Arterial spectral waveform analysis in the prediction of diabetic foot ulcer healing

Pasha Normahani,1 Rishi Agrawal,1 Viknesh Sounderajah,1Prodromos Tsinaslanidis,1† Patrick Musonda,2 Zaheer Mehar,3 Katarzyna Powezka,1 Vasiliki Bravis,4 Mohammed Aslam1 and Usman Jaffer1

Abstract
Objective: We assessed the association between (1) severity of vessel wall calcification, (2) number of patent vessels at the ankle and (3) arterial spectral waveform features, as assessed on a focused ankle Duplex ultrasound (DUS), and healing at 12-months in a cohort of patients who had their diabetic foot ulcers conservatively managed.
Research design and methods: Scans performed on 50 limbs in 48 patients were included for analysis. Patient health records were prospectively reviewed for 12-months to assess for the outcome of ulcer healing.
Results: We identified that the number of waveform components, peak systolic velocity, systolic rise time and long forward flow as well as the number of vessels patent at the ankle on DUS, may be useful independent predictors of healing, as noted by the trend towards statistical significance.
Conclusion: Arterial spectral waveform features may be useful in predicting the chance of diabetic foot ulcer healing.

Keywords
vascular ultrasound; arterial spectral waveform; peripheral arterial disease; diabetic foot

Introduction
Peripheral arterial disease (PAD) is an important independent predictor of lower limb ulcer healing in patients with diabetes. However, the natural course of patients with arterial disease and diabetic foot ulceration remains unclear. Although re-vascularisation has been shown to be an effective treatment strategy, limb salvage rates following conservative treatment are approximately 54%, whilst foregoing the risk profile inherent to interventional procedures.1 The ability to accurately predict the chance of wound healing would assist clinicians in the management of patients presenting with diabetic foot ulceration.

As such, wound classification systems such as WiFi have been validated for this purpose.2 Bedside tests assessing flow and perfusion to the foot have also been demonstrated to have some utility in stratifying risk.3 However, little is known regarding the usefulness of arterial spectral waveform analysis. Duplex Ultrasound (DUS) is well-established practice in determining the anatomical distribution of arterial disease and it has been postulated that the arterial spectral waveform at the ankle can provide useful information regarding the upstream and downstream state of the vasculature in addition to assessing the burden of arterial calcification.

In this study, we aim to evaluate whether there is an association between (1) severity of vessel wall calcification, (2) number of patent vessels at the ankle and (3) arterial spectral waveform features as assessed on a focused ankle DUS and healing at 12-months in a cohort

1 Imperial Vascular Unit, Imperial College NHS Healthcare Trust, London, UK
2 School of Medicine, Health Policy & Practice, University of East Anglia, London, UK
3 West Middlesex University Hospital Diabetic Foot Service, Chelsea and Westminster Hospital NHS Foundation Trust, Isleworth, London, UK
4 Department of Diabetes and Endocrinology, St Mary’s Hospital, Imperial College NHS Healthcare Trust, London, UK

Corresponding author: Pasha Normahani, Imperial Vascular Unit, Imperial College NHS Healthcare Trust, QEQM building, St Mary’s Hospital, Praed Street, London W21NY, UK.
Email: p.normahani@imperial.ac.uk
of patients who have had their diabetic foot ulcers conservatively managed.

**Research design and methods**

The study was approved by the National Research Ethics Committee (reference no. 17/LO/1447).

**Data collection**

Data were collected as part of a previously published study exploring the effectiveness of a multi-centre training programme to teach focused DUS examination of the anterior and posterior tibial arteries at the level of the ankle for the detection of PAD in diabetes. As part of the training programme, consecutive patients presenting to diabetic foot clinics at a teaching hospital in London and a district general hospital in London were invited to take part in the study and provided informed consent. A fully qualified vascular scientist performed the scan on each patient. All scans performed in this study utilised the Mindray M7 (Shenzhen, China) Portable Ultrasound System with a linear 6 to 14 MHz transducer.

Data were collected regarding components of the waveform (monophasic, biphasic, triphasic, occluded), peak systolic velocities (PSV), the systolic rise time (RT), the presence or absence of spectral broadening, infilling of the spectral window and long forward flow in diastole. The latter three variables were only collected for mono- and bi-phasic waveforms. Additionally, data were collected regarding the number of patent vessels at the ankle (anterior and posterior tibial arteries) and the level of vessel wall calcification, which was classified as either mild/moderate or severe (mild = visible calcification, no acoustic shadowing; moderate = short segments of acoustic shadowing; severe = long segments of acoustic shadowing). Descriptions of duplex ultrasound parameters are presented in Table 1.

