It is possible that these new vasodilators may prove to be useful in the prevention of spasm in arterial grafts.

Calcium antagonists have been used as antispastic drugs in arterial grafting either alone [27] or in combination with NTG [5, 6, 28]. Diltiazem contributed to the successful revival of the RA after this graft was abandoned for almost 20 years because of serious spasm problems [27], although diltiazem is 15-fold less potent than nifedipine in IMA [9] and has little effect on human RA contractions [19, 29]. Further, verapamil is more potent than diltiazem in human vessels [16] and is available in injection form; therefore, it was recommended to be included in the antispastic protocols [5, 6]. Calcium antagonists relax blood vessels through reduction of Ca^{2+} influx by blocking voltage-operated (L-type) calcium channels, which is the major mechanism for the depolarizing agent K^+ to contract vessels, and are particularly effective in preventing or treating K^+-induced contraction in either IMA [9] or RA [19, 29]. However, calcium antagonists such as nifedipine are less effective in contraction mediated by receptors such as thromboxane A_2 (TXA_2) receptors [9], α-adrenoceptors [30], endothelin-1 (ET) [31], or vasopressin (VP1 receptors) mediated contraction.

As to the systemic use of calcium antagonists, diltiazem [27] or verapamil [5, 6] was recommended in RA grafting for at least 6 months. More recently, owing to advanced surgical technique, it does not seem to be necessary, but the definitive role of the systemic use of calcium antagonists postoperatively on the long-term patency needs to be further investigated.

Phosphodiesterase Inhibitors

As modulators of vascular smooth muscle tone, intracellular cyclic adenosine monophosphate (cAMP) and cGMP are controlled through synthesis by cyclases and through hydrolysis by PDEs that are classified into at least five types. The PDEIII inhibitors such as amrinone or milrinone are known to inhibit cGMP–inhibitable low Km cAMP PDE [32]. The effect of the PDEIII inhibitor milrinone on the IMA [11, 33] or RA [34] and PDEIIIA inhibitor olprinone on the GEA and RA [35] have been shown effective, and it is noted that the effect of milrinone on the IMA is superior to that on the RA. In systemic use, after cardiopulmonary bypass, perioperative continuous infusion of milrinone, compared with nifedipine, results in a significantly lower incidence of myocardial ischemia and myocardial cell damage [36].

Alpha-Adrenoceptor Antagonists

Both IMA [37] and RA [38, 39] are α1-adrenoceptor–predominant artery. However, the IMA has little α2-adrenoceptor function [37] whereas the RA has significant α2-adrenoceptor function [38], although the RA is also α1-adrenoceptor predominant. That is the rationale for using α-adrenoceptor antagonists such as phenoxybenzamine as antispastic drugs in CABG as an effective agent to prevent catecholamine-mediated spasm of the RA [39, 40]; and it was reported that phenoxybenzamine is more effective and less harmful to the endothelium than papaverine in the prevention of RA vasospasm [41, 42]. Conversely, however, theoretically, α-adrenoceptor antagonists are only effective in reversing the contraction evoked by the α-adrenoceptor, implying that α-adrenoceptor antagonists may only be effective in one specific mechanism of spasm and could be insufficient when the spasm is related to other mechanisms, for example, due to other receptor mechanisms or due to the mechanism related to the L-type calcium channel. The