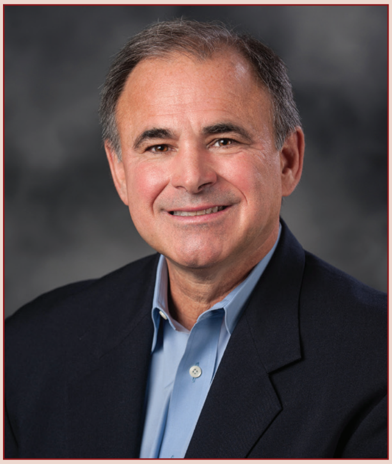
Effectively Screening PAD Patients for CLI



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Hello and welcome to the September edition of *Vascular Disease Management*. I have decided to comment on the submission by Dainis Krievins and colleagues about the high prevalence of asymptomatic ischemia-producing coronary stenosis in patients with critical limb ischemia: anatomic and functional assessment with coronary CT-derived fractional flow reserve (FFR_{CT}).

There has been great debate as to what constitutes an ideal cardiovascular evaluation of patients presenting with peripheral arterial disease (PAD). Most of this debate has been centered around the evaluation of patients with planned vascular interventional or surgical procedures. These studies have primarily been centered around the safety of proceeding with the surgery or intervention but have not addressed the issue of avoiding subsequent long-term cardiovascular mortality. I think the debate should widen to include all patients diagnosed with any form of PAD as multiple studies have demonstrated that PAD is associated with high rates of subsequent cardiovascular mortality. The poor long-term survival is predominately secondary to subsequent ischemic cardiac events. Patients with PAD may not experience angina secondary to diminished exercise capacity or faulty anginal warning related to diabetes mellitus which is highly prevalent in this patient cohort. In my opinion the debate should not center on whether or not the patient will survive a surgical or interventional procedure out to thirty days, but should also center on patient survival in the ensuing five-year period.

Present screening methods utilized to evaluate patients with PAD have substantial limitations. Exercise based studies are suboptimal in most patients as exercise capacity is limited. Studies utilizing chemical provocation only determine if there is ischemia at a single point in time and do not have the capability of distinguishing those patients who have completely normal coronary anatomy and do not require extensive follow-up from those who have significant coronary disease but may not yet have associated ischemia but need careful subsequent monitoring. Chemical provocation is poorly tolerated by many patients. CTA alone provides anatomical definition but does not reveal the physiological significance of lesions. CTA is limited by the need to administer iodinated contrast (which has risk of allergic reactions and contrast induced nephropathy) and is of limited utility in those with markedly elevated calcium scores because of blooming artifact. Coronary angiography is invasive, is associated with bleeding risk and the risk of contrast administration, is expensive, and doesn't give physiological information without the risk associated with traversing the coronary arteries. FFR_{CT} is associated with the same risk as CTA but has the advantage of providing not just anatomical delineation but physiological significance of the coronary obstructive disease as well. FFR_{CT} has been validated in patients with coronary symptoms to correlate with invasive physiological studies. I suspect that the FFR_{CT} studies may be less accurate in patients with congestive heart failure but those patients may warrant invasive investigation based on congestive heart failure. FFR_{CT} will have limitations where there is severe coronary calcification. It is my opinion that FFR_{CT} has great promise in evaluating patients with no symptoms from underlying coronary artery disease. The images of obstructive coronary disease when shown to the patient can motivate behavioral change improving medication and follow-up compliance. The physiological data may lead to appropriate revascularization.

This report in patients presenting with critical limb ischemia and no coronary symptoms demonstrated evidence of asymptomatic ischemia producing coronary artery stenoses in 77% of the entire cohort with multivessel ischemia noted in 42%. The study is limited as the patient cohort is small, is single center, and is limited to patients presenting with critical limb ischemia. Larger multicenter studies are needed including patients with asymptomatic PAD, those with claudication only, and those with aneurysmal disease. Long term follow-up is necessary to determine if this modality can influence what is presently dismal five-year morbidity and mortality outcomes. I believe that this relatively non-invasive technology has profound potential to improve what are presently suboptimal outcomes in patients presenting with PAD.

