RELATIONSHIP OF INFRAGENICULAR ARTERIAL PATENCY WITH ANKLE-BRACHIAL INDEX AND TOE-BRACHIAL INDEX IN CRITICAL LIMB ISCHEMIA

by

MATTHEW C. BUNTE, M.D.

Submitted in partial fulfillment of the requirements

For the degree of Master of Science

Thesis Advisors: Drs. James Spilsbury & Mehdi H. Shishehbor

Clinical Scholars Research Program

CASE WESTERN RESERVE UNIVERSITY

May, 2014
CASE WESTERN RESERVE UNIVERSITY
SCHOOL OF GRADUATE STUDIES

We hereby approve the thesis/dissertation of

Matthew C. Bunte, M.D.

Candidate for the degree of Master of Science*.

Committee Chair

James C. Spilsbury, Ph.D., M.P.H.

Committee Member

Thomas E. Love, Ph.D.

Committee Member

Dennis Stacey, Ph.D.

Committee Member

Mehdi H. Shishehbor, D.O., Ph.D., M.P.H.

Date of Defense

March 10, 2014

*We also certify that written approval has been obtained for any proprietary material contained therein.
TABLE OF CONTENTS

LIST OF TABLES......................................................................................................................... 4
LIST OF FIGURES.......................................................................................................................... 5
LIST OF ABBREVIATIONS............................................................................................................. 6
ABSTRACT...................................................................................................................................... 7
INTRODUCTION............................................................................................................................. 8
METHODS...................................................................................................................................... 10
RESULTS....................................................................................................................................... 15
DISCUSSION................................................................................................................................. 20
CONCLUSIONS............................................................................................................................. 26
APPENDIX..................................................................................................................................... 27
BIBLIOGRAPHY............................................................................................................................. 38
LIST OF TABLES

Table 1: Baseline characteristics according to ABI subgroups............................27

Table 2: Baseline characteristics according to number of infragenicular arterial runoff vessels..........................................................28

Table 3: Comparison of ABI based on presenting patient characteristics.......29

Table 4: Final multivariable logistic regression used to model associations between clinical variables and abnormal lower extremity runoff...........30
LIST OF FIGURES

Figure 1: Distribution of ABI by number of infragenicular arterial runoff...........31
Figure 2: ABI and TBI by number of patent infragenicular arterial runoff runoff arteries.................................................................................................................................32
Figure 3: Trend of ABI and TBI by patency of the anterior tibial, posterior tibial and peroneal arteries..................................................................................................................................................33
Figure 4: ABI and TBI by presenting Rutherford Classification..........................34
Figure 5: Distribution of non-invasive testing by Rutherford Classification.........35
Figure 6: Distribution of non-invasive testing relative to infragenicular runoff........................................................................................................................................................................36
Figure 7: TBI and TSP distribution among ABI subgroups.................................37
LIST OF ABBREVIATIONS

1. ABI: ankle-brachial index
2. CAD: coronary artery disease
3. CLI: critical limb ischemia
4. CVA: cerebrovascular accident
5. IQR: interquartile range
6. PAD: peripheral arterial disease
7. PPG: photoplethsmography
8. RC: Rutherford classification
9. TBI: toe-brachial index
10. TIA: transient ischemic attack
11. TSP: toe-systolic pressure
Relationship Of Infragenicular Arterial Patency With Ankle-Brachial Index And Toe-Brachial Index In Critical Limb Ischemia

Abstract

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The relationship between ankle-brachial index (ABI) and toe-brachial index (TBI) remains uncertain relative to features of clinical status and lower extremity arterial runoff among patients with critical limb ischemia (CLI). From July 2011 to February 2013, 116 consecutive patients with CLI were evaluated with non-invasive testing and subsequent lower extremity angiography, which were compared against clinical severity. There was a significant association between Rutherford classification and arterial runoff (p=0.003) that was not observed with ABI (p=0.28). Among patients with ischemic tissue loss, 29% had a normal or mildly reduced ABI. In multivariable analysis, the odds of abnormal arterial runoff were associated with increased age, ABI, and Rutherford classification. In the evaluation of CLI, assessment of clinical severity may be a more valuable predictor of infragenicular runoff than ABI alone. Further prospective analysis of non-invasive testing may enhance the diagnostic accuracy among patients with CLI.
INTRODUCTION

For patients with critical limb ischemia (CLI), including those with resting leg pain or ischemic limb wounds, prompt diagnosis of arterial disease provides opportunity to improve tissue perfusion, relieve pain, and promote wound healing. Current guidelines recommend the use of ankle-brachial index (ABI), among other tests, for the diagnosis of peripheral arterial disease (PAD) (Anderson, Halperin et al. 2013). However, the ABI has important limitations that uniquely impact the interpretation of test results among patients with the most advanced forms of PAD (Aerden, Massaad et al. 2011, Aboyans, Criqui et al. 2012).

