Silent Coronary Ischemia in a Patient With Critical Limb Ischemia: Diagnosis and Management Using Coronary CT-Derived Fractional Flow Reserve (FFR_{CT})

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Abstract: Patients with symptomatic peripheral arterial disease are at high risk of premature cardiovascular death as a result of coronary artery disease. Coronary ischemia may be silent and unsuspected due to lack of chest pain symptoms, and clinical guidelines recommend preoperative cardiac testing only if the results have the potential to alter patient management. A new noninvasive diagnostic test, coronary CT-derived fractional flow reserve (FFR_{CT}), can reliably identify ischemia-producing coronary stenosis and has the potential to alter patient management. This case example outlines the successful management of a patient with critical limb ischemia and femoral pseudoaneurysm who was found to have severe silent coronary ischemia by pre-operative coronary computed tomography angiogram and FFR_{CT} assessment.

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Patients with symptomatic peripheral arterial disease (PAD) are at high risk of cardiovascular death due to coexistent coronary artery disease (CAD).[1] Mortality is particularly high in patients with critical limb ischemia (CLI), with reported mortality rates of 20% within 6 months of diagnosis and greater than 50% at 5 years.[2-3] Patients with PAD have reduced exercise capacity and often have no symptoms of anginal chest pain to prompt cardiac diagnostic testing. Although it is well known that patients undergoing surgical or interventional treatments for PAD are at increased risk of postoperative myocardial infarction and death, preoperative cardiac testing is recommended only if results have the potential to alter the treatment plan.[4] Thus, the extent of functionally significant CAD in patients without cardiac symptoms who undergo treatment for PAD is largely unknown, leaving them at risk for early and late cardiovascular death.

A newly introduced noninvasive diagnostic modality, coronary CT angiography (CTA)-derived fractional flow reserve (FFR_{CT}), provides a unified anatomic and functional assessment of coronary artery disease, which can reliably identify ischemia-producing coronary lesions.[5] It accurately reflects invasively measured fractional flow reserve (FFR)[6] and can help to guide patient management decisions.[7-9] Coronary CTA and FFR_{CT} analysis is now being used in the United States, Europe, Canada, and Japan to evaluate patients with stable chest pain and to select patients with evidence of coronary ischemia for invasive coronary angiography and coronary revascularization.

The first report of the use of coronary CTA and FFR_{CT} for preoperative assessment of patients with PAD revealed a high

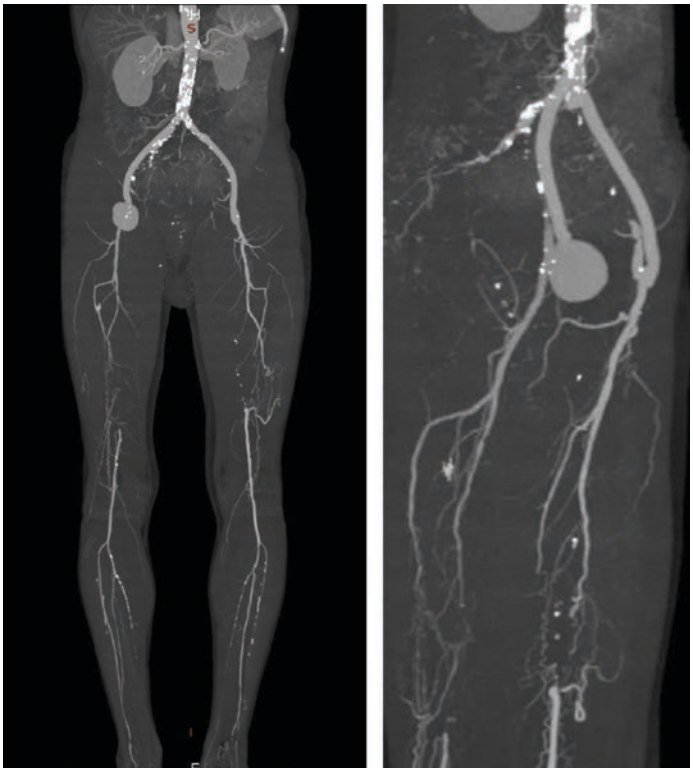

Figure 1. Case example of a patient with critical limb ischemia and right femoral pseudoaneurysm after multiple revascularizations seen on computed tomography angiography images.