High Prevalence of Asymptomatic Ischemia-Producing Coronary Stenosis in Patients With Critical Limb Ischemia:

Anatomic and Functional Assessment With Coronary CT-Derived Fractional Flow Reserve (FFR_{CT})

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Abstract: Objectives. The purpose of this study was to determine the prevalence of unsuspected hemodynamically significant coronary stenosis in patients with no cardiac history who are undergoing surgery for critical limb ischemia (CLI) and to assess the potential benefit of FFR_{CT} analysis in patient management. **Methods.** Stable CLI patients with no evidence of coronary artery disease (CAD) who were scheduled for lower extremity revascularization underwent pre-op evaluation with coronary CT angiography-derived fractional flow reserve (FFR_{CT}) in a prospective IRB-approved study. Ischemia-producing coronary stenosis was defined as FFR_{CT} ≤0.80 distal to >30% CT stenosis with severe ischemia defined as FFR_{CT} ≤0.70. Major adverse coronary events (MACE) were evaluated at 30 and 90 days. **Results.** Asymptomatic, ischemia-producing coronary stenosis was found in 37 of 54 patients (69%), and severe lesion-specific ischemia was present in 23 patients (43%). Multi-vessel ischemia was present in 21 patients (38%). Lower extremity revascularization was performed as scheduled in 49 patients (91%) and postponed in 5 (1 with PCI, 1 with CABG, 3 with medical treatment). In 24 patients with severe or multi-vessel ischemia, elective coronary angiography was performed post-operatively with coronary revascularization in 16 (12 with PCI and 4 with CABG). There have been no MACE events at 30- and 90-day follow-up. **Conclusions.** CLI patients with no cardiac history undergoing limb salvage surgery have a high prevalence of asymptomatic ischemia-producing coronary stenosis which may put them at increased risk. Pre-operative diagnosis with FFR_{CT} analysis may increase focus on peri- and post-operative cardiac care and improve outcomes. The value of selective post-op coronary revascularization to improve survival of CLI patients requires further study.

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Key words: Critical limb ischemia, coronary ischemia, coronary CT angiography, fractional flow reserve, limb salvage surgery

Patients with critical limb ischemia (CLI) are at high risk for amputation and cardiovascular mortality. While surgical and interventional treatments have resulted in significant reductions in major amputation,[1,2] mortality rates exceed 20% at 6 months[3] and over 50% at 4 years.[4] The majority of deaths are due to coronary artery disease (CAD), which is often unrecognized due to lack of chest symptoms and the limited ability of CLI patients to ambulate. The relationship between peripheral arterial disease (PAD) and CAD is well known,[5] and symptomatic PAD is a consistent and powerful independent predictor of CAD events and mortality including increased risk of post-operative myocardial ischemia and reduced 5-year survival.[6] Nonetheless, current guidelines do not recommend systematic pre-operative cardiac testing of patients undergoing peripheral vascular surgery, since testing usually does not lead to modification of management strategy[7,8] and the lack of available evidence demonstrating that pre-operative coronary revascularization improves outcome.[9] Thus, the true extent of coronary disease is unknown in most patients undergoing treatment for CLI, leaving them at high risk for early and late cardiac events. The observation that even without symptoms of coronary disease, myocardial infarction is the leading cause of death in CLI patients and the recognition that "sick legs are rarely attached to healthy individuals" highlights the need for improved cardiac diagnostics to improve outcomes of CLI patients.[10]