The ABI is a quick, convenient, office-based comparison of systolic blood pressure between the ankle and arm that is ubiquitous in the evaluation of peripheral arterial disease. The indexed limb pressures are often stratified, from mild to severe, to characterize the severity of limb malperfusion. This ranking is often considered a reflection of arterial disease, whereby a severely reduced ABI indicates severe arterial obstruction. Nevertheless, among patients with CLI, a congruent relationship of low ABI with severe arterial obstruction is frequently not observed. In fact, vascular calcification and serial stenosis within the arteries of patients with CLI can provide falsely elevated ABI results. As a consequence, ostensibly normal or mildly abnormal ABI results can result in inappropriate dismissal or minimization of the severity of PAD. Therefore, to ensure the delivery of limb-saving treatments to patients with CLI, ABI results must be considered in the context of clinical presentation as well as other complimentary non-invasive testing.
Digital subtraction angiography remains the gold standard for diagnosis across the spectrum of PAD, although has its own limitations (Norgren, Hiatt et al. 2007). Alternative tests, such as toe-brachial index (TBI) and toe-systolic pressure (TSP), among others, may augment the sensitivity of the CLI evaluation (Norgren, Hiatt et al. 2007). Concurrent testing with ABI, TBI, and TSP is not widely performed in the initial assessment of CLI, nor are comparisons thereof reported in the literature. To our knowledge, there exist no studies that simultaneously consider a wide range of ABI, TBI, and TSP results, confirmed with detailed angiographic findings, among a population of CLI patients. Such a characterization of noninvasive testing would benefit patients with CLI by offering earlier lower extremity revascularization and reduced rates of major limb amputation.

Therefore, we present an observational analysis describing the unique relationship of indexed ankle and toe blood pressure with angiographic findings among consecutive CLI patients. Based on previously published results and our clinical experience, we hypothesize that ABI, TBI, and TSP will decrease as clinical status worsens and distal limb perfusion is reduced among the arteries below the knee (i.e., infragenicular arterial outflow). Because TBI and TSP are considered more accurate markers of small-vessel arterial disease that characterizes CLI, we also hypothesize that the accuracy of ABI to predict infragenicular arterial obstruction is diminished. Finally, this report characterizes the clinical factors most commonly associated with non-invasive test results and infragenicular arterial runoff in a CLI population. In that context, this study explores the association between clinical disease severity and infragenicular arterial runoff.
METHODS

Patient Population

Between July 2011 and February 2013, 116 consecutive patients with CLI were retrospectively identified after presenting to the Department of Vascular Medicine and subsequently underwent lower extremity angiography at Cleveland Clinic. After Institutional Review Board approval, patient characteristics, details of non-invasive and invasive arterial assessments were collected.

Study Population, Definitions, and Study Variables

The Rutherford-Baker Classification (RC) system provides an objective scale to describe a clinical continuum of peripheral arterial disease (Rutherford, Baker et al. 1997). The scale ranges from 1-6, including patients with mild, moderate, and severe ambulatory limb claudication (i.e., RC 1, RC 2, and RC 3). CLI is represented by resting limb pain (i.e., RC 4) as well as those with mild and major ischemic tissue loss (i.e., RC 5 and RC 6, respectively); therefore, this study population includes only those patients classified as RC 4-6.

Several clinical variables were retrospectively collected from the medical record. Age, gender, race, body-mass index, creatinine clearance, and RC were recorded at the time of diagnosis. Historical variables were also collected at the time of ABI, including presence of hypertension, hyperlipidemia, diabetes mellitus, current/former tobacco abuse, coronary artery disease, prior cerebrovascular accident (CVA) or transient ischemic attack (TIA), prior lower extremity revascularization for PAD, and prior partial or total limb amputation for ischemia
tissue loss. The baseline characteristics for the cohort were summarized by ABI subgroups (Table 1) and by the number of infragenicular runoff vessels (Table 2).

**Procedures**

*Non-Invasive Hemodynamic Assessment*

The ABI is the ratio of systolic pressure in the ankle to the systolic pressure in the arm (i.e., brachial pressure). The ABI was performed with patients supine for 5-10 minutes prior to checking the brachial pressure in the arms. Next, the ankle pressures were performed over the dorsalis pedis and posterior tibial arteries on each leg. The ABI was calculated by indexing the higher of the two ipsilateral ankle pressures divided by the higher of the arm pressures. In a similar fashion, TBI was calculated using a single systolic pressure at the great toe compared to the higher of the two brachial systolic pressures. All measurements were performed using photoplethsmography (PPG) and in accordance with Intersocietal Accreditation Commission – Vascular Testing standards (Intersocietal Accreditation Commission 2012).

Seventeen (15%) patients had a non-diagnostic ABI result due to heavily calcified, non-compressible arteries at the ankle. These patients were sub-grouped as having a non-compressible ABI. The remaining 99 patients were sub-grouped by ABI as follows: normal ABI, 0.9-1.4 (n=14); mildly reduced ABI, 0.7-0.9 (n=15); moderately reduced ABI, 0.4-0.7 (n=48); and severely reduced ABI, < 0.4 (n=22). ABI subgroups are clinically relevant and are used to qualify the degree of ABI abnormality.
Assessment of toe blood pressure in the ipsilateral limb at the time of ABI was available in 39 patients. TBI and TSP were also assessed by PPG. A TBI $\geq 0.70$ was considered normal (Hirsch, Haskal et al. 2006, Norgren, Hiatt et al. 2007, Rooke, Hirsch et al. 2011). For a comparison to RC subgroups and arterial runoff, TBI was sub-grouped as follows: normal TBI, $\geq 0.70$ (n=4); mildly reduced TBI, 0.40-0.69 (n=7); moderately reduced TBI, 0.20-0.39 (n=19); severely reduced TBI, < 0.20 (n=9). In a similar manner, TSP was classified as follows: normal TSP, $\geq 60$ mmHg (n=12); mildly reduced TSP, 30-59 mmHg (n=15); moderately reduced TSP, 15-29 mmHg (n=11); severely reduced TSP, < 15 (n=1). A TSP < 30 mmHg has been associated with ischemic rest pain although tissue loss may be noted when TSP < 50 mmHg (Norgren, Hiatt et al. 2007).

Lastly, because of the reported association between diabetes mellitus and inaccurate ABI results, we compared results of ABI, TBI, and TSP between diabetic and non-diabetic patients.