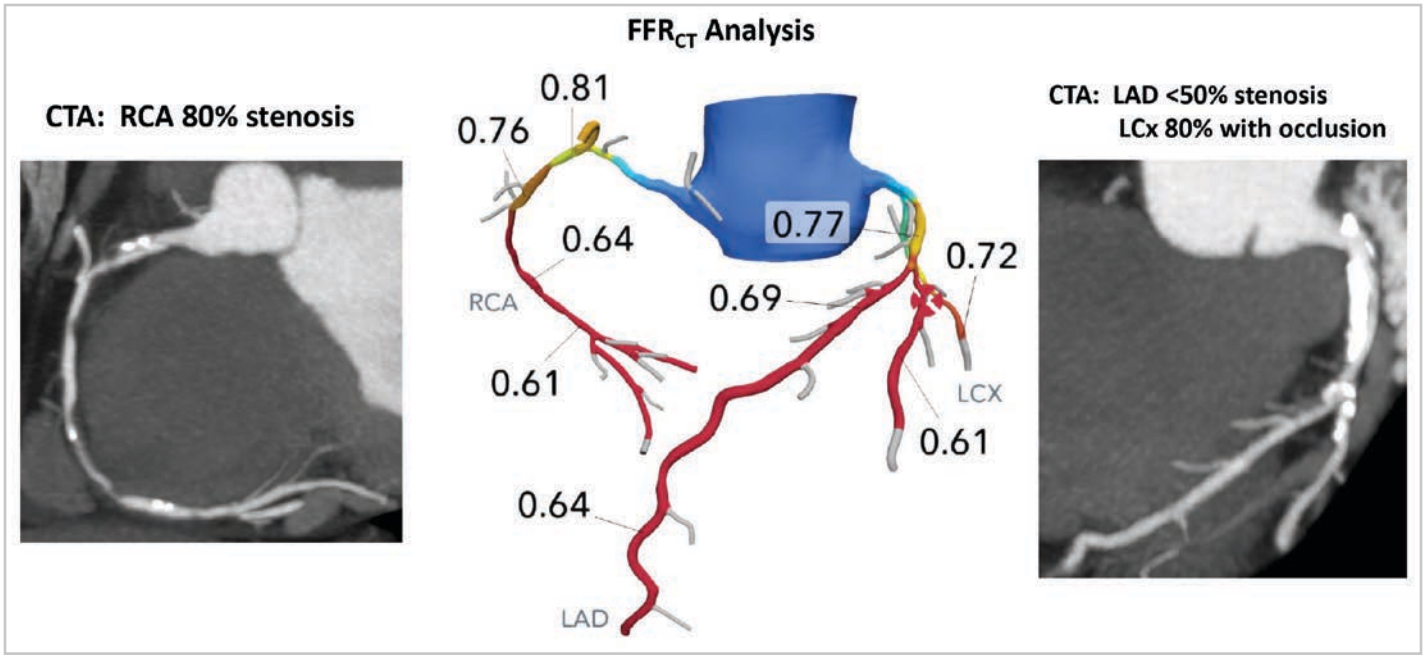

Figure 2. Coronary computed tomography angiography (CTA) demonstrated 80% right coronary artery (RCA) stenosis, <50% stenosis of the left anterior descending coronary artery (LAD), 75% stenosis of the right coronary artery (RCA) and 80% stenosis of the left circumflex coronary artery (LCx) with distal occlusion with extensive calcification, and the total Agatston score was 1623. FFR$_{CT}$ analysis showed FFR$_{CT}$ in the LAD 0.64, in the RCA O.61 and in the LCx 0.72 with distal occlusion.

prevalence of asymptomatic (silent) coronary ischemia in patients with CLI who were admitted for lower extremity revascularization.[10] Among 54 CLI patients with no cardiac history of symptoms of coronary ischemia, 37 patients (69%) were found to have one or more ischemia-producing coronary stenoses.[10] This was an unexpected finding that highlighted the severity of coronary disease and the need for coronary care of this patient population. This case report outlines the management of a patient with severe combined coronary and peripheral ischemia.

