Calcium-Channel Blockers in Patients with Radial Artery Grafts.

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Abstract

The use of radial artery (RA) grafts for coronary bypass surgery has recently gained newer attention since it has been associated with significant reduction in the risk of midterm cardiac events. Surprisingly the use on the RA graft as second 'best' conduit has been limited among the surgical community. There may be several explanations for the little popularity of the RA graft; one of the reasons that could prevent surgeons to include the RA in the daily surgical armamentarium it is that patients with RA grafts may require postoperative calcium-channel blocker (CB) therapy. Due to the thick muscular wall, it seems possible that the RA would needs CB in order to prevent spasm and ameliorate patency. CBs are, however, associated with important side effects; also they have hypotensive effect that can hamper the use of other therapy such as beta-blocker or angiotensin-converting enzyme inhibitors. The evidence supporting the use of CB after RA graft (either in the early phase or as chronic calcium-blocker (CCB)) is weak. A the post-hoc analysis from the 'RADIAL' (Radial Artery Database International ALliance), showed that in patients with RA, the use of CB for at least 12 months was associated with better clinical and angiographic outcomes at mid-term follow-up, but confounders and bias may be responsible for the reported findings (as healthier patients are more likely to tolerate CB) . This review aims to summarize current evidences available on the topic and to serve as benchmark for evidence-based decision-making for CB prescription after RA grafting.

Introduction

The first use of the RA as conduit for coronary artery bypass grafting is dated back in 1973 when Carpentier and colleagues published a case series of 30 patients[1]; the authors explored the RA potential due to the larger diameter, ease of dissection and generally more suitability for suturing. Ten months after the operation all the graft were opened, however they warned against early optimism because it needed to be 'ascertained whether the arterial conduits were threatened by the same modifications as those observed in the venous grafts'[2]. Later on, in fact, the authors advised RA use to be discontinued because of a 30% incidence of graft occlusion.

Shortly after, other Authors also reported high rates of spasm and early occlusion and eventually the RA was abandoned for some times[3].

Out of serendipity, almost 20 years later, a patient in whom postoperative angiography showed total occlusion was restudied and surprisingly the RA was fully patent, most importantly, with no evidences of atherosclerotic disease. Three other patients were re-studied, with similar angiographic results. These findings attracted newer attention of the potential use of RA as alternative graft for coronary surgery. Hence, Carpentier restarted the RA use, this time using CB, during and after the operation[2] and in 1992, published a paper titled: 'Revival of the radial artery for coronary artery bypass grafting', where significant improved patency was reported[4].

It was suggested that the 'key' for preserving RA patency perhaps was the use of CB since the very early start of the harvesting and the prescription as chronic antispastic agents. The concern of spasm with the RA

use is indeed related to its unique histologic structures that significantly differ from all the other conduits routinely used for CABG.

The anatomy and morphology of the radial artery

Arteries can be classified into three types: a) type 1: 'somatic' b) type 2: 'splanchnic' c) type 3: 'limb arteries'[5, 6]. The RA is an example of type 3 artery. As the other arteries, the RA has three layer of tunica. The tunica intima is a thin layer with a prominent internal elastic membrane. The tunica media contains myocytes, connective tissue and elastic fibers. The tunica adventitia is very prominent and mainly consists of collagen and elastic fibers, fibroblast and clusters of smooth muscle cells. Notably, there are also adventitial sympathetic and parasympathetic nerves that might be involved in arterial spasm.

The RA is also defined as 'muscular artery' given the abundant myocytes in the media layer [7]. The more muscular media compared to the left internal mammary artery (LIMA) is the theoretical background for the described concerns of RA spasm[8]. Chester et al. demonstrated that there are more muscle cells in the proximal RA vessel compared to the distal RA, as well as variation in the profile of adrenoceptors along the RA vessel[9].

Notably, the RA vasa vasorum do not penetrate into the media and nutrients and oxygen are provided by luminal diffusion; this may suggest that its use as free graft should not be subjected to ischemic events over the long term. However that was challenged by other studies. van Son and colleagues measured a mean width in the media of the RA approximately 500 μm, as opposed to 330 μm for that of the LIMA, 280 μm for that of the gastroepiploic artery and 240 μm for the inferior epigastric artery[10]. These authors suggested that the RA thick media layer can be prone to fibrosis by the time, given the low oxygen penetration at this level[10].