*Angiographic Assessment*

Normally, the anterior tibial artery, posterior tibial artery, and peroneal artery form a collateral network of arterial perfusion to the foot. Occlusion of one or more of these major arteries below the knee (i.e., infragenicular arteries) often contributes to the development of CLI. Therefore, angiographic assessment guides limb reperfusion strategies important in the treatment of CLI.

In this study, all patients received lower extremity angiography performed at a median 10.5 days (interquartile range (IQR), 3-21) following an office-based ABI.
89 patients (77%) had available angiograms that included infragenicular arterial segments. These segments were recorded as patent (≤50% arterial narrowing), stenotic (>50% arterial narrowing), or occluded. A point was given toward a total runoff score, ranging from 0 to 3, for each non-occluded arterial segment that reached the ankle. Patients were then sub-grouped by the number of infragenicular arteries providing lower leg runoff, as follows: none (n=9); one-vessel (n=31); two-vessel (n=33); and three-vessel (n=16). Angiographic findings were then summarized relative to demographic and historical information, vital statistics, laboratory values, and noninvasive hemodynamic assessment, including ABI and TBI. Among the remaining, 27 patients (23%) underwent angiograms that did not provide imaging of infragenicular arterial runoff (e.g., iliac artery angioplasty) and were therefore not included in this analysis.

**Statistical Analysis**

Continuous variables were summarized as median with corresponding IQR. Categorical variables are summarized as percentages. Comparisons of continuous variables were performed with the Wilcoxon rank-sum test with continuity correction. Comparisons of categorical variables were performed with the Fisher exact test. The Kruskal-Wallis test was used when comparing means among > 2 continuous variables. To test significance of patient characteristics between infragenicular arterial runoff subgroups, results were reported as p-values of multiple comparisons. Logistic regression was used to model associations between clinical factors and having less than 3-vessel infragenicular runoff. To avoid over-
fitting of data, a stepwise model path with an analysis of deviance function (stepAIC function) was used for stepwise variable selection (MASS package) to simplify an initial model of 18 variables (Akaike Information Criteria = 71.4) to one of 9 variables (Akaike Information Criteria = 57.0). A two-sided alpha level of 0.05 was used for all superiority testing. All data were analyzed and figures generated using R software (Version 2.13.1, The R Foundation for Statistical Computing, 2011).
RESULTS

Baseline Characteristics

Among 116 patients presenting with CLI the median age was 66 years (IQR, 60-79), 39% were female, and 70% had diabetes mellitus (Table 1). A non-diagnostic ABI was observed among 17 (15%) patients due to non-compressible vessels (Table 1). Among the remaining patients, the median ABI was 0.57 (IQR, 0.43-0.80). Overall, 85 (73%) had an ABI < 0.9, whereas 14 (12%) had a normal ABI (0.9-1.4). A moderately reduced (0.40-0.69) ABI was the category most commonly observed (49%).

In univariable analysis, the ABI did not correlate with age (p=0.82), body-mass index (p=0.57), or creatinine clearance (p=0.44). One-third had a previously attempted revascularization (i.e., lower extremity bypass grafting or endovascular intervention) procedure for PAD and 15% had prior amputation related to arterial insufficiency. Patients with no prior attempt at lower extremity revascularization tended to have a higher ABI (p = 0.02) (Table 3). A significantly higher ABI was also noted among patients presenting with a history of prior amputation (p = 0.02); accordingly, a history of prior amputation was often noted in the normal ABI subgroup (43%) (Table 1).

Arterial Runoff

Qualitatively, normal or mildly-reduced ABI results were distributed across all infragenicular runoff groups (Figure 1). The highest median ABI results were noted among patients with the lowest number of infragenicular arterial runoff
vessels (Table 2). The lowest median ABI was noted in the 1-vessel runoff group [0.49, (IQR, 0.39-0.70)], whereas the highest was noted in the 0-vessel runoff group [0.63, (IQR, 0.57-0.69)]. ABI values trended lower as distal limb perfusion improved (Figure 2). Nevertheless, across all infragenicular runoff groups, ABI was not significantly different (p=0.28) (Figure 2).

The trends for TBI were generally contrary to those of ABI. Interestingly, patients with 3-vessel infragenicular arterial runoff had the highest median TBI [0.48 (IQR, 0.30-0.66)], whereas those with no infragenicular runoff had the lowest TBI [0.27 (IQR, 0.15-0.42)] (Figure 2). Consequently, TBI values trended higher as arterial supply to the distal extremity improved (Figure 2). Similar to ABI results, TBI results were not significantly different relative to the number infragenicular runoff vessels (p=0.89).

When analyzed by patency of unique infragenicular arterial segment, ABI trends were notable (Figure 3). In fact, the median ABI was lowest when the infragenicular artery was patent; the highest ABI was noted when these same segments were occluded. This finding was noted across all three arterial distributions (i.e., anterior tibial artery, posterior tibial artery, or peroneal artery). Therefore, based on patency status the ABI tended to increase with worsening stenosis in the anterior tibial artery (p=0.013) and posterior tibial artery (p=0.002). For the peroneal artery, the trend for ABI by arterial patency status was similar although not significantly different (p=0.15). Conversely, in the same arterial segments, median TBI was highest among patent arteries. When compared across
the spectrum of patency for individual vessels, TBI results for any of the 3 vascular segments were not significantly different.

Abnormal infragenicular runoff, defined by having < 3-vessel arterial perfusion to the distal limb, was associated with several clinical variables. Stepwise multivariable logistic regression was used to model associations between abnormal runoff and these factors. The odds of having an abnormal arterial runoff were increased by advanced age (p=0.05), hyperlipidemia (p=0.05), and elevated ABI (p=0.01) (Table 4). A history of prior CAD (p=0.04) and improved creatinine clearance (0.01) were associated with reduced odds of having abnormal runoff.