Recently, a new diagnostic modality, coronary CT angiography (CTA)-derived fractional flow reserve (FFR_{CT}), has been introduced into clinical practice for the non-invasive evaluation of patients with suspected CAD. FFR_{CT} technology is based on anatomic information provided by coronary CT with mathematical simulation of hyperemic coronary blood flow and computation of fractional flow reserve values throughout the coronary tree.[11] Prospective clinical trials have shown good correlation of computed FFR_{CT} to invasively measure fractional flow reserve (FFR) with accurate differentiation of patients with ischemia-producing stenosis from those with non-functional disease.[12-14] The clinical usefulness of FFR_{CT} analysis is well documented,[15-19] and FFR_{CT} is now being used to evaluate patients with suspected CAD in the

United States, Canada, Europe, and Japan. However, FFR_{CT} has not yet been used to evaluate CAD in patients with peripheral arterial disease who are at increased risk of cardiovascular death but often present without chest pain symptoms.[20] The purpose of this study is to determine the prevalence of unsuspected hemodynamically significant coronary stenosis in CLI patients and to assess the potential benefit of FFR_{CT} analysis in patient management.

METHODS

Study design

This single-center observational study was designed to evaluate the usefulness of coronary CTA-derived FFR_{CT} for pre-operative evaluation of patients undergoing elective peripheral vascular surgery. It is focused on the population of peripheral vascular patients with no chest symptoms or known coronary artery disease who are at risk of post-operative myocardial infarction and death and for which guidelines do not recommend routine pre-operative non-invasive coronary artery testing. The primary study endpoint is the major adverse cardiac event (MACE) rate consisting of death, myocardial infarction, acute coronary syndrome or unplanned coronary intervention at 30 days. Longer-term MACE time points are 90 days and 1 year.

Study population

The study population comprised patients with symptomatic peripheral vascular disease and no cardiac history or chest symptoms who were scheduled for elective peripheral vascular surgery at the Pauls Stradins Clinical University Hospital, Riga, Latvia. Inclusion criteria included admission to the hospital for elective peripheral vascular surgery, absence of prior cardiac history, coronary angiography or coronary intervention, absence of chest symptoms, and pre-operative clearance for vascular surgery in accordance with 2014 ESC/ESA guidelines on non-cardiac surgery.[21] Exclusion criteria included history of cardiac disease or chest symptoms, need for urgent or emergent surgery, contraindication or inability to obtain coronary CT angiography, and contraindication to beta-blocking agents or nitroglycerin. The study design was approved by the institutional review board (IRB) and each patient signed informed consent. From October 2017 to June 2018, 62 patients with critical limb ischemia and no cardiac history were enrolled in the study, and FFR_{CT} analysis was performed in 54 patients, who are the subject of this report.

Coronary CTA data acquisition

Coronary CTA was performed using a single-source 64-detector row scanner (GE Optima) with retrospective or prospective electrocardiographic gating in accordance with the Society of Cardiovascular Computed Tomography guidelines.[22] Oral and/or intravenous beta-blockers targeting a heart rate of <60 beats/minute were administered, and sublingual nitrates were also administered to ensure coronary vasodilation. Data acquisition was performed with 100 kV tube voltage in patients with BMI <20 kg/m^2 and 120 kV in patients with BMI >20 kg/m^2, 490-540 mA, rotation 0.35 s, standard kernel. An initial non-enhanced scan was performed for assessment of Agatston score.[23] Significant coronary CT stenosis was defined as ≥50% stenosis in a major epicardial coronary artery ≥2.0 mm in diameter.

FFR_{CT} analysis

Coronary CT image datasets were sent for off-site computational analysis (HeartFlow, Inc.) through a secure web-based interface. CTA image datasets were evaluated for image artifacts using a pre-defined scoring system,[24] and cases appropriate for FFR_{CT} analysis were processed. Of 62 cases sent, 8 were returned because of excessive image artifacts and 54 cases were processed. The primary reasons for return of cases were image misregistration or excessive motion. Of note, despite high levels of coronary calcification, no case was returned because of excessive calcification. Case processing resulted in a quantitative 3-dimensional anatomic model of the aortic root and coronary arteries with color-coded display of FFR_{CT} values throughout the coronary tree. In each case, the FFR_{CT} analysis was returned to the hospital in less than 24 hours and was available to the treating physicians

Table 1. Baseline characteristics (N = 54).

