Endothelial dysfunction or anything else?

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Chronic kidney disease (CKD) is commonly defined as an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m² for at least 3 months, with or without kidney damage.¹ According to this definition, the prevalence of CKD is 63 million people in the United States, and it is associated with increased risk of cardiovascular events related to an accelerated atherogenesis in medium and small arteries.^{1,2} In addition to traditional risk factors (hypertension, diabetes mellitus, and dyslipidemia), several uremia-specific risk factors, such as oxidative stress, homocysteinemia, endothelial dysfunction, platelet aggregation, decreased concentration of transforming growth factor β 1, chronic inflammation and vascular calcification, may have an important role in the rapid progression of atherosclerosis inducing coronary artery disease and graft failure.^{3,4}

Intimal hyperplasia, hyalinosis, and smooth muscle cell hypertrophy represent the main pathologic expression of the nephroangiosclerosis.⁵ An increased risk of postoperative mortality and morbidity with decreased eGFR has been previously described among patients undergoing coronary artery bypass grafting.⁶⁻⁹ Cooper and associates⁸ reported that operative mortality rose from 1.8% in patients with mild renal dysfunction (eGFR of 89-60 mL/min/1.73 m²) to 4.3% in patients with moderate renal dysfunction (eGFR of 59-30 mL/min/1.73 m²) and to more than 9% in those with severe dysfunction. Interestingly, in patients with an eGFR less than 30 mL/min/1.73 m², the use of internal thoracic artery (ITA) grafts in patients with CKD not dependent on hemodialysis was seen to be protective against operative death when compared with the use of venous grafts.⁸

ITA is the most important conduit used in coronary artery bypass grafting and is associated with excellent outcomes and long-term patency relative to the saphenous vein graft. The lower tendencies of ITA toward spasm and development of atherosclerosis are explained by the absence of a significant muscular component and the increased production of nitric oxide in basal and stimulated states.¹⁰ Consequently, ITA should be the first

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Central Message

Endothelial dysfunction and other uremia-specific risk factors may have an important role in the rapid progression of atherosclerosis and graft failure.

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revascularization option for patients with CKD.¹¹ Little is known, however, about the patency of arterial grafts in patients with CKD.

In their article in this issue of the *Journal*, Kinoshita and colleagues¹² add evidence that endothelial dysfunction may play a significant role in the progression of arterial graft failure. Specifically, under inhibition of cyclooxygenase with indomethacin, Kinoshita and colleagues¹² found that acetylcholine produced a concentration-dependent relaxation in patients with an eGFR greater than 60 mL/min/1.73 m². This relaxation was less evident in patients with an eGFR between 30 and 60 mL/min/1.73 m², whereas a mild contraction was observed in patients with severe CKD (eGFR <30 mL/min/1.73 m²), suggesting that nitric oxide was not produced by the endothelium. The relaxation was abolished in the presence of nitric oxide synthase inhibitors or endothelium removal, highlighting the importance of the endothelial function in the ITA. Interestingly, the vasodilator response to the sodium nitroprusside was comparable among the 3 levels of renal function.

The report of Kinoshita and colleagues¹² gives us 2 important messages. First, the endothelial function of ITA grafts is always impaired at the time of coronary artery bypass grafting. As consequence, patients with CKD are at higher risk for graft failure than are those with normal renal function. Nevertheless, subanalysis of Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT IV) study revealed no differences in the rates of saphenous

vein or ITA graft failure and repeat revascularization at 1 year in patients with and without CKD, suggesting that preoperative renal dysfunction has less influence on graft outcomes.¹³ This conclusion raises the question of whether CKD is a risk factor for worse outcomes or just the expression of several comorbidities.

Second, the use of vasodilators such as dihydropyridine calcium channel blockers might balance the mild contraction induced by the lack of endothelial function. In this setting, Fan and colleagues¹⁴ have shown that cilnidipine (a dihydropyridine fourth-generation calcium channel blocker) relaxes ITAs through the increase production of nitric oxide by enhancement of endothelial nitric oxide synthase. A dihydropyridine calcium channel blocker therefore might become the standard treatment of patients with CKD undergoing coronary artery bypass grafting surgery.

Despite these considerations, the article of Kinoshita and colleagues¹² presents several biases that might have an impact on the ratio of contraction to relaxation. Specifically, no information is reported regarding the usage of β -blockers as well as calcium channel blockers. Furthermore, the ITA was always harvested in a skeletonized manner, and trauma would potentially be present.

In conclusion, Kinoshita and colleagues¹² have demonstrated that endothelial function of ITA is modified in presence of any stage of CKD. Other uremia-specific risk factors should also be considered, however, as they certainly have an important role in the rapid progression of atherosclerosis and graft failure. In the light of these results, I encourage Kinoshita and colleagues¹² to perform a well-designed study looking at the long term ITA patency, taking into consideration all potential risk factors and biases for adverse outcome.

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