**ABI Relative to Rutherford Classification**

Based on presenting severity of CLI, patients were distributed relatively evenly by clinical severity of symptoms; 30 (26%) patients presented with Rutherford Class 4 CLI (i.e., ischemic rest pain), 43 (37%) with Class 5 CLI (i.e., minor ischemia tissue loss), and 43 (37%) with Class 6 CLI (i.e., major tissue loss with gangrene) (Table 1). Interestingly, 87% of patients without tissue loss (i.e., Rutherford Class 4 CLI) had a moderate or severely reduced ABI result, or non-compressible arteries. Conversely, 25 (29%) of 86 patients with arterial insufficiency wounds (i.e., RC 5-6) had a normal or mildly reduced baseline ABI.

When evaluated by clinical severity, the median ABI rose as Rutherford classification increased, indicating more advanced limb ischemia (Figure 4). In fact, a majority of patients with a normal ABI (57%) had the most severe limb ischemia (i.e., RC 6 CLI) (Table 1). However, despite these interesting trends, ABI was not
statistically different across Rutherford classification subgroups (p=0.24). Similarly, TBI was not significantly different across RC subgroups (p=0.42) (Figure 4).

Overall, there was a significant association between Rutherford classification and infragenicular runoff (p=0.003). Specifically, when clinical severity worsened, so did the arterial runoff below the knee. The converse was also true; patients with the lowest clinical severity (i.e. RC 4) commonly had 3-vessel infragenicular arterial runoff (p=0.01).

Normal ABI and severely reduced ABI results were most frequently noted in the presence of tissue loss (i.e., RC 5 and RC 6) (Figure 5). TBI results < 0.4 were more frequently noted in the RC 5 and 6 groups. Among patients with RC 5 or RC 6 tissue loss, 65% had a TSP < 50 mmHg. Furthermore, 34% of CLI patients with available toe pressure assessment had a TSP < 30 mmHg. A TSP < 30 mmHg was noted in 29% of patients with rest pain alone. Among patients with gangrenous tissue loss (i.e., RC 6 CLI), 53% had a TSP < 50 mmHg. Patients with a normal ABI and TSP were noted in all 4 arterial runoff groups (Figure 6). Limited statistical power prevented further analysis of TBI and TSP results among subgroups.

**ABI Relative to TBI and TSP**

Among 38 CLI patients with available ABI and TBI results, 22 (58%) had an ABI < 0.9 and TBI < 0.7. Conversely, 4 (11%) patients had a normal ABI (0.9-1.4) and normal TBI (≥0.7). Overall, 91% of patients with CLI had a TBI < 0.7.

Figure 7 demonstrates the relationship between TBI and TSP among ABI subgroups. Moderately or severely reduced TBI results were most frequently noted
in the presence of tissue loss. Among patients with tissue loss, 65% had a TSP < 50 mmHg. Among patients with rest pain alone, only 29% had TSP < 30 mmHg. Across all patients with available results of indexed ankle and toe pressures, ABI did not correlate with TBI (p=0.23) or TSP (p=0.27).

**ABI In Diabetes**

The median ABI did not differ among those with [0.59 (IQR, 0.44-0.83)] or without diabetes [0.52 (IQR, 0.41-0.74)] (p=0.30). Overall, 15% of patients had a non-compressible ABI, of which 71% had diabetes. Median TBI was similar among those with [0.29 (IQR, 0.20-0.39)] and without diabetes [0.31 (IQR, 0.22-0.48)] (p=0.69). For patients with diabetes, the median TSP was 41 mmHg (IQR, 25-62 mmHg), which was not significantly different from results of non-diabetic patients (p=0.85).
DISCUSSION

CLI is frequently associated with multilevel arterial disease, including suprainguinal “inflow” lesions and infrainguinal “outflow” disease. Those with infragenicular disease have a particularly poor prognosis (Gray, Grant et al. 2010) and represent a population that can be challenging to diagnose (Aerden, Massaad et al. 2011, Aboyans, Criqui et al. 2012). This analysis highlights the limitations of noninvasive assessment for CLI, while reinforcing the value of clinical assessment, to predict distal limb perfusion. In this study, ABI provided a modest representation of clinical severity. In fact, the highest median ABI results were noted in subgroups with the poorest arterial runoff. Such findings support current guidelines that call for additional testing in the initial assessment of CLI (Norgren, Hiatt et al. 2007). Among this retrospectively identified CLI population, a striking majority (91%) had an abnormal TBI (< 0.7) compared to only 73% of patients with an ABI < 0.9. Although trends for TBI and TSP were more congruent with clinical severity that was ABI, limited statistical power in this analysis precluded further conclusions.

While the ABI remains a principal test in assessing PAD, the test has important limitations particularly when applied to the most severe forms of arterial disease. Variations in technique and expertise in interpreting test results limit the accuracy of the ABI (Aboyans, Criqui et al. 2012). The reproducibility of the test worsens with advanced arterial disease, with higher interobserver variability during ABI interpretation (Aboyans, Criqui et al. 2012). Second, in the presence of heavily calcified, non-compressible infragenicular arteries characteristic of CLI, the ABI often delivers non-diagnostic results (Aboyans, Ho et al. 2008, Suominen,
Third, the ABI underestimates the extent of microvascular occlusive disease, with a weak correlation to angiographic atherosclerosis (Aerden, Massaad et al. 2011). This analysis provides qualification of ABI results among patients with CLI, and should alert the clinician to the need for heightened scrutiny when interpreting ABI results among patients with CLI.

