Editorial Commentary

Has the surgeon's nightmare of graft spasm been solved?

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Arterial grafts have long-term patency superior to that of vein grafts but have may develop spasms that can lead to potentially life-threatening complications. The internal thoracic artery (ITA) transplanted into the coronary artery system can function not only as a non-diseased living conduit (1) but also as a source of favorable metabolic substances that protect the coronary artery from atherosclerotic progression. Grafts of the radial artery and gastric aorta are more prone to spasm than grafts of the ITA (2). Further, the endothelial function of saphenous vein bypass grafts decreases with age. Thus, age should be a factor when considering graft maintenance (3). In 1998, Nishioka *et al.* (4) provided the first evidence of significantly higher nitric oxide secretion by the ITA graft compared with by the saphenous vein graft in late postoperative coronary artery bypass grafting (CABG) surgery patients by measuring nitric oxide metabolites in the blood at the distal end of the graft in response to acetylcholine stimulation. Kitamura *et al.* also published reports on the patency of the ITA (5,6). Thus, the ITA is more resistant to vasospastic reactions and less spasmodic than coronary arteries or other arterial grafts.

However, ITA spasms can still occur depending on the dissection procedure or the environment after harvesting although rarer than other arterial grafts (2). Although rare, ITA graft spasm has been reported (7); early postoperative spasms were first reported in 1987 (8). Vyas *et al.* (9) reported a 29-year-old man with left ITA spasm in the immediate postoperative period following CABG. The patient was started on nitroglycerin infusion after confirming the diagnosis; however, he continued to experience signs and symptoms of ongoing myocardial infarction correlating with the region of the left ITA graft. The patient subsequently required a second CABG, wherein the left ITA graft to the anterior descending artery was bypassed with a reverse saphenous venous graft, following which the patient's symptoms ultimately subsided (9). As repeat surgery is sometimes necessary in such cases, preventing ITA spasms has been a long-standing issue for surgeons.

Although there have been various reports about antispastic agents (10,11), there is no single vasodilator that can prevent or treat arterial graft spasms from all mechanisms of contraction. The most reliable and optimal effects in contemporary CABG surgery may come from pharmacologic vasodilators that target all of these various mechanisms (12). Vasodilatory agents, including calcium channel blockers, phosphodiesterase inhibitors, papaverine, and nitroglycerin, are used to prevent vasospasm during or after surgical intervention and to increase blood flow (10). Many studies have been conducted on this subject. For example, Takeuchi *et al.* (13) compared the reactivity of the

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left ITA to three drugs—phosphodiesterase III inhibitor, papaverine hydrochloride, and isosorbide dinitrate—and found that a phosphodiesterase III inhibitor was the most effective in increasing the blood flow of left ITA grafts for CABG. In support of the validity of multiple mixtures, as an intraluminal or topical solution for graft preparation, a cocktail of calcium antagonists and nitroglycerin may have a synergistic effect on the ITA (14). Even in a critical situation with lethal spasm, the administration of a combination of nitroglycerin and verapamil via intraluminal injection has been reported to successfully relieve spasm in arterial grafts and is a lifesaving procedure (15).

Although fasudil is originally intended to improve cerebral vasospasm and associated cerebral ischemic symptoms after subarachnoid hemorrhage surgery, it is also effective in preventing acetylcholine-induced myocardial ischemia in patients with angina (16,17). Hypercontraction of the coronary arteries is dependent on intracellular Ca^{2+} concentration (10,11). The intracellular Ca^{2+} concentration increases due to Ca^{2+} release and influx from inside and outside the cell. Then, a complex is formed with calmodulin, and myosin light-chain kinase is activated. Consequently, myosin light-chain kinase is phosphorylated and cross-reacts with actin, which causes vascular smooth muscle to contract. Conversely, Rho kinase is an important molecular switch that regulates vascular smooth muscle contraction and relaxation in a Ca^{2+}-independent manner (18). The Rho kinase inhibitor fasudil hydrochloride hydrate (fasudil) specifically and potently causes remission of coronary spasm (16). Because fasudil and nitrates have completely different mechanisms of action, fasudil has a different vasodilating effect. Fasudil can induce coronary dilatation by additional administration of fasudil after nitrate administration (19). Many case reports cite strong evidence for the usefulness of intracoronary administration of fasudil in patients with multidrug-resistant or refractory coronary spasms (20,21). In addition, fasudil has been objectively demonstrated to be superior to the conventionally used nitrates and nicorandil in the remission of coronary spasms. However, there have been no randomized controlled trials or observational studies to date, that compare them. Along with conventionally used coronary dilators such as nitrates, intracoronary administration of fasudil should be considered as an option for refractory coronary spasms (11). If the cocktail solution of fasudil and nitroglycerin used in this study (22) is able to prevent vasospasm more potently, it would be clinically useful. Nevertheless, as this study was conducted *in vitro* (22), additional patients may benefit from future *in vivo* studies. Furthermore, because the authors used discarded ITA segments (22), this study was not invasive, and the number of study subjects can be easily increased.

We previously reported the benefits of direct injections into the coronary artery for the treatment of coronary artery spasms (23), and we believe that the cocktail of fasudil and nitroglycerin used in this study (22) can be used in coronary artery spasm. If this is clinically applicable for severe ischemic attacks caused by coronary angina pectoris, many more patients can be saved. Reports have indicated that coronary microvascular dysfunction may be related to activation of the Rho kinase pathway, which results in inhibition of vasodilation by reactive oxygen species and nitric oxide, as well as enhancement of vasoconstrictor activity by endothelin-1 (24,25). In patients with epicardial coronary artery spasm and high microcirculatory resistance, Rho kinase inhibition reduced microcirculatory resistance. This result suggested that Rho kinase is involved in the pathogenesis of coronary microvascular dysfunction (11,20,26). Further studies on this topic are warranted.

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