Local factors and systemic hormones can modulate RA vasoconstriction acting at the level of the receptors in the vascular smooth cells. The RA endothelium is pivotal in regulating smooth muscle activity[5]. Vasodilation in fact can be achieved by the release of endothelium derived nitric oxide, prostaglandin and prostacyclin. Endothelin -1, thromboxane A2 and prostaglandin 2a are among the most potent vasoconstrictors. In terms of systemic hormones, angiotensin II and arginine vasopressin are both potent vasoconstrictor even at low concentration acting by opening calcium channels and via the α1-adrenergic receptor[5].

Remarkably, there is also evidence of cross-talk between signaling pathway that mediate vascular contraction and those that are involved with muscle cell growth; RA vessel contraction and spasm can be an important step in the activation of growth-promoting pathways[11].

There are some concerns with regard to pre-existing disease in the radial artery; analysis from histological specimens from 177 radial arteries showed increased prevalence of intimal thickening, medial sclerosis and calcification in the radial artery compared to other conduits[12].

In summary, the functional and morphological anatomy of the RA is very complex and the way it reacts to internal or external stimuli remains, also, not fully understood. There are a number of mechanisms that can be responsible for vasodilation and vasoconstriction; thereby, it is unlikely that a single agent could completely eliminate RA spasm.

Best evidence topics (BETs) supporting the use of CB after RA graft

There are few randomized controlled trials (RCT) and some comparative studies that investigated the early and chronic role of CB after RA grafting (Table 1). However, given the high patency rate of the RA grafts, it is possible that all the published studies were largely underpowered to detect even moderate differences in outcome.

In Broadman et al. study[13], sixty patients underwent post operative angiography between 1 day and 40 weeks; of these 28 were on CB. Patency rate of the radial arteries was 95.7% and there was no association with CB usage.

Acar et al.[3] followed up 50 patients. At long-term follow-up angiography (5-7 years) there were no differences in terms of graft failure among patients on CB treatment (N=27) versus the one who had not CB (N=23).

Possati et al[14] followed up 90 patients with RA. All patients received diltiazem for a year postoperatively and 51 patients stopped the medication during the follow-up. There was no difference in graft patency between patients who continued or suspended CB. The same group reported similar results in 2003[15]. Similarly, Arena et al. did not find differences in terms of graft patency in patients with or without 6-months CB therapy[16].

Shapira et al.[17] randomized 161 patients to postoperative diltiazem or nitrates; key in-hospital and follow-up clinical end points such as mortality, major morbidity, myocardial infarction, use of inotropic agents and need for cardiac catheterization, and reintervention were similar between the two groups.

A 2001 RCT from Gaudino et al.[18] assigned 57 and 63 patients to early regimen (1 year) and to chronic regimen CB respectively. After 5 years, patients were reassessed clinically and by stress myocardial scintigraphy; 87 of them were re-studied angiographically. They found no differences regarding either the clinical and scintigraphic results or the RA angiographic status. They concluded that after the first post-operative year the continuation of CB did not affect RA graft patency or clinical and scintigraphic results.

In 2005, the same author randomized 53 and 47 patients to receive and to no receive CCB immediately after RA grafting[19]. At 1-year follow-up all patients were reassessed clinically and scintigraphically; 83 of them were re-studied angiographically. Again, no differences in terms of clinical outcome, scintigraphic result and patency rate was found between groups.

Gaudino et al. in fact questioned the chronic use of CB since they demonstrated that 1 year after implantation in the coronary artery circulation, the RA tends to lose the muscular component, becoming similar to the LIMA[20].

Moran et al.[21] followed-up 63 and 52 patients after RA grafting with and without CB respectively. Coronary angiographies were obtained at 1-year in 50 patients. No differences were observed for clinical and angiographic end points in the patients that received CB compared with those who had not.

Cameron et al.[22] performed angiogram 5 years post RA grafting in 50 patients; 37 of these patients received CB. The patency rate was high (89%) and no correlation with CCB usage was found.

A post-hoc analysis of the Radial Artery Patency Study[23] found that among 440 RA patients, the incidence of RA spasm was not associated with the compliance with the prescribed postoperative CB, although compliance with CB use was high (419 of 440 patients).