Perhaps the most important limitation of ABI among CLI patients is a weakened ability to detect severe below-knee arterial disease. False negative (e.g., ‘normal’ or ‘mildly reduced’) ABI results mislead the noninvasive evaluation of CLI patients that potentially restricts consideration for reperfusion options. It is easy to see how this could happen. Because ABI is reported as the higher of the anterior tibial or posterior tibial pressure signals, a relatively normal Doppler signal in one tibiopedal branch might be obscured by an entirely absent or abnormal signal in the other branch, such that the calculated ABI is within the normal range (Aboyans, Criqui et al. 2012). The merits of angiosome-directed endovascular revascularization are apparent and should be carefully considered in context of both ipsilateral ankle pressures and the clinical presentation (Bunte and Shishehbor 2013).

It has been suggested that the ABI provides a weak correlation to angiographic atherosclerosis (Aerden, Massaad et al. 2011). Those results are also suggested with this analysis. As demonstrated in Figure 2, median ABI tended to increase despite worsening degrees of stenosis. To the contrary, TBI tended to congruently decline in the presence of worsening arterial disease. So, what causes the ABI to be rise in the face of poorer limb perfusion? The answer is likely
multifactorial. First, vascular calcification is associated with an abnormally elevated ABI (>1.4), and both are strongly associated with occlusive PAD. Diabetes has been reported as a dominant factor associated with noncompressible, calcified vessels often represented by an elevated ABI (Aboyans, Criqui et al. 2012). In our cohort, 16% of patients had indeterminate ABI results due to vascular calcification. Another explanation may be that systolic blood pressures may be preserved in one ankle vessel (e.g., anterior tibial/dorsalis pedis artery) relative to the other vessel (e.g., posterior tibial artery), thereby providing a deceptive elevation of ABI. Diffuse collateralization of the infragenicular arteries, particularly from the peroneal artery, may also maintain sufficient systolic pressure to the ankle but not necessarily to the foot. Therefore, when vascular calcification is present the results of office-based testing, such as ABI and TBI, must be scrutinized and qualified. More importantly, the diagnosis of CLI should not be dismissed in the presence of a “normal” or “mildly reduced” ABI.

While an important prognostic tool, the ABI is adversely influenced by vascular calcification (McDermott, Liu et al. 2004, Arain, Ye et al. 2012). Studies elsewhere importantly highlight that a normal ABI does not exclude the presence of PAD (Suominen, Rantanen et al. 2008, Aboyans, Criqui et al. 2012). In one study, nearly 25% of patients referred for screening had a normal ABI yet a TBI result suggestive of PAD (Suominen, Rantanen et al. 2008). In this cohort, 12% of subjects with rest pain or ischemic tissue loss had a normal ABI (0.9-1.4). Patients most likely to have a normal ABI included those with Rutherford 6 PAD, poor infragenicular runoff, and a history of prior amputation. In any case, when flow to
the ankle is preserved, the often less calcified and more compliant arteries of the toe more accurately represent true distal perfusion.

In patients with severe diffuse vascular disease, the TBI may offer a more accurate representation of flow to the foot. This seemed to be the case in our study. In contrast to ABI, the median TBI tended to worsen with clinical severity of CLI and angiographic findings. However, the usefulness of TBI among patients with suspected PAD has been questioned. First, the reliability of TBI and TSP among patients with suspected PAD remains modest (Romanos, Raspovic et al. 2010). Furthermore, Brooks and colleagues determined the TBI offers little advantage over ABI alone without heavy calcification; only among patients with ABI > 1.3 did TBI offer superior diagnostic utility (Brooks, Dean et al. 2001). Only 3 of 174 patients in the Brooks analysis had rest pain and none had ischemic tissue loss. Studies among patients with suspected PAD have used lower normal limits ranging from < 0.6 to < 0.75 with reported sensitivity ranging from 90-100% and specificity of 65-100% (Hoyer, Sandermann et al. 2013). Among healthy populations not suspected to have PAD, normal lower limits for TBI range from 0.49-0.74 (Hoyer, Sandermann et al. 2013). Similarly, TSP has been suggested as a complimentary test when CLI is suspected, although studies to validate recommendations are lacking. Although our toe pressure analysis is limited in statistical power, these findings suggest the potential importance of toe pressure assessment in evaluating patients with CLI.
Limitations

Patients in this analysis were retrospectively selected by a diagnosis of CLI and having diagnostic angiography, although a number of patients did not have angiography complete with imaging of the infragenicular arteries. For example, patients that underwent revascularization of above-the-knee “inflow” disease (e.g., to the iliac or superficial femoral arteries) did not have distal arterial runoff below the knee. Our analysis was further limited by reduced statistical power due to a relatively small number of patients with toe-pressure assessment at the time of ABI. The absolute number of patients within any particular ABI or angiographic subgroup was also limited. Opportunity for bias exists given the retrospective nature of data collection and potentially inconsistent interpretation of disease severity. Despite limitations in our analysis, efforts are currently underway to enhance the understanding of noninvasive and angiographic assessment in CLI with prospective registries (Mustapha, Saab et al. 2013, Sarode 2013).

This analysis focused on the ankle-brachial index, and not ankle systolic pressure, which is the currently recommended non-invasive physiologic confirmation of CLI (Norgren, Hiatt et al. 2007). Variations of brachial-ankle blood pressure relationships have been suggested to be more sensitive than the current standard for ABI assessment (Aerden, Massaad et al. 2011, Nead, Cooke et al. 2013), although were not evaluated in this analysis.