Age (years)	66 ± 9
Age range (years)	49-86
Male	39 (72%)
Female	15 (28%)
Comorbidities	
Hypertension	46 (85%)
Hyperlipidemia	26 (48%)
Diabetes mellitus	7 (13%)
Smoking	22 (41%)
Medications	
Antihypertensive	37 (69%)
Statin therapy	29 (54%)
Insulin	7 (13%)
Antiplatelet or anticoagulant agents	33 (61%)
Presenting symptoms	
Claudication	49 (91%)
Rest pain	30 (56%)
Ulceration	12 (22%)
Paresthesia	34 (63%)
Ankle-brachial index (pre-op)	0.48 ± 0.11
Range of ankle indices	0.31-0.87

Data provided as mean ± standard deviation, range, or number (%).

Table 2. Patient characteristics according to coronary CTA and FFR_{CT} (N = 54).

Coronary CTA Agatston score	1199 ± 1163
Range of coronary CTA Agatston score	16-4810
Coronary CTA Agatston score >400	38 (70%)
Coronary CTA Agatston score >1000	23 (43%)
Coronary CTA stenosis ≥50%	35 (65%)
Coronary CTA stenosis ≥70%	16 (30%)
Coronary CTA left main stenosis ≥50%	5 (9%)
FFR_{CT} ≤0.80	37 (69%)
FFR_{CT} ≤0.80 with multivessel disease	21 (38%)
FFR_{CT} ≤0.70	23 (43%)
FFR_{CT} >0.80	17 (31%)

Data provided as mean ± standard deviation, range, or number (%).
CTA = computed tomography angiography; FFR_{CT} = fractional flow reserve derived from coronary computed tomography angiography.

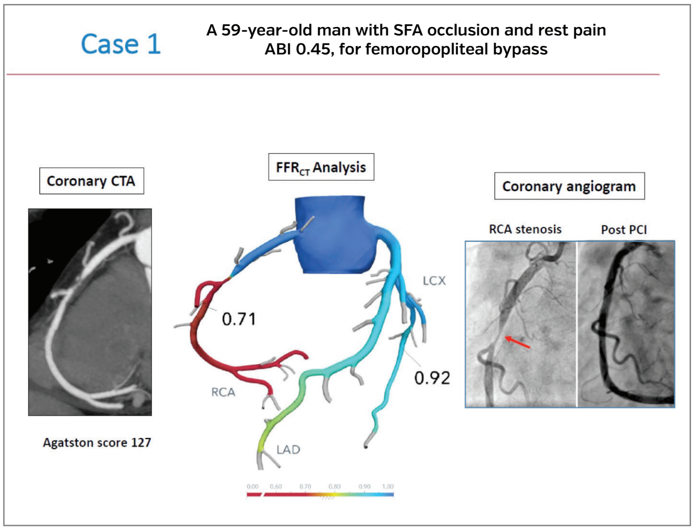

Figure 1. A 59-year-old man with ischemic rest pain of the right foot and limiting claudication (<50 meters) was admitted for femoropopliteal bypass. Ankle-brachial index (ABI) was 0.45, and computed tomography angiography (CTA) demonstrated long-segment superficial femoral artery (SFA) occlusion. The patient had no cardiac history and no chest symptoms. Coronary CTA demonstrated 80%-90% right coronary artery (RCA) stenosis with little calcification, and the total Agatston score was 127. FFR_{CT} analysis showed FFR_{CT} 0.71 just past the stenosis and FFR_{CT} 0.68 in the distal RCA. Femoropopliteal bypass was performed as planned with complete relief of symptoms. One month later, coronary angiography confirmed the presence of 95% stenosis in the RCA, and percutaneous coronary intervention with a drug-coated stent was performed with complete resolution of the stenosis.

for patient-management decisions. The presence of ischemia-producing coronary stenosis was defined as FFR_{CT} ≤0.80 distal to a CT stenosis >30% in one or more coronary arteries ≥2 mm in diameter. Severe lesion-specific ischemia was defined as FFR_{CT} ≤0.70 distal to a CT stenosis >30% in a ≥2 mm in diameter vessel.

