Radial Artery Grafts' String-Sign – Role of Graft Spasm and Competitive Flow.

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ABSTRACT

Introduction: Radial artery graft is prone to vasospasm and a small proportion developed string-sign. We investigated the role of vasospasm and competitive flow in radial artery graft string-sign. **Materials & Methods:** From May 1998 to April 1999, 101 patients (mean age of 59.5 ± 7.1 yr) recruited to the RSVP trial, underwent coronary angiography at 3.7 ± 1.1 months after CABG. **Result:** A total of 193 grafts (71 radial artery grafts; 122 saphenous vein grafts) were screened. All radial artery grafts were patent, compared with 96% of saphenous vein grafts. Five saphenous vein grafts (4%) were totally occluded and another 1.6% had anastomotic narrowing. Five radial artery grafts (7%) had diffuse string-sign and another 4 (6%) had anastomotic narrowing. Radial artery graft with string-sign had a mean diameter of 1.14 ± 0.25 mm. All responded to nitrate infusion significantly with a mean diameter of 1.38 ± 0.34 mm ($p=0.04$). These diameter changes were still significantly smaller than the mean diameter of normal radial artery grafts ($p<0.0001$). Retrospective analyses of preoperative angiograms confirmed presence of non-significant stenosis (<70%) in 3 patients. **Conclusion:** Our findings indicated that competitive flow and diffuse graft vasospasm may contribute to the pathogenesis of radial artery graft string-sign.

Keywords: **Radial artery, string-sign, competitive flow, vasospasm**

INTRODUCTION

The term 'String-sign' was first used to describe diffuse narrowing of internal thoracic artery grafts (ITAG) to the left anterior descending (LAD) coronary arteries, with a reported incidences ranging from 2-11%.[1, 2]

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ported incidences ranging from 2-11%.[1, 2] It has since been reported in other arterial conduits used for coronary bypass surgery such as right gastroepiploiac artery (RGEA), inferior epigastric artery (IEA) and more recently in the radial artery grafts (RAG).[3-5] Reported incidence of this phenomenon in RAG ranges from 7-10%. [6]

Various explanations have been put forward for the cause of arterial grafts 'string-sign' such as damage during harvesting by electrocautery, inflammation in postcardiotomy syndrome or a steal phenomenon by larger branches of the ITAG but the most plausible of this is competitive flow from a non-significantly stenosed native coronary artery. [(7)] The underlying mechanism is also uncertain but has been thought to be associated with diffuse graft spasm resulting from reduced flow state secondary to competitive flow from the native coronary artery. [(7)] We assessed the significance of competitive flow by examining preoperative and post-operative angiograms in patients proven to have RAG 'string-sign' and tested the hypothesis that if the primary cause of 'string-sign' is indeed of diffuse graft spasm, then infusion of nitrates directly into the grafts during angiography should relieved the spasm and re-established complete patency and flow.

Materials and Methods

Patient population.

From May 1998 to April 1999, 142 patients undergoing myocardial revascularisation surgery at the Royal Brompton Hospital were recruited into our prospective randomized Radial artery versus Saphenous Vein Patency (RSVP) trial to compare angiographic patency rates of RAG with saphenous vein graft (SVG). [8] Ethics approvals were obtained from the Royal Brompton Hospital Ethics Committee. Written informed consent was obtained from all patients preoperatively. Study design of the RSVP trial has previously been described. [8] In brief, patients recruited were pre-operatively randomised to receiving either a RAG or SVG to the circumflex (Cx) artery. The internal thoracic artery (ITA) was grafted onto the LAD and all other territories (right coronary artery (RCA) and Diagonal (D)) were grafted using SVG or RAG if it was not randomised to the Cx artery, according to the surgeon's discretion. Early graft patency and physiological graft flow response data at 3 months after surgery, from the first consecutive 100 patients have recently been published. [8]

Surgical Technique

RA was harvested as described by Reyes et al at the same time as the ITA and long saphenous vein (LSV) using conventional sharp dissections and ligaclips. [9] Both conduits were distended gently with heparinised whole blood (HWB) to physiological pressure (<200 mmHg), to check for leaks and to rinse the conduit free of clots. We have previously shown that distension to this physiological pressure does not adversely affect the vasoreactivity of the RA conduit.[8, 10] Both conduits were stored in HWB with Verapamil (1mg Verapamil/10mls HWB) until ready for grafting.