In a contemporary guideline statement, patient-specific clinical features associated with interpretation of ABI represent an unmet research need (Aboyans, Criqui et al. 2012). To that end, we hope that our findings highlight the limitations of
ABI and prompt clinicians to consider alternative diagnostic tests and maintain a high level of clinical suspicion when considering a patient to have CLI. Further understanding of the relationship between angiographic findings and clinical severity becomes even more relevant when considered in context of future registries and clinical studies that assess patients with severe arterial disease.
CONCLUSION

Among patients with CLI, ABI is a modest predictor of infragenicular arterial patency. In fact, assessment of clinical severity may have a stronger association with infragenicular runoff than ABI. Therefore, when CLI is suspected despite normal or mildly reduced ABI results, additional testing such as toe pressure assessment and invasive angiography may help to confirm diagnosis and guide treatment. Currently, it remains unclear whether TBI might improve diagnostic accuracy in such circumstances. Nevertheless, these findings are supportive of ongoing prospective registries evaluating complimentary non-invasive testing. To that end, CLI patients might receive enhanced scrutiny with appropriate diagnostic testing that offers the opportunity to prevent amputation.
# APPENDIX

**Table 1: Baseline characteristics according to ABI subgroups.** Characteristics are listed for 116 consecutive patients referred for critical limb ischemia and separated by sub-category of ABI results.

<table>
<thead>
<tr>
<th>BASELINE CHARACTERISTICS</th>
<th>OVERALL (N=116)</th>
<th>Normal ABI (0.9-1.4) (n=14)</th>
<th>Mildly reduced ABI (0.7-0.89) (n=15)</th>
<th>Moderately reduced ABI (0.4-0.69) (n=48)</th>
<th>Severely Reduced ABI (&lt;0.4) (n=22)</th>
<th>Non-compressible ABI (&gt;1.4) (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, median, IQR)</td>
<td>66 (60-79)</td>
<td>73 (57-81)</td>
<td>61 (60-72)</td>
<td>65 (59-73)</td>
<td>72 (62-84)</td>
<td>65 (60-82)</td>
</tr>
<tr>
<td>Female (n,% )</td>
<td>45 (39%)</td>
<td>4 (29%)</td>
<td>6 (40%)</td>
<td>17 (35%)</td>
<td>11 (50%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>Caucasian (n,% )</td>
<td>71 (61%)</td>
<td>10 (71%)</td>
<td>6 (40%)</td>
<td>30 (62%)</td>
<td>13 (59%)</td>
<td>12 (71%)</td>
</tr>
<tr>
<td>Hypertension (n,% )</td>
<td>114 (98%)</td>
<td>14 (100%)</td>
<td>15 (100%)</td>
<td>47 (98%)</td>
<td>22 (100%)</td>
<td>16 (94%)</td>
</tr>
<tr>
<td>Hyperlipidemia (n,% )</td>
<td>105 (91%)</td>
<td>12 (86%)</td>
<td>13 (87%)</td>
<td>44 (92%)</td>
<td>21 (95%)</td>
<td>15 (88%)</td>
</tr>
<tr>
<td>Diabetes mellitus (n,% )</td>
<td>81 (70%)</td>
<td>10 (71%)</td>
<td>11 (73%)</td>
<td>33 (69%)</td>
<td>15 (68%)</td>
<td>12 (71%)</td>
</tr>
<tr>
<td>Tobacco abuse, current or former (n,% )</td>
<td>89 (77%)</td>
<td>12 (86%)</td>
<td>11 (73%)</td>
<td>37 (77%)</td>
<td>17 (81%)</td>
<td>12 (71%)</td>
</tr>
<tr>
<td>Prior CAD (n,% )</td>
<td>65 (56%)</td>
<td>12 (86%)</td>
<td>8 (53%)</td>
<td>27 (56%)</td>
<td>10 (45%)</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>Prior CVA or TIA (n,% )</td>
<td>23 (20%)</td>
<td>3 (21%)</td>
<td>2 (13%)</td>
<td>11 (23%)</td>
<td>4 (18%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Prior PAD revascularization (n,% )</td>
<td>30 (34%)</td>
<td>4 (29%)</td>
<td>2 (13%)</td>
<td>18 (38%)</td>
<td>12 (55%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Prior amputation (n,% )</td>
<td>17 (15%)</td>
<td>6 (43%)</td>
<td>1 (7%)</td>
<td>4 (8%)</td>
<td>2 (9%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Body Mass Index (median, IQR)</td>
<td>27.1 (23.9-29.8)</td>
<td>25.5 (22.9-25.8)</td>
<td>27.1 (25.0-35.5)</td>
<td>29.1 (25.3-31.7)</td>
<td>24.1 (20.2-29.5)</td>
<td>25.5 (22.9-32.0)</td>
</tr>
<tr>
<td>Creatinine Clearance (mL/min, median, IQR)</td>
<td>62.6 (42.4-90.9)</td>
<td>62.0 (44.2-91.7)</td>
<td>66.6 (42.3-125.2)</td>
<td>75.1 (57.2-103.2)</td>
<td>48.7 (34.0-62.3)</td>
<td>60.1 (18.0-85.8)</td>
</tr>
<tr>
<td>Rutherford Classification (n,% )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>30 (26%)</td>
<td>1 (7%)</td>
<td>3 (20%)</td>
<td>18 (38%)</td>
<td>4 (18%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>5</td>
<td>43 (37%)</td>
<td>5 (36%)</td>
<td>7 (47%)</td>
<td>17 (35%)</td>
<td>10 (45%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>6</td>
<td>43 (37%)</td>
<td>8 (57%)</td>
<td>5 (33%)</td>
<td>13 (27%)</td>
<td>8 (36%)</td>
<td>9 (53%)</td>
</tr>
</tbody>
</table>
Table 2: Baseline characteristics according to number of infragenicular arterial runoff vessels. Characteristics are listed for 116 consecutive patients referred for critical limb ischemia. Among 89 patients with available angiography below the knee, these characteristics were separated into subgroups by the number of infragenicular arteries providing runoff to the distal lower extremity. A p-value < 0.05 indicates a significant difference in the values of individual characteristics between runoff subgroups.