CASE REPORT

A 77-year-old man with a history of smoking, hypertension, and PAD was admitted to the hospital with 3-week history of ischemic rest pain in the right foot and a painful, pulsating mass in the right groin. Past history included a right femoropopliteal saphenous vein bypass for limiting claudication 4 years ago, as well as a left iliofemoral bypass 3 years ago. The patient's femoropopliteal bypass became occluded 2 years ago, at which time a right iliofemoral bypass was performed. The patient had limited exercise tolerance and had no cardiac history, with no chest pain symptoms or shortness of breath. An aortic/peripheral CT angiogram revealed patent iliofemoral bypasses bilaterally, a right femoral pseudoaneurysm, and bilateral superficial femoral artery (SFA) occlusions (**Figure 1**). Right ankle-brachial index (ABI) was 0.48 and left ABI was 0.51. Preoperative assessment in the hospital included routine blood testing and a normal resting electrocardiogram. Preanesthesia evaluation confirmed the absence of cardiac symptoms or significant cardiopulmonary findings with clearance for scheduled vascular surgery. The patient was then invited to participate in a prospective study of anatomic-functional assessment of CAD with CTA-FFR$_{CT}$, signed informed consent, and underwent standard coronary CT angiography with β-blockers for heart rate control and nitroglycerine for coronary dilation. Coronary CTA data were sent for computational analysis to HeartFlow, Inc, Redwood City, California, for FFR$_{CT}$ analysis. Results of both CTA and FFR$_{CT}$ were available to treating physicians prior to the scheduled surgery.

Coronary CTA revealed extensive coronary calcification with Agatston score 1623, <50% stenosis of the left anterior descending coronary artery (LAD), 75% stenosis of the right coronary artery (RCA), and 80% stenosis of the left circumflex coronary artery (LCx) with distal occlusion. FFR$_{CT}$ analysis revealed severe 3-vessel coronary ischemia with computed FFR$_{CT}$ in the LAD 0.64, in the RCA O.61, and in the LCx 0.72 with distal occlusion (**Figure 2**). These results were provided to the treating physicians with guidance on the patient's management provided by the Vascular Team, which consisted of vascular surgery, cardiology, anesthesiology, and cardiac surgery clincians.

In view of the patient's pressing clinical symptoms of peripheral ischemia and symptomatic femoral pseudoaneurysm, the patient underwent vascular surgery as scheduled under spinal anesthesia with β-blockade and close cardiac monitoring. The femoral pseudoaneurysm was resected and femoral endarterectomy and profundaplasty were performed. The patient was stable throughout the procedure, had no cardiac complications, and was relieved of ischemic rest pain. He recovered from surgery uneventfully and was discharged on the 7th postoperative day on antiplatelet medi-