Patient management and follow-up

Patient management was at the discretion of the treating physicians with guidance by the Vascular Team comprised of vascular surgeons, cardiologists, anesthesiologists, cardiac surgeons, and radiologists. Major adverse cardiac events (MACE), comprised of death, myocardial infarction, acute coronary syndrome, or urgent revascularization, were recorded at 30 days, 3 months, and 12 months after enrollment.

RESULTS

Patient characteristics

The baseline characteristics of 54 CLI patients with CTA and FFR_{CT} analysis are shown on **Table 1**. Each patient had one or more indicators of critical limb ischemia, including rest pain, paresthesia, ulceration, or tissue loss. Severe, limiting claudication was present in 91%. Ankle-brachial index was 0.48±0.11 (mean±SD), with a range of 0.31-0.87. No patient had a history of cardiac disease or chest symptoms and all were scheduled for surgery.

Coronary CT angiography

Coronary CTA results are shown on **Table 2.** Calcium scoring revealed a high degree of coronary calcification with a mean Agatston score of 1199±1163 (range 16 to 4810). In 23 patients (43%), Agatston score was >1000. Coronary CT stenosis ≥50% was present in one or more vessels in 35 patients (65%) and was ≥70% in 16 patients (30%). Left main stenosis ≥50 was present in 5 patients.

FFR_{CT} analysis

FFR_{CT} analysis revealed the presence of ischemia-producing coronary stenosis with FFR_{CT} ≤0.80 in 37 patients (69%), and of these 21 (57%) had multi-vessel ischemia. Severe lesion-specific ischemia with FFR_{CT} ≤0.70 was present in 23 patients (43%). In 17 patients (31%), there was no evidence of coronary ischemia, with FFR_{CT} >0.80 in all vessels.

Patient management

In view of the absence of cardiac symptoms and the pressing need to treat the critical limb ischemia, the vascular surgery procedure was performed as planned in 49 patients (91%). In 5 patients, the vascular procedure was postponed: 2 for coronary angiography and coronary revascularization (one PCI and one CABG) and 3 for medical treatment. There were no post-operative cardiac or vascular complications and no MACE events at 30-day follow-up.

Post-operative cardiac care

All patients received optimal medical therapy including statins and anti-platelet agents. No patient developed angina or chest symptoms. On the basis of pre-operative FFR_{CT} findings, patients were selected for further evaluation with elective coronary angiography. The primary selection criteria included the severity of ischemia (FFR_{CT} ≤0.70), the presence of multi-vessel disease and proximal location of the lesion. In 24 patients, coronary angiography was performed 1-3 months post-surgery with coronary revascularization in 16 patients (30% of total population); 12 had percutaneous coronary interventions and 4 had coronary artery bypass grafting. At 90-day follow-up there have been no MACE events in the 54 CLI patients.