<table>
<thead>
<tr>
<th>BASELINE CHARACTERISTIC</th>
<th>OVERALL (n=116)</th>
<th>None (n=9)</th>
<th>One-vessel (n=31)</th>
<th>Two-vessel (n=33)</th>
<th>Three-vessel (n=16)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, median, IQR)</td>
<td>66 (60-79)</td>
<td>72 (61-74)</td>
<td>78 (63-85)</td>
<td>64 (58-71)</td>
<td>62 (54-66)</td>
<td>0.01</td>
</tr>
<tr>
<td>Female (n,% )</td>
<td>45 (39%)</td>
<td>0</td>
<td>18 (58%)</td>
<td>11 (33%)</td>
<td>6 (38%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Caucasian (n,% )</td>
<td>71 (61%)</td>
<td>6 (67%)</td>
<td>20 (65%)</td>
<td>17 (52%)</td>
<td>10 (62%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hypertension (n,% )</td>
<td>114 (98%)</td>
<td>8 (89%)</td>
<td>30 (97%)</td>
<td>33 (100%)</td>
<td>16 (100%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hyperlipidemia (n,% )</td>
<td>105 (91%)</td>
<td>8 (89%)</td>
<td>28 (90%)</td>
<td>30 (91%)</td>
<td>13 (81%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Diabetes mellitus (n,% )</td>
<td>81 (70%)</td>
<td>7 (78%)</td>
<td>18 (58%)</td>
<td>25 (76%)</td>
<td>12 (75%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Tobacco abuse, current or former (n,% )</td>
<td>89 (77%)</td>
<td>5 (56%)</td>
<td>17 (55%)</td>
<td>28 (85%)</td>
<td>16 (100%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior CAD (n,% )</td>
<td>68 (59%)</td>
<td>6 (67%)</td>
<td>21 (68%)</td>
<td>18 (55%)</td>
<td>11 (69%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Prior CVA or TIA (n,% )</td>
<td>23 (20%)</td>
<td>3 (33%)</td>
<td>8 (26%)</td>
<td>7 (21%)</td>
<td>3 (19%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Prior PAD revascularization (n,% )</td>
<td>39 (34%)</td>
<td>3 (33%)</td>
<td>11 (35%)</td>
<td>10 (30%)</td>
<td>7 (44%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Prior amputation (n,% )</td>
<td>17 (15%)</td>
<td>1 (11%)</td>
<td>5 (16%)</td>
<td>8 (24%)</td>
<td>2 (13%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Body Mass Index (median, IQR)</td>
<td>27.1 (23.0-31.6)</td>
<td>27.1 (26.8-32.1)</td>
<td>25.6 (22.5-31.0)</td>
<td>26.9 (23.7-33.3)</td>
<td>30.0 (27.7-33.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Creatinine Clearance (mL/min, median, IQR)</td>
<td>62.6 (42.4-98.0)</td>
<td>58.2 (43.7-64.8)</td>
<td>50.0 (34.2-64.3)</td>
<td>75.2 (49.0-103.9)</td>
<td>99.0 (60.0-137.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Rutherford Classification (n,% )</td>
<td>4 39 (26%)</td>
<td>1 (11%)</td>
<td>4 (13%)</td>
<td>9 (27%)</td>
<td>9 (56%)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>5 43 (37%)</td>
<td>3 (33%)</td>
<td>12 (39%)</td>
<td>11 (33%)</td>
<td>3 (19%)</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>6 43 (37%)</td>
<td>5 (56%)</td>
<td>15 (48%)</td>
<td>13 (39%)</td>
<td>4 (25%)</td>
<td>0.37</td>
</tr>
<tr>
<td>*Ankle-brachial index (median, IQR)</td>
<td>0.57 (0.43-0.80)</td>
<td>0.63 (0.57-0.69)</td>
<td>0.49 (0.39-0.70)</td>
<td>0.58 (0.41-0.94)</td>
<td>0.51 (0.33-0.63)</td>
<td>0.35</td>
</tr>
<tr>
<td>Toe-brachial index (median, IQR)</td>
<td>0.29 (0.20-0.42)</td>
<td>0.27 (0.15-0.39)</td>
<td>0.28 (0.20-0.38)</td>
<td>0.29 (0.21-0.32)</td>
<td>0.48 (0.30-0.66)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

†27 patients did not have infragenicular runoff performed during lower extremity angiography
*17 patients were excluded due to a non-compressible baseline ABI
Table 3: Comparison of mean ABI based on presenting patient characteristics. A significantly higher mean ABI was noted among patients presenting with no prior PAD revascularization (p = 0.02) and prior amputation (p = 0.02). The mean ABI was not significantly different across other characteristics. Comparisons performed with the Wilcoxon sum-rank test. A p-value < 0.05 indicates a significant difference.

