Minimally Invasive Testing for Critical Limb Ischemia: Are You a Believer or a Nonbeliever?

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Believing can be difficult, because by definition, belief is achieved without considerable supporting evidence. The standard minimally invasive testing procedure for peripheral arterial disease (PAD) is ankle brachial index (ABI). An ABI <0.9 is regarded as evidence for the diagnosis of PAD. With that testing, we mainly follow and diagnose the “common PAD patient” who is presenting with claudication as the main symptom. Screening with ABI to detect PAD in a general patient population cohort is recommended by guidelines (TASC II/ESC) for specific patient populations. For the most severe cohort in PAD, patients with critical limb ischemia (CLI), the same screening tools are proposed. In the TASC II paper, Norgren et al state that “for patients with ulcers or gangrene, the presence of CLI is suggested by an ankle pressure less than 70 mmHg or a toe systolic pressure less than 50 mmHg.”

We tend only to see what is obvious at first sight but not what might be written in parentheses. The authors of the TASC II document stated in 2007 that “it is important to understand that there is not complete consensus regarding the vascular hemodynamic parameters required to confirm diagnosis of CLI.”

The hemodynamic parameters applied and used for the TASC paper are referring to the TIDE OVER concept, published in Diabetes Care in June 1989. This concept refers to the fact that if the perfusion pressure drops below 30 mmHg, an ischemic ulcer might occur, whereas the minimal perfusion pressure needed for ulcer healing is >80 mmHg.

In a subchapter of the TASC II paper that addresses investigations for CLI, the authors are more specific. For diabetic patients, they recommend the additional measurement of toe pressures (critical level <50 mmHg) and tcPO₂ measurements (critical level <30 mmHg). However, they also state that investigation of microcirculation (usually used as a research tool) is necessary in CLI, as CLI is associated with reduced total flow as well as maldistribution of flow and activation of an inflammatory process. A combination of tests to assess healing and quantify flow may be indicated due to the rather poor sensitivity and specificity of the single test. Tests should include capillaroscopy, fluorescence videomicroscopy, laser doppler fluxmetry, and anatomic imaging.

Available Data on Minimally Invasive Testing

Despite these recommendations, these testing parameters have not been widely implemented. Also, for the screening process of PAD, those minimally invasive tests have not proven to be accurate enough.

Xu et al published a structured review on 8 studies comprising 2,043 patients (or limbs). The result...
indicated that although strict inclusion criteria on studies were formulated, different reference standards were found in these studies, and methods of ABI determination and characteristics of populations varied greatly. High levels of specificity (83.3% to 99.0%) and accuracy (72.1% to 89.2%) were reported for an ABI ≤.90 in detecting ≥50% stenosis, but there were different levels of sensitivity (15% to 79%). Sensitivity was low, especially in elderly individuals and patients with diabetes. And with the fact that diabetes is found in a much higher percentage of patients with CLI than claudicants (~40% in claudicants vs ~75% in CLI; data from IN.PACT SFA vs IN.PACT DEEP4,5) that makes this simple minimally invasive diagnostic tool unacceptable for CLI testing from first sight.

Vallabhaneni et al evaluated the current accepted hemodynamic parameters in 283 limbs with CLI for the value to accurately stratify patients at high risk for limb loss. The authors concluded that CLI is associated with a high mortality, but not all patients with currently defined hemodynamic criteria for CLI are at high risk of limb loss. Patients with a toe pressure between 31 mmHg and 50 mmHg (41% of the cohort) not receiving revascularization or not responding hemodynamically to revascularization, experienced a low risk of limb loss. The authors therefore recommend revising the hemodynamic criteria for CLI to better identify patients at high risk for limb loss who require intervention to improve outcomes.

Bunte et al confirmed the relationship between ABI and TBI and infragenicular arterial patency in CLI. Among patients with any ischemic tissue loss (N=89; noninvasive testing + angiographic follow-up), 29% had an ABI between 0.7 and 1.4. Patients with rest pain alone had reduced odds of abnormal arterial run-off in univariate (OR 0.75, 95% CI 0.63–0.90; P=.002) but not multivariate (P=.50) analysis. Advanced age, increased ABI, reduced creatinine clearance, hyperlipidemia, and prior coronary artery disease were predictive of abnormal infragenicular run-off. Despite limitations in statistical power, median TBI, compared to ABI, tended to increase when infragenicular arterial run-off was preserved. Overall, the association of TBI with abnormal run-off was not significant (P=.38). In the evaluation of CLI, nearly one-third of patients with any ischemic tissue loss had a normal or mildly reduced ABI. Assessment of TBI may augment the diagnostic accuracy of ABI in the diagnosis of CLI.

The most recent publication highlighting the limitations of current hemodynamic parameters gained by minimally invasive testing is an analysis from the IN.PACT DEEP randomized trial on the limitations of the societal guideline recommendations for hemodynamic parameters to diagnose CLI by Shishehbor et al. Only 14 of 237 patients (6%) had an ABI <0.4. Abnormal ankle pressure, defined as <50 mm Hg if Rutherford category 4 and <70 mm Hg if Rutherford category 5 or 6, was found only in 37 patients (16%). Abnormal toe pressure, defined as <30 mmHg if Rutherford category 4 and <50 mmHg if Rutherford category 5 or 6, was found in 24 of 40 patients (60%) with available measurements. Importantly, 29% of these 24 patients had an ABI within normal reference ranges.

A univariate multinomial logistic regression found no association between the above hemodynamic parameters and the number of diseased infrapopliteal vessels. However, there was a significant paradoxical
association where patients with Rutherford category 6 had higher ABI and ankle pressure than those with Rutherford category 5. Similarly, there was no association between ABI and pedal arch patency.

**FUTURE DIRECTIONS**

Revascularization is the cornerstone of management for CLI; objective visualization of diseased arteries is needed. The hemodynamic measurements currently recommended by the societal guidelines are not consistent and have significant limitations in patients with critical limb ischemia.

Toe pressure, rather than ABI or ankle pressure alone, may be a better measure of perfusion in all patients with CLI. New measurement methods could include functional imaging of the foot with perfusion angiography in CLI. New alternatives for proof of impaired blood flow to wounds are needed to identify diseased vessels and improve patient outcomes.

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