All proximal anastomoses were performed onto the ascending aorta with 6/0 prolene sutures. Distal anastomoses were made to the largest branch of the main circumflex (stenosis >70%), or a suitable intermediate or diagonal if the true circumflex was non dominant, with 7/0 prolene. Post-operatively all patients were started on a course of diltiazem 60mg tds for 6 weeks unless contra-indicated by hypotension or bradycardia.

Follow-up angiogram

Follow-up angiograms were performed in first consecutive 101 patients (99 Male; 2 Female) with a mean age of 59.5 ± 7.1 yr, at a mean of 3.7 ± 1.1 months after surgery to assess early RAG and SVG patency. Patients' demographics of all 101 patients are shown in table 1. There was no statistical significant

difference between the two groups. All cardiac medications and caffeine containing beverages were stopped for 24 hours prior to cardiac catheterisation. Five and 7 ch angiographic catheters and omnipaque contrast medium was used in all cases. Frames acquisition was set at 25F/sec. Heart rate and blood pressure were recorded through out the study.

Ethical approval was obtained from the Royal Brompton Hospital Ethics Committee to screen only grafts to the RCA and Cx (Study graft) arteries excluding the LAD in non-symptomatic patients. A total of 193 grafts, 101 (62 RAG; 39 SVG) grafted to Cx territory and 92 (9 RAG; 83 SVG) to RCA territory, were screened. As part of the protocol for the trial, 300 mg of nitrates were infused through any RAG with string-signs to rule out any graft spasm which may be present.

Primary endpoint was angiographic graft patency of both grafts. Graft diameter and degree of stenosis were assessed using quantitative coronary angiography (QCA, Medis NL) with site specified to proximal or distal anastomoses and body of graft. Analysis was performed by an independent investigator. Mean Diameter from perfectly patent RAG were used for comparison. Severity of preoperative target coronary artery lesions was analysed retrospectively in patients with RAG string-signs to investigate the significance of competitive flow.

Table 1: Patients' Demographics.

	RA (n=62)	LSV (n=39)
Mean Age (yr)	58.7 ± 6.3	59.4 ± 8.2
Sex (M/F)	61/1	38/1
CCS Angina Grading	2.0 ± 0.1	2.2 ± 0.2
NYHA Grading	1.3 ± 0.1	1.5 ± 0.1
Unstable Angina	32.8%	41.0%
Cardiac Risk Factors		
Diabetes	8.2%	20.5%
Hypertension	59.0%	51.3%
Smoking History	78.7%	71.8%
Hypercholesteraemia	77.1%	82.1%
Previous MI	49.2%	59.0%
Operative Details		
Mean Grafts/person	3.3 ± 0.1	3.3 ± 0.1
Mean Bypass Time	97.9 ± 3.0	96.0 ± 3.7
Mean X-Clamp Time	52.6 ± 2.1	50.5 ± 3.1
Post-Operative Data		
Intubation time		
(<3-12 hrs>)	28	17
(<12-24 hrs)	30	17
(>24 hrs)	3	5
ICU Stay (hrs)	23.1 ± 1.9	26.9 ± 3.8
Blood Loss (ml)	907.4 ± 84.8	999.9 ± 153.6
Hospital Stay	6.8 ± 0.4	6.9 ± 0.4

Note: There are no significant differences between the two groups.

Statistics.

Nominal data and patency rates between the two grafts were analysed using Chi square test (Microsoft excel, USA) for proportions. All pre and post-GTN RAG diameters were represented as mean ± SD and changes in diameter were analysed using paired student t-test (Microsoft excel, USA) with significance set at 5%.