Patient electronic health records (eHR) were prospectively reviewed for 12-months following initial presentation to assess for the outcome of ulcer healing.

**Statistical analysis**

For the purpose of analysis, the single best vessel (as assessed by the quality of the waveform: number of components followed by the absence of adverse features such as broadening, infilling and long forward flow) was used for analysis. The Shapiro-Wilk W-test and q-q plot were used to confirm that the continuous data were not normally distributed. Duplex ultrasound predictor variables were input into a binomial logistic regression model. Logit probabilities were converted to odds ratios. All analyses were performed using R (R version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org).

**Results**

A total of 83 limbs in 65 patients were scanned. Patients without active foot disease (n = 19) and those who had undergone re-vascularisation (n = 14) during the 12-month period following scanning were excluded from analysis. Therefore, results from scans performed on 50 limbs in 48 patients were included for analysis. Patient demographics are presented in Table 2. Twenty-seven out of 50 diabetic foot wounds (54%) healed within the 12-month follow-up period. Adjusted odds ratios for DUS predictor variables are presented in Table 3.

**Discussion**

This is the first study to investigate the association between arterial spectral waveform features and the likelihood of diabetic foot ulcer healing. We included only conservatively managed patients because revascularisation after detecting PAD will ultimately influence the clinical outcome. This group allows us to exclusively investigate the role of ischaemia in wound healing without the influence of revascularisation. These patients received the same non-surgical care when compared to those patients undergoing revascularisation.

Although our study is underpowered, we have identified that certain spectral waveform features, such as the number of waveform components, PSV, RT and long forward flow in diastole as well as the number of vessels patent at the ankle on DUS, may be useful independent predictors of diabetic foot ulcer healing, as noted by the trend towards statistical significance. The ability to predict the chance of ulcer healing using arterial spectral waveform analysis is particularly attractive given that visual waveform analysis is one of the most accurate bedside diagnostic tool for the detection of PAD in people with diabetes. Therefore, risk assessment can be made at the time of presentation, which may in turn inform the urgency of onward vascular surgery referral, anatomical imaging and revascularisation, if required.

Better characterisation of flow profiles in the tibial vessels can give useful information regarding both the ‘up- and down-stream’ status of the arterial tree. Loss of pulsatility, long RT and low PSV are suggestive of severe upstream stenosis or occlusion and a long forward flow may be suggestive of distal vasodilatation in response to infection or ischaemia. In the future, we aim to further characterise waveform features that may be relevant to
**Table 1.** Description of duplex parameters.

| Feature                  | Description | Example | Description       |
|--------------------------|-------------|---------|-------------------|
| Components               |             |         |                   |
| Monophasic               |             | ![Monophasic waveform](image1) | Monophasic waveform |
| Biphasic                 |             | ![Biphasic waveform](image2) | Biphasic waveform |
| Triphasic                |             | ![Triphasic waveform](image3) | Triphasic waveform |
| Peak systolic velocity   |             | ![Measurement of peak systolic velocity](image4) | Measurement of peak systolic velocity |
| Systolic rise time       |             | ![Measurement of systolic rise time](image5) | Measurement of systolic rise time |
| Spectral broadening      | Yes         | ![Broad biphasic waveform](image6) | Broad biphasic waveform |

(Continued)
| Feature                  | Description | Example                                      | Description                                      |
|-------------------------|-------------|----------------------------------------------|--------------------------------------------------|
| No                      | Narrow biphasic waveform | ![Image](image1) | ![Image](image2) |
| Infilling               | Yes         | ![Image](image3) | ![Image](image4) | Loss of spectral window |
| No                      | Spectral window is maintained | ![Image](image5) | ![Image](image6) |
| Long forward flow       | Yes         | ![Image](image7) | ![Image](image8) | Monophasic waveform with long forward flow in diastole |
| No                      | Monophasic waveform with absent forward flow in diastole | ![Image](image9) | ![Image](image10) |
| Vessel wall calcification | Mild       | ![Image](image11) | ![Image](image12) | Visible calcification but no acoustic shadowing |
| Severe                  |              | ![Image](image13) | ![Image](image14) | Long segments of acoustic shadowing |
ulcer healing in order to develop new criteria that could be integrated into established or novel classification systems for more accurate grading of ischaemia. A previous study showed that integrating skin perfusion pressure assessment into the WIfI classification system resulted in more accurate staging.6

Although the presence of PAD is a major determinant of ulcer healing, other factors must also be considered when determining the chance of ulcer healing. The National Diabetic Foot Care Audit analysed data on over 27,000 ulcers and identified 15 important variables including the presence of PAD, size and number of ulcers, gender, inactive charcot, duration of diabetes, acute comorbidities and time to first expert assessment.7 Evidence is also emerging that diligent wound care, including regular debridement, dressings and offloading are also important predictors of healing.8,9

### Author Contributions

P.N. is guarantor of the manuscript. P.N., R.A., P.T., Z.M. and K.P. contributed to data collection. P.N., P.M. and U.J. contributed to data analysis. P.N., V.S., U.J., V.B. and M.A. contributed to preparation and editing of the manuscript.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: P.N. is funded by a National Institute for Health Research (NIHR) Academic Clinical Fellowship award for this research project.