Finally, a post-hoc analysis of the Radial Artery Database International ALliance analyzed[24] patient-level database included 732 patients (502 on CCB). At median follow-up of 55 months, CCB therapy of at least 1 year was found to be associated with significantly lower risk of MACE and RA graft occlusion.

Nevertheless, despite the lack of definitive evidences, the use of CB after RA grafting is considered 'routine' in many centers. A 2003 survey of Canadians cardiac units showed that the vast majority of the surgeons and physicians prescribed CB or other forms of anti-spastic therapy after RA grafting[25].

Table 1. Best evidences Topics (BETs): 'Calcium-channel use after RA grafting'.

Study, Year	Study type	Calcium Channel Blocker	Groups	Follow-up	Conclusion
Broadman et al. Sample size=60 1996[13]	Case control	Diltiazem 240 mg daily	a) N=28 with CB b) N=28 no CB	Mean 3-months	No difference in terms of patency rate between the two groups

Acar et al[3] Sample size=50 1998	Case control	Diltiazem 250 mg daily	a) N=27 with CB b) N=23 no CB	4/7-years	No differences in terms of graft failure
Possati et al.[14] Sample size=68 1998	Case-control	Diltiazem 120 mg twice a day	After the 1 year those without scintigraphic or angiographic evidence of RA territory ischemia assigned to: a) N=29 continued CB b) N=31 suspended CB	5-years	No differences in RA graft status could be shown between groups who continued or suspended therapy with calcium channel blockers after 1 year.
Arena et al Sample size=50 2000[16]	RCT	Nifedipine 40 daily for 6 months post-op	a) N=26 with CB b) N=24 no CB	16-24 months	No difference in terms of patency rate between the two groups
Shapira et al.[17] Sample size=161 2000	RCT	Diltiazem and GTN	a) N=77 patients with diltiazem infusion for 24 h and daily for 6 months thereafter n=77 b) N= 84 patients with GTN infusion for 24 h and daily nitrate therapy for 6 months thereafter.	6-months	Major in-hospital and follow-up clinical end points (mortality, major morbidity, myocardial infarction, use of inotropic agents, the need for cardiac catheterization, and reintervention) similar between the study groups
Gaudino et al. [18] Sample size=120 2001	RCT	Diltiazem 120 mg/day	a) N=57 patients suspended CB after 1 year b) N=63 patients with chronic CB use	5 -year	No difference in graft patency, graft reactivity, myocardial ischemia or clinical outcomes
Moran et al.[21] Sample size=115 2001	Case-control	Diltiazem 1 μg/kg/min intraoperatively then 180 mg/day for 1 year	a) N=63 patients with CB b) N=52 patients with no CB	1-year	The degree of the native coronary artery stenosis influenced the patency rate of RA, independent of the CB

Possati et al.[15] Sample size=90 2003	Case-control	Diltiazem 120 mg daily	After 1 year, a) N=51 patients stopped CB b) N=49 patients on CB	105±9 months	No differences in graft patency between two groups
Cameron et al.[22] Sample size=50 2004	Case-control	Diltiazem / amlodipine / verapamil /nifedipine	a) N=37 with CB b) N=23 no CB	5-years	No correlation found between CB usage and angiographic patency
Gaudino et al.[19] Sample size=100 2005	RCT	Diltiazem 120 mg daily	a) N=53 patients with CB early regimen b) N=47 patients with no CB	1-year	No difference graft patency / reactivity / ischemia
Radial Artery Patency Study[23] Sample size=440 2006	RCT Post-hoc analysis	Nifedipine for 6 months post-op	a) N=419 patients with compliance to CB b) N=21 patients with no compliance to CB	1-year	The incidence of string sign (RA spasm) was not affected by the compliance with the prescribed CB.
Radial Artery Database International ALliance[24] Sample size=732 2019	RCT Post-hoc analysis	Diltiazem / amlodipine	a) N=502 patients with CB B) N=230 patients with no CB	Median angiographic follow-up 55 months	CB therapy was found to be consistently associated with a significant lower risk of MACE and RA graft occlusion
CB: Calcium-channel blocker. MACE: Major adverse cardiac events. RCT: randomized controlled trial.	CB: Calcium-channel blocker. MACE: Major adverse cardiac events. RCT: randomized controlled trial.	CB: Calcium-channel blocker. MACE: Major adverse cardiac events. RCT: randomized controlled trial.	CB: Calcium-channel blocker. MACE: Major adverse cardiac events. RCT: randomized controlled trial.	CB: Calcium-channel blocker. MACE: Major adverse cardiac events. RCT: randomized controlled trial.	CB: Calcium-channel blocker. MACE: Major adverse cardiac events. RCT: randomized controlled trial.