Results

All RAG (100%) were patent with no incidence of complete occlusive disease as compared with 96% of SVG (5/122 SVG showed complete occlusion). There was no statistical significant difference between the two groups in terms of early angiographic graft patency. However 13% of RAG showed compromised flow with 6% having more than 75% stenosis in the proximal or distal anastomoses, which did not respond to GTN infusion. Seven percent of RAG (5/71) had diffused narrowing typical of string-sign. Only 87% of RAG were

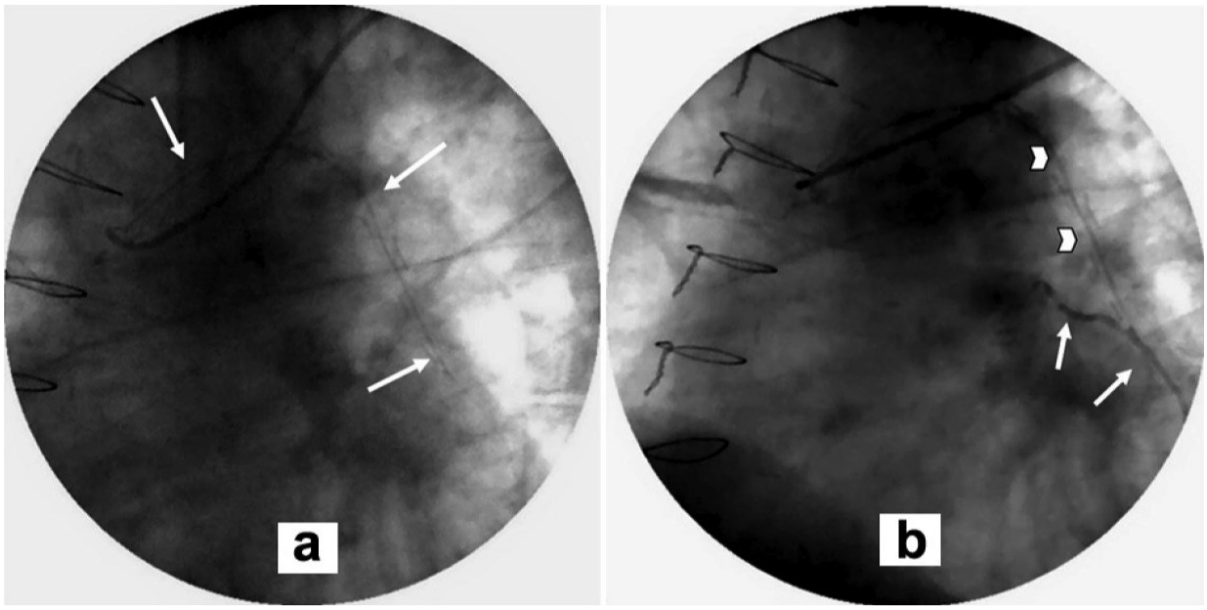

Figure 1: RA Grafts 'String-Sign'. (a) Angiographic frame showing RA graft string-sign at early angiography with minimal contrast in the native coronary artery (white arrows). Retrospective analysis of preoperative angiogram confirmed non-significant stenosis in target coronary artery. (Figure 2). (b) Post GTN infusion into the graft. There was an increase in contrast delivery into the graft with increase in luminal diameter of the graft (arrow heads) and presence of contrast in the native coronary artery (White arrows).

considered perfectly patent. There were no string-sign observed in any of the vein grafts screened but 1.6% (2/122) had anastomotic narrowing greater than 50% in the distal anastomoses.

Compromised RAG assessments

Five of the 71 RAG screened were found to be diffusely narrowed and classified as 'string-sign' (fig. 1a). Pre-operative angiograms analysis revealed non-significant lesions (<70%) in 3 cases only.

Mean RAG diameter in all 5 patients with 'string-sign' were 1.14 ± 0.25 mm (95% CI: 0.84 mm, 1.45 mm). Post nitrate infusion, the mean RAG diameter increased significantly to 1.38 ± 0.34 mm (95% CI: 0.96 mm, 1.80 mm, p=0.04), as shown in figure 1b. Dilatation to nitrate infusion in all 5 grafts ranges from 3.8% to 62.4%. Pre and post nitrate mean diameters of all 5 RAG with 'string-sign' were significantly smaller than normal mean RAG diameter 2.2 ± 0.5 mm (95% CI: 2.04mm, 2.45 mm, p<0.0001). Thus all 5 RAG with string-sign failed to achieve full dilatation despite nitrates infusion. All patients were asymptomatic at time of graft angiography.