### ORCID iDs

Pasha Normahani [https://orcid.org/0000-0002-6362-7535](https://orcid.org/0000-0002-6362-7535)

Prodromos Tsinaslanidis [https://orcid.org/0000-0001-6059-2720](https://orcid.org/0000-0001-6059-2720)

### References

1. Forsythe RO, Brownnigg J, Hinchliffe RJ. Peripheral arterial disease and revascularization of the diabetic foot. Diabetes Obes Metab 2015; 17(5): 435–444.
2. Mills JL, Conte MS, Armstrong DG, et al. The society for vascular surgery lower extremity threatened limb classification system: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg 2014; 59(1): 220–234.e1–2.
3. Wang Z, Hasan R, Firwana B, et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. J Vasc Surg 2016; 63(2): 295–368.e2.
4. Normahani P, Agrawal R, Bravis V, et al. Effectiveness of a multicenter training programme to teach point-of-care vascular ultrasound for the detection of peripheral arterial disease in people with diabetes. J Foot Ankle Res 2018; 11: 41.
5. Forsythe RO, Apelqvist J, Boyko EJ, et al. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: a systematic review. Diabetes Metab Res Rev 2020; 36(Suppl. 1): e3277.
6. Kimura T, Watanabe Y, Tokuoka S, et al. Utility of skin perfusion pressure values with the society for vascular

### Table 2. Demographics of participants.

| Factor                                      | Value (Percentage) |
|---------------------------------------------|--------------------|
| n                                           | 48                 |
| Gender = male (%)                           | 32 (66.7)          |
| Age (mean (SD))                             | 67.6 (11.7)        |
| Diabetes type = Type2 (%)                   | 44 (91.7)          |
| Duration of diabetes (mean (SD))            | 19.3 (10.1)        |
| Renal failure = yes (%)                     | 16 (33.3)          |
| Retinopathy = yes (%)                       | 26 (54.2)          |
| Myocardial infarction = yes (%)             | 7 (14.6)           |
| Angina = yes (%)                            | 9 (18.8)           |
| Heart failure = yes (%)                     | 6 (12.5)           |
| Stroke = yes (%)                            | 6 (12.5)           |
| Hypertension = yes (%)                      | 34 (70.8)          |
| Neuropathy = yes (%)                        | 39 (81.2)          |

### Table 3. Adjusted odds ratios for DUS predictor variables.

| Factor                                      | Odds ratio (95% CI) | p value |
|---------------------------------------------|---------------------|---------|
| Waveform                                    |                     |         |
| Tri/bi-phasic                               | Ref                 |         |
| Monophasic                                  | 4.61e-13 (6.99e-3, 3.04e-15) | 0.06   |
| Peak systolic velocity (PSV)                | 1.07 (0.10, 1.15)   | 0.08   |
| Systolic rise time (RT)                     | 1.24e-57 (3.41e-97, 4.50e-2) | 0.06   |
| Calcium load                                |                     |         |
| Mild/moderate                               | Ref                 |         |
| Severe                                      | 1.95e-2 (5.56e-5, 6.81) | 0.19   |
| Spectral broadening                         | No                  |         |
| Yes                                         | 4.29 (0.03, 548.79) | 0.56   |
| Long forward flow in diastole               | No                  |         |
| Yes                                         | 38.18 (0.84, 1731.72) | 0.06   |
| Infilling of spectral window                | No                  |         |
| Yes                                         | 1.92e-13 (∞,∞)      | 0.99   |
| Number of vessels patent at the ankle       |                     |         |
| 2 vessels                                   | Ref                 |         |
| 1 vessel only                               | 7.47e-3 (3.06e-2, 1.82) | 0.08   |
7. NHS Digital. National diabetes foot care audit fourth annual report, 2019. https://www.hqip.org.uk/resource/national-diabetes-foot-care-audit-fourth-annual-report/ (accessed 03 May 2020).

8. Alexiadou K, Doupis J. Management of diabetic foot ulcers. *Diabetes Ther* 2012; 3(1): 4.

9. Game FL, Hinchliffe RJ, Apelqvist J, et al. A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev* 2012; 28(Suppl. 1): 119–1141.