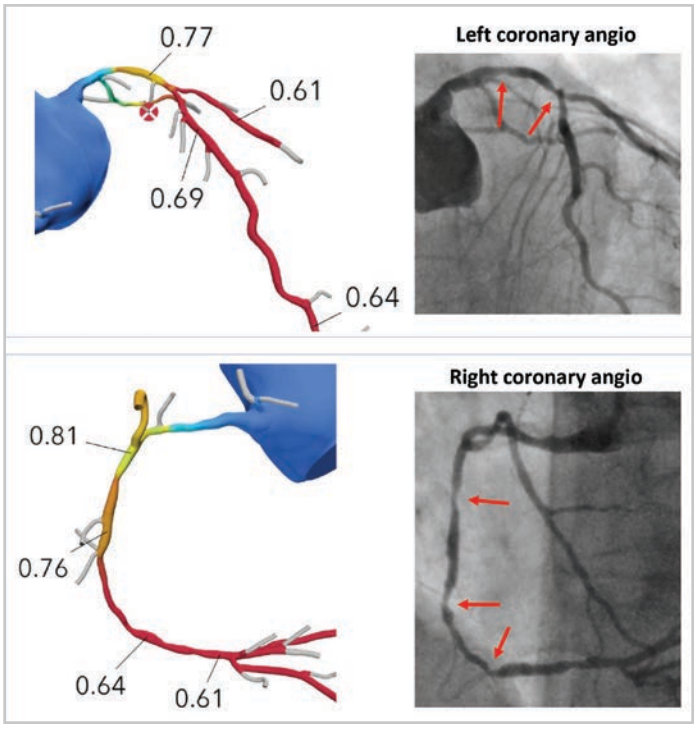

Figure 3. Diagnostic coronary angiography confirmed the presence of left main stenosis, 70% LAD stenosis, 80% RCA stenosis and left circumflex stenosis and occlusion. Red arrows show corresponding to FFR_{CT} blood flow reductions found in angiography.

cation (aspirin and clopidogrel bisulfate), β-blockers, ivabradine, atorvastatin, and antihypertensive medication (Presteram).

Two weeks after the procedure, the patient underwent diagnostic coronary angiography, which confirmed the presence of left main stenosis, 70% LAD stenosis, 80% RCA stenosis, and left circumflex stenosis and occlusion (**Figure 3**). The patient had no symptoms of peripheral ischemia and no symptoms of coronary ischemia. One month later, the patient underwent elective coronary artery bypass with left internal mammary artery to LAD, right internal mammary artery to LCx and saphenous vein bypass to the RCA. The patient had an uneventful postoperative recovery and was continued on optimum medical therapy. One year later, he is free of rest pain, has nonlimiting long-distance claudication, has no chest pain, and feels well.

DISCUSSION

The finding of significant coronary artery disease in this patient comes as no surprise, as it is well known that 50% to 70% of patients undergoing peripheral vascular surgery have evidence of significant CAD by preoperative coronary angiography.[11] Despite the well-known risk of perioperative cardiac complications and reduced long-term survival in patients undergoing vascular surgery,[12] routine preoperative cardiac assessment is not recommended since prospective randomized trials have shown no survival benefit from coronary revascularization.[13] Thus, most peripheral vascular revascularization procedures are performed with specific knowledge regarding the status of coronary artery disease in patients without cardiac symptoms.

What is unique about this case is the unexpected finding of severe, silent coronary ischemia in this patient, requiring limb salvage surgery. This came about as a result of the patient's participation in a prospective clinical study of a new cardiac diagnostic modality, noninvasive fractional flow reserve (FFR_{CT}), which can reliably identify the presence of ischemia-producing coronary stenosis.[6,10] FFR_{CT} analysis revealed severe 3-vessel coronary ischemia with FFR_{CT} in the LAD 0.64, RCA 0.61, and LCx 0.72 and presented the treating physicians with the question of how best to manage this patient's clinically demanding peripheral vascular disease in the presence of severe, asymptomatic (silent) coronary ischemia.