Only 1 patient agreed for reangiography at 1 year which revealed continual presence of the RAG string-sign (Figure 2a) which showed further increased in luminal angiographic diameter with GTN infusion down the graft (Figure 2b).

Discussion

'String-sign' in coronary bypass grafts is an interesting phenomenon and was first described in ITAG. [1] This phenomenon has also been reported in RAG and other arterial grafts. [3-6] The causes or underlying mechanism is still uncertain but there are lots of anecdotal reports implicating competitive flow from native coronary arteries as a possible cause. [1, 7] Evidence for this were mainly from analysis of pre-operative and post-operative angiograms in grafts with string-sign, showing non-significantly stenosed (<75-90%) lesions in the native coronary arteries and the re-establishment of patency and flow several years later with the progression of the native coronary disease. [1, 5]

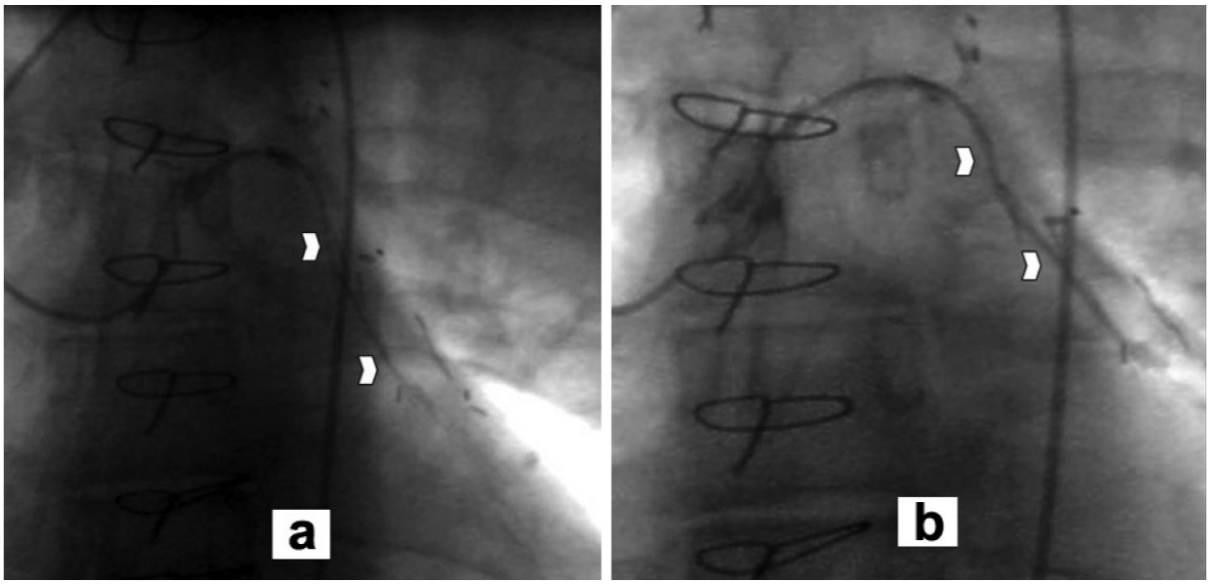

Figure 2: RA Grafts 'String-Sign' at 1 year angiography. (a) Angiographic frame showing the same RA at 1 year angiography which revealed a slight increase in the luminal diameter of the graft (white arrowheads). Again the lesion in the target coronary artery was non-significant. (b) Post GTN infusion into the graft showing an increase in luminal diameter of the graft at 1 year (white arrowheads).

The degree of target coronary stenosis at which string-sign will not occur is also uncertain. This has previously been reported to be in the order of more than 75% but recent multivariate analysis data from Miwa et al have shown a risk of RAG string-sign associated with a stenosis of less than 90%. [6] According to data from Miwa et al, then all 5 patients in our study who developed string-sign had non-significantly stenosed target coronary arteries. Of the 3 patients in our group who had RAG to the Cx artery as part of the RVSP trial, only 2 patients had stenosis that satisfied the RSVP criteria with stenosis of 80-90%. In the remaining patient, the intended target Cx artery was found to be small and the RA was grafted to the intermediate coronary artery, which on retrospective analysis of the preoperative angiogram was found to be non-stenosed (Figure 3). The last 2 patients had RAG to the RCA at the surgeon's discretion as the SVG was randomised to the Cx artery. Both RCA had stenosis which were less than 70% (50% and 70%).