Case examples

Representative case examples showing CTA and FFR_{CT} results and patient management strategy are shown in **Figures 1 and 2.**

DISCUSSION

While it is well known that patients with peripheral vascular disease are likely to have coronary artery disease, this is the first study to demonstrate the remarkable degree of unsuspected, hemodynamically significant coronary disease in patients with critical limb ischemia. Despite the absence of symptoms, almost 70% of CLI patients were found to have ischemia-producing coronary stenosis by FFR_{CT} with severe ischemia in more than 40% of patients. This high prevalence and degree of functionally significant coronary disease is surprising in light of the fact that none of the patients had clinical evidence of coronary disease. However, it is consistent with the known high rate of early coronary mortality seen in CLI patients and is also consistent with the knowledge that surgical procedures can be performed safely in most high-risk patients with modern anesthesia and good medical care. Thus, while most CLI patients undergoing lower extremity revascularization survive their procedures uneventfully with avoidance of amputation, many suffer early cardiac events with high subsequent cardiovascular mortality. This has led to the use of amputation-free survival as the primary endpoint in clinical trials of lower-extremity revascularization for CLI.[3] In this study, we utilized a new non-invasive diagnostic strategy, FFR_{CT} to evaluate CAD in critical limb ischemia patients, and demonstrated its potential usefulness in identifying patients who may be at high risk of coronary events and death. While no conclusions on the clinical relevance of our findings can be drawn from this initial experience, our study highlights the high prevalence of unsuspected functionally significant coronary disease in this patient population and the need for further investigation.

The importance of determining the functional significance of coronary lesions for guiding treatment strategy in patients with stable CAD is now well established.[25] This can be readily accomplished by measurement of FFR during invasive coronary angiography. FFR is a surrogate for myocardial ischemia, which is the single most important factor to influence clinical outcome in patients with CAD.[26,27] Patients with hemodynamically significant stenosis (FFR ≤0.80) benefit from revascularization,[28,29] whereas

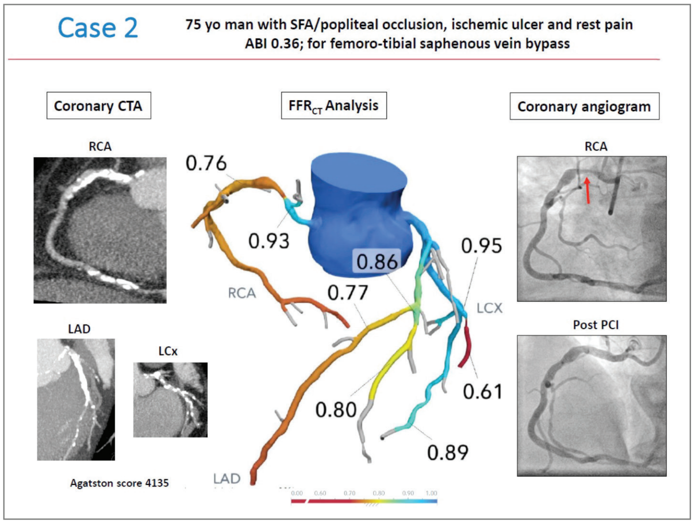

Figure 2. A 75-year-old man with severe rest pain and ischemic ulceration was admitted for femoral-tibial saphenous vein bypass. Ankle-brachial index was 0.36. The patient had no cardiac history or chest pain. Coronary computed tomography angiography (CTA) showed severe coronary calcification with an Agatston score of 4135 but no coronary stenosis >50%. FFR_{CT} analysis showed multi-vessel hemodynamically significant coronary stenosis with FFR_{CT} 0.76 in the right coronary, 0.77 in the left anterior descending, and 0.61 in the left circumflex (LCX) artery. Lower extremity bypass was performed as scheduled with no complications. Six weeks later, coronary angiography demonstrated 95% right coronary artery (RCA) stenosis, 80% left anterior descending (LAD) stenosis, and 75% LCX stenosis. Percutaneous coronary intervention with a drug-coated stent was performed in the RCA with good angiographic result. FFR = fractional flow reserve.