Choice of calcium-channels blockers after RA grafting and side effect

There is a wide range of CB; however, there are three main chemically divergent groups: dihydropyridines (eg, nifedipine, amlodipine, nicardipine, clevidipine and nicorandil), phenylalkylamines (eg, verapamil), and benzothiazepines (eg, diltiazem)[26].

The choice of CB to prevent RA spasm has been empirical.

At least theoretically, all CB derivatives can be used to prevent RA graft spasm; nevertheless it has been demonstrated that dihydropyridine are the most potent vasodilator[27]. However, the vast majority of the studies published in literature used diltiazem as antispasmodic agent (table 1).

He and colleagues in a in-vitro study found that nifedipine was 19.5-fold more potent than verapamil and 31.6-fold more potent than diltiazem in RA precontracted with potassium; also, its efficacy on prevention of RA spasm was shown by the observation that at the usual plasma concentration, nifedipine significantly reduced RA contraction, whereas neither verapamil nor diltiazem had any effect on the RA contraction at equal concentration[26].

Diltiazem may have significant negative chronotropic and inotropic effects. Its early use can increase the requirement for temporary cardiac pacing in the post-operative period.

Amlodipine is a more selective CB, thereby with less effect on the myocardium.

However, Kloner et al.[28] reported that in patients with amlodipine, edema occurred in 24%, headache in 8.8% and in fatigue and dizziness in >4%.

Notably, the potential hypotensive effect of the CB may preclude the use of other secondary prevention therapies such as beta-blockers or angiotensin-converting enzyme inhibitors.

Polypharmacy is also an important concern and has been associated with increased risk of cardiac events[29].

Key factors influencing the RA patency

Besides the CB prescription, whose utility is still under investigation, there are other factors that might influence RA graft patency or at least 'interact' with the CB in order to contribute to RA longevity[30]. Briefly, those are:

a) appropriate coronary target selection b) meticulous and scrupulous harvesting technique (either open or endoscopic) and a c) a general 'no touch technique', avoiding hyperinflation of the conduits that can lead to potential for damage of the RA intima and internal elastic lamina.

With regard to target selection, rather than the location of the target vessel it seem far more important to consider the severity of the coronary stenosis; the reversal of one case of string sign concomitant with the progression of the coronary stenosis, although anecdotal, further underscore the influence of native, competitive flow on RA graft[15]. Royse and colleagues[31]defined 70% coronary stenosis as the 'cut-off' point; below this degree of stenosis the long-term patency of the RA was found to be significantly reduced. Desai and colleagues recommended the use of RA graft only for severely stenotic vessel (>90%)[32].

The most common adopted vasodilators for intraoperative dilatation during RA harvesting are CB, papaverine, nitrates and phenoxybenzamine, without clear evidence of superiority of one of them[33]. To date, no significant advantages related to skeletonizaton of the conduit, endoscopic harvesting, or utilization of the harmonic scalpel during surgical harvesting have been reported[33]; yet it seem advisable during graft preparation, to avoid hyperinflation and distension of the conduit since would result in damage of the endothelium and the elastic laminae.

Conclusions

Recent studies have demonstrated superior performance of RA as second conduit for CABG[34]. Nevertheless, it remains unclear whether its patency rate is related to correct indications (e.g. critical coronary artery stenosis), less invasive and/or no-touch harvesting techniques or to the use of antispasmodic drugs.

There are some evidences that support the use CB to ameliorate RA patency[24], however given the lack of large randomized trials on the specific topic (CCB versus no-CCB), final conclusions and recommendations cannot be drawn.

Importantly, the side effects of CB grafting are not negligible and should be taken into account in clinical decision-making.

Finally, understanding the triggers and mechanisms that regulate RA vessel tone and its response to endogenous and exogenous stimulation is pivotal in optimizing RA use as bypass conduit.

Abbreviations

CABG= Coronary artery bypass grafting

CB= Calcium-channel blocker

CCB= Chronic calcium-channel blocker

LIMA= Left internal mammary artery

RA= Radial artery

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