The underlying mechanism proposed for 'string-sign' in RAG was that of persistent diffuse graft spasm possibly due to the increase contractile response to serotonin early after grafting. [11] This early hyper-reactivity to serotonin becomes attenuated with time probably leading to spasm resolution and thus to disappearance of conduit irregularities and even reopening of previously closed grafts. [11]

We have shown here that the 5 RAG with string-sign only partially responded to

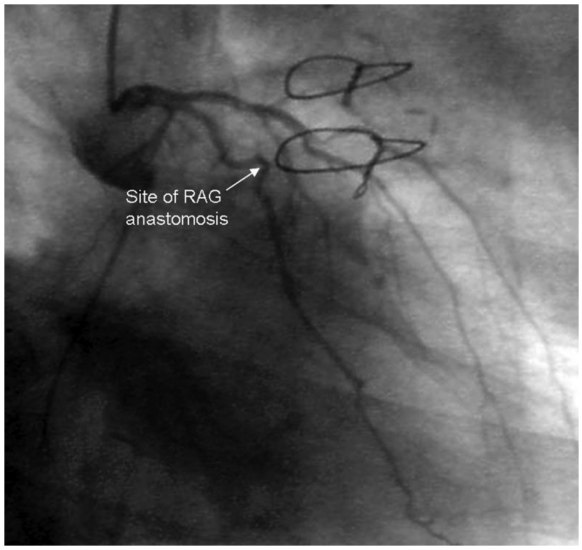

Figure 3: Retrospective analysis of coronary angiogram revealed a non-significantly stenosed target Intermediate coronary artery which account for competitive flow phenomenon leading to RAG string-sign as seen in figure 1.

GTN infusion, although the diameter increase was statistically significant. The failure to fully dilate suggests that diffuse graft vasospasm may play a limited role in RAG string-sign. Likewise, the chronic use of calcium channel blockers such as diltiazem has not been shown to improve RAG patency as was reported by other investigators. [12, 13]

We hypothesize that the phenomenon of arterial graft string-sign is a physiological process rather than one of pathology. Due to competitive flow from the native coronary artery, flow in the graft is reduced. This reduction in graft flow resulted in reduction of flow velocity and wall shear stress which leads to a reduction in synthesis of NO by the endothelium. [14] This ultimately leads to an imbalance between vasorelaxation by NO and vasoconstriction modulated by a host vasoactive substance such as adrenaline, noradrenaline, serotonin, thromboxane A2, endothelin etc. [15] The net effect is an excessive of vasoconstriction leading to diffuse vasospasm in the graft. Thus the reduction in graft luminal diameter may be an adaptive response to a state of low flow through the graft resulting from competitive flow through the native coronary artery. [7] With progression of the native coronary artery stenosis, leading to a reduction of flow through the native coronary artery, the graft flow will steadily increase. Increase flow results in an increase in flow velocity and wall shear stress resulting in increase production of NO and ultimately to reopening of the graft. [14]

However it still remains a clinical controversy whether to graft a RA or any arterial grafts to a coronary vessel with less than 70-90% stenosis. The fact that observation of ITAG and RAG which were compromised by 'string-sign' at early angiography and later found to be patent when flow through the native coronary arteries were reduced as the proximal coronary lesions progressed to significant or critical degree, implies that such grafts are not occluded but merely in a quiescence state like natural arterial collaterals. [1] Furthermore, all our patients with RAG string-sign were asymptomatic and did not complain of any angina at follow-up. Therefore, we may view RAG with string-sign as sleeping or dormant grafts.

Conclusions

The presence of competitive flow from the native coronary arteries which are non-significantly stenosed, combined with some degree of diffuse graft vasospasm may play a vital role in the pathogenesis RAG 'string-sign'. However, the degree at which a stenosis becomes significant varies considerably and has been suggested by recent multivariate analysis to be more than 90%. Although we believed that RAG string-sign are a physiological state of low flow rather than a diseased state, based on current evidence, we would still suggest grafting RA to a target coronary artery with stenosis greater than 90%.

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