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>ABI</th>
<th>Baseline characteristic</th>
<th>ABI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Gender</td>
<td>0.55</td>
<td>Male Gender</td>
<td>0.63</td>
<td>0.13</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.60</td>
<td>Non-white</td>
<td>0.59</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.60</td>
<td>No hypertension</td>
<td>0.57</td>
<td>0.96</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.59</td>
<td>No hyperlipidemia</td>
<td>0.65</td>
<td>0.45</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.61</td>
<td>No Diabetes</td>
<td>0.57</td>
<td>0.41</td>
</tr>
<tr>
<td>Current or former tobacco abuse</td>
<td>0.60</td>
<td>No tobacco abuse</td>
<td>0.60</td>
<td>0.95</td>
</tr>
<tr>
<td>Prior CAD</td>
<td>0.64</td>
<td>No prior CAD</td>
<td>0.54</td>
<td>0.13</td>
</tr>
<tr>
<td>Prior CVA/TIA</td>
<td>0.55</td>
<td>No prior CVA/TIA</td>
<td>0.61</td>
<td>0.75</td>
</tr>
<tr>
<td>Prior PAD revascularization</td>
<td>0.52</td>
<td>No prior PAD revascularization</td>
<td>0.64</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior amputation</td>
<td>0.82</td>
<td>No prior amputation</td>
<td>0.56</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Table 4: Final multivariable logistic regression used to model association between clinical variables and abnormal lower extremity runoff. Arterial blood flow below the knee (i.e., infragenicular arterial runoff) is supplied by 3 arteries that arise at the knee and extend to the distal leg: the anterior tibial artery, posterior tibial artery, and peroneal artery. For the purpose of this analysis, the presence of less than 3-vessel runoff was considered abnormal. The odds of having abnormal arterial runoff was increased with increasing age, elevated ABI, and a history of hyperlipidemia. Conversely, the odds of abnormal runoff as reduced in the presence of prior CAD or an increase in creatinine clearance.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10-years)</td>
<td>2.10</td>
<td>1.03-5.03</td>
<td>0.05</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>19.4</td>
<td>1.11 – 457.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.14</td>
<td>0.01 – 1.10</td>
<td>0.10</td>
</tr>
<tr>
<td>Prior CAD</td>
<td>0.15</td>
<td>0.02 – 0.80</td>
<td>0.04</td>
</tr>
<tr>
<td>Prior CVA/TIA</td>
<td>4.84</td>
<td>0.68 – 62.8</td>
<td>0.16</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>0.73</td>
<td>0.56 – 0.90</td>
<td>0.01</td>
</tr>
<tr>
<td>(per 10 mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABI (per 0.1)</td>
<td>1.74</td>
<td>1.21 – 2.81</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; CVA: cerebrovascular accident; TIA: transient ischemic attack, ABI; ankle-brachial index
Figure 1: Distribution of ABI by number of infragenicular arterial runoff. Across all runoff groups, a moderately reduced ABI was the most common result. Severely reduced or non-compressible ABIs were observed most frequently among patients with at least 1-vessel runoff. A normal ABI (0.9-1.4) was most frequently noted among the 1- or 2-vessel runoff groups. 41 patients were excluded due to missingness of an interpretable ABI and/or infragenicular angiographic results.
Figure 2: ABI and TBI by number of patent infragenicular arterial runoff arteries. Panel A. The lowest median ABI was noted in the 1-vessel runoff group [0.49, (IQR, 0.39-0.70)], whereas the highest was noted in the 0-vessel runoff group [0.63, (IQR, 0.57-0.69)]. Across infragenicular runoff groups, ABI was not significantly different across subclasses (p=0.28). Panel B. The lowest median TBI [0.27, (IQR, 0.15-0.39)] was noted in the 0-vessel runoff group, whereas the highest median TBI [0.48, (IQR, 0.30-0.66)] was observed in the 3-vessel runoff group. Across vessel runoff groups, TBI was not significantly different (p=0.89).
Figure 3: Trend of ABI and TBI by patency of the anterior tibial, posterior tibial and peroneal arteries. Panel A. For each vessel, the ABI is reported according to vessel patency. Across the 3 infragenicular arteries, the median ABI tended to be higher in the presence of an occluded versus patent segment. Panel B. Unlike ABI, the median TBI tended to be lower in the presence of an occluded versus patent segment.
Figure 4: ABI and TBI by presenting Rutherford Classification. **Panel A.** The median ABI unexpectedly improved from Rutherford class 4 [0.50, IQR 0.44-0.61], Rutherford class 5 [0.54, IQR 0.40-0.79], and Rutherford class 6 [0.61, IQR 0.48-0.85], although there was no significant difference in ABI across all subgroups (p=0.24). **Panel B.** Similarly, the median TBI was not significantly different between Rutherford class 4 [0.32, IQR 0.19-0.44], Rutherford class 5 [0.24, IQR 0.18-0.32], and Rutherford class 6 [0.30, IQR 0.21-0.52] subgroups (p=0.42).
Figure 5: Distribution of non-invasive testing by Rutherford Classification.

**Panel A.** Normal ABI and severely reduced ABI results were most frequently noted in the presence of tissue loss (i.e., Rutherford class 5 and Rutherford class 6). **Panel B.** TBI results < 0.4 were more frequently noted in the RC 5 and 6 groups. **Panel C.** A normal TSP (> 60 mmHg) was noted in all 3 Rutherford subgroups and most commonly in the groups with severe tissue loss.
Figure 6: Distribution of non-invasive testing relative to infragenicular runoff. **Panel A.** Patients with 0-vessel runoff had the fewest ABI results and no patients with normal runoff were noted to have a normal ABI (0.9-1.4). **Panel B.** TBI results < 0.4 were more noted most frequently in the groups with abnormal arterial runoff (<3-vessel runoff). **Panel C.** A normal TSP (> 60 mmHg) was noted in all 4 arterial runoff subgroups.
Figure 7: TBI and TSP distribution among ABI subgroups. Results from CLI patients with available ABI and TBI (n=36) (Panel A) and ABI and TSP (n=35) (Panel B) are included below. A moderately reduced TBI was most often noted among those with normal ABI. Normal TBI and TSP results were most commonly observed with mildly reduced ABI.
BIBLIOGRAPHY


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