patients with non-functional stenosis (FFR >0.80) do well on medical therapy alone with excellent long-term outcome without intervention.[25,27,30,31] Importantly, relieving myocardial ischemia by revascularization improves the unfavorable prognosis of patients with ischemia-producing stenosis as shown by the results of the FAME 2 study.[31,32] Furthermore, the depth of coronary ischemia, as evidenced by the degree to which FFR values are below the FFR ≤0.80 threshold, is an important prognosticator of future cardiac events.[32,33] While all prospective FFR studies have been conducted in patients with symptomatic coronary disease evaluated in the cardiac catheterization laboratory, there is no reason to believe that the findings regarding long-term outcome are not applicable to patients with asymptomatic coronary artery disease with similar degrees of lesion-specific ischemia, particularly in view of the fact that as many as 50% of sudden cardiac deaths and acute myocardial infarctions occur in patients with no prior symptoms of heart disease.[34] Since patients with peripheral arterial disease are at increased risk for coronary artery death irrespective of the presence of chest symptoms,[20] the ability to estimate fractional flow reserve non-invasively may provide benefit, particularly as a pre-operative test to diminish the risk of peri-operative myocardial infarction and death.[35]

Risk stratification on the basis of FFR findings in CAD patients with respect to the presence, extent, and depth of lesion-specific ischemia may be of value in treatment planning and patient management. Thus, while many patients with invasively measured FFR in the grey zone of 0.75-0.80 may not require revascularization, virtually all patients with symptomatic coronary disease and FFR <0.75 may benefit from revascularization.[30] In this study, we utilized an even lower threshold to define severe lesion-specific ischemia, FFR_{CT} ≤0.70 and found that despite this level of unsuspected ischemia in almost half the patients, lower extremity revascularization and limb salvage were achieved in almost all patients with no adverse cardiac events. The extent to which knowledge of the coronary ischemic burden may have increased focus on intra- and post-operative care is not known, but the safety of addressing the critical limb ischemia first is supported by a favorable 30-day outcome.

During the post-operative recovery period, in hopes of improving survival, patients were selected for invasive coronary angiography based on the extent and depth of coronary ischemia as shown by FFR_{CT} rather than on the basis of clinical coronary symptoms. Overall, 30% of this non-chest pain critical limb ischemia patient population has undergone elective coronary revascularization with no major adverse cardiac events during 90-day follow-up. Determining the value of such coronary revascularization on long-term survival of these patients will require longer-term follow-up and such follow-up is ongoing. However, these promising early results suggest the need for prospective, controlled clinical trials in this area.

It should be noted that patients with critical limb ischemia often have high levels of vascular calcification and that coronary CT angiography is not recommended for patients with high coronary calcification (Agatston score >400) because of inaccuracies in defining the coronary lumen due to calcium blooming artifacts.[36] Patients in this study had a mean Agatston score >1000 and while this may have affected CT stenosis evaluation, it did not impede FFR_{CT} analysis. The discordance between CTA stenosis and FFR_{CT} analysis in severely calcified coronaries can be seen in the case example 2. In a substudy of the prospective NXT study, the accuracy of FFR_{CT} was shown to be preserved in patients with calcified vessels using measured FFR as the reference standard.[37] Thus, calcification does not appear to be a limitation in the use of FFR_{CT} in CLI patients.

Limitations of this study include the small number of patients, lack of a control group, and short follow-up. Nonetheless, this study demonstrates the feasibility of CT-derived FFR_{CT} as a non-invasive approach to identify functionally significant coronary artery disease in patients with no cardiac symptoms who are at high risk of coronary mortality.

CONCLUSION

Patients with critical limb ischemia who require limb salvage surgery have a high prevalence of asymptomatic ischemia-producing coronary stenosis which may put them at risk for myocardial infarction and death. Pre-operative assessment with coronary CTA and FFR_{CT} can identify patients with hemodynamically significant coronary lesions and may increase focus in peri-operative cardiac care to reduce cardiac complications. Selective coronary angiography and elective coronary revascularization of severely ischemic lesions may provide benefit, but longer-term prospective studies are needed to determine its role in improving survival of patients with critical limb ischemia. ■

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