The need for prompt treatment for the patient's peripheral vascular disease was clear. The patient's ischemic rest pain placed him at risk of gangrene and limb loss, and this was compounded by the presence of a painful and tender femoral pseudoaneurysm, rupture of which would precipitate an emergent situation with attendant high mortality. At the same time, the patient had severe 3-vessel coronary ischemia with very low FFR_{CT} values in each vessel, putting the patient at high risk for a coronary event or sudden death. The increased risk for patients with 3-vessel and left main disease is well known, and the adverse consequences of silent myocardial ischemia are well documented.[14] Prospective clinical trials have shown the benefit of coronary revascularization of patients with stable chest pain and coronary ischemia by invasive FFR measurement[15-16] with an increased risk of death and myocardial ischemia in those with silent coronary ischemia.[17] Furthermore, the prognostic importance of the severity or depth of coronary ischemia as determined by invasively measured FFR value is well documented.[18] A meta-analysis of outcome studies in relation to FFR values has shown that cardiac risk is inversely related to the FFR value such that the lower the FFR value below 0.80, the higher the risk of adverse cardiac events, with high cardiac event rates for patients with FFR below 0.70.[18] For patients with chest pain symptoms, cardiac risk in relation to the FFR value is a continuum, and the lower the FFR value below 0.80, the higher the risk of adverse cardiac events, with high cardiac event rates for patients with FFR below 0.70.[18] Patients with CLI have been shown to have a high prevalence (69%) of asymptomatic ischemia-producing stenosis by FFR_{CT} analysis with severe ischemia ($FFR_{CT} \leq 0.70$) in 43% of patients.[10] This patient falls into the high-risk, severe coronary ischemia category, but randomized clinical trials have shown no clear survival benefit of coronary revascularization prior to elective vascular surgery procedures.[19] Thus, following cardiology consultation and risk/benefit discussion with the patient, the scheduled vascular surgery procedure was carried out as planned with close cardiac and hemodynamic monitoring with no cardiac complications.

Surviving the stress of major vascular surgery without cardiac events is often taken as evidence of lack of significant coronary disease. Indeed, this patient had already survived 3 prior vascular surgery operations in the past 4 years without cardiac complica-

tions. Now that he had survived yet another peripheral revascularization procedure, was it safe to assume his coronary risk was low or should coronary revascularization be considered? The natural history of medically treated hemodynamically significant coronary stenosis in patients with stable coronary disease in the FAME 2 study has recently been reported.[20] Among patients with coronary stenoses and FFR ≤ 0.80, the rate of death, myocardial ischemia, or need for coronary revascularization over a 2-year period was 39%.[21] A meta-analysis of FFR studies reporting patient outcomes demonstrated a continuous relationship between the numeric FFR value and subsequent outcomes, with lower FFR values indicating worse outcomes and the higher the FFR value the better the outcome.[18] The dose-response relationship between the actual FFR value and clinical outcome medical therapy has been confirmed by Barbato et al.[22] Thus, patients with very low FFR will have the greatest benefit of revascularization.[18] This patient, with 3-vessel coronary ischemia with very low FFR_{CT} values of 0.6-0.7, would be expected to have a 2-year major adverse coronary event rate in the range of 50% and could expect to derive great benefit from revascularization.[23]

Accordingly, the patient underwent elective, postoperative coronary angiography that confirmed the findings of the FFR_{CT} analysis. Because of the severity and multiplicity of lesions, the patient was scheduled for elective coronary bypass surgery, which was performed 6 weeks after the vascular surgery operation. The patient recovered uneventfully and at 1-year follow up is well with no chest symptoms and nonlimiting long-distance claudication. This favorable patient outcome is encouraging and demonstrates the benefit of a Vascular Team approach to the management of patients with complex multisite atherosclerosis as recommended in the 2017 ESC-ESVS guidelines for the treatment of patients with peripheral vascular disease.[24] While this patient underwent peripheral vascular repair followed by elective coronary revascularization, other patients may be best treated with prevascular surgery, coronary revascularization, or medical therapy alone. The value of CTA-FFR_{CT} in decision making and treatment planning has been demonstrated in patients with suspected coronary disease[7, 25,26] and should now be evaluated in patients with peripheral vascular disease.

CONCLUSION

In patients with CLI needing surgery, preoperative evaluation with coronary CTA and FFRCT may reveal the presence of severe, unsuspected coronary ischemia. This information may help guide treatment planning and patient management. The rationale of initial treatment with peripheral vascular surgery followed by elective coronary artery bypass surgery and favorable 1-year outcome is described. Further studies are needed to better define the role of coronary CTA and FFRCT in preoperative evaluation of patients with peripheral vascular disease. ■

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