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(71) Applicant (for all designated States except US): **UNIVERSITY COLLEGE CARDIFF CONSULTANTS LIMITED** [GB/GB]; 30-36 Newport Road, Cardiff CF24 0DE (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **WILLIAMS, Dean** [GB/GB]; Ysbyty Gwynedd Penrhogarnedd, Bangor, Gwynedd LL57 2PW (GB). **HARDING, Keith, Gordon** [GB/GB]; Wound Healing Research Unit, Cardiff University, Heath Park, Cardiff CF14 4XN (GB).

(74) Agents: **FYLES, Julie, Marie** et al.; Wynne-Jones Laine & James, Morgan Arcade Chambers, 33 St Mary Street, Cardiff CF10 1AB (GB).

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(54) Title: IMPROVEMENTS RELATING TO THE DETECTION OF LOWER LIMB DISEASE

(57) Abstract: The invention relates to a method for screening for peripheral limb disease comprising the use of Doppler sound to investigate the presence of reverse flow in peripheral blood vessels.



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IMPROVEMENTS RELATING TO THE DETECTION OF LOWER LIMB DISEASE

The invention relates to a method for detecting peripheral limb disease and, in particular, lower limb disease which is, typically, common in individuals suffering from diabetes. Further, the invention relates to the use of waveform instrumentation, and in particular a hand held for device for use in the aforementioned method.

Foot related disease is the most common cause for hospital admission amongst the diabetic population and is recognised as the most common cause of non-traumatic lower limb amputation in the western world. People with diabetes are over 20 times more likely to undergo an amputation compared to the rest of the population (1) and since this population is growing it is placing increasing demands on healthcare provision.

The main risk factors in the development of diabetic foot disease are peripheral neuropathy and peripheral arterial occlusive disease. The detection of significant arterial disease is vital to the prevention and treatment of foot disease. The unreliable nature of the symptoms and signs of lower limb arterial insufficiency in diabetes means that non-invasive tests are essential to achieve effective screening (2,3). The European Working Group on critical leg ischaemia recommends an additional, non-invasive vascular assessment for patients with diabetes and foot ulceration (4).

Commonly employed screening techniques used in assessing lower limb perfusion are the palpation of foot pulses and calculation of the Ankle-brachial

pressure index (ABPI) and/or Toe-brachial pressure index (TBI).

There is continued debate regarding the influence of peripheral neuropathy and arterial calcification on the reliability of vascular screening in diabetes. Calcification due to medial sclerosis secondary to autonomic neuropathy and calcified atherosclerotic plaques cause increased arterial rigidity, potentially making palpation of foot pulses more difficult and artificially elevating the ankle systolic blood pressure and ABPI measurement (5). The recent International Consensus on the Diabetic Foot (ICDF) guidelines suggested that an ABPI of 1.156 be the upper limit above which measurements are deemed unreliable (6). TBI is then an alternative test, but the influence of arterial calcification and neuropathy on toe pressures is uncertain (7-11).

It can therefore be seen that there is a need to provide an alternative and more accurate method and means for the diagnosis, and more preferably, the early diagnosis of peripheral limb, and more particularly, foot related disease.

Doppler waveform analysis is used in Colour Duplex Imaging (CDI) to grade the severity of arterial stenotic disease, but there is uncertainty regarding its accuracy when used alone in assessing the severity of lower limb arterial disease (12,13).

Despite this prejudice in the field, we decided to investigate the relevance of waveform analysis in determining peripheral limb disease and in particular lower limb arterial disease in diabetes. We have therefore aimed to evaluate the efficacy of using foot pulses, ABPI, TBI and Doppler waveform analysis in screening for lower limb arterial disease in diabetes.

As a result of our investigations we have found that contrary to

uncertainties expressed by co-workers in the field waveform analysis can be used to predict peripheral limb disease and, moreover, is a more accurate predictor than existing techniques such as the palpation of foot pulses, the calculation of ankle-brachial pressure index (ABPI) and/or toe-brachial pressure index (TBI) – i.e. established techniques when used to screen for lower limb disorders.

Accordingly, we have identified a new method for evaluating tissue for the presence of disease and in particular vascular disease, which in this particular application is used for determining vascular disease in diabetes and, more especially, lower limb arterial disease in diabetes.

According to a first aspect of the invention there is provided a method for screening for peripheral limb disease comprising:

- a) exposing vascular peripheral tissue to a selected wave energy and performing Doppler analysis thereon in order to generate data indicative of the nature of fluid flow in, or through, said vascular tissue;
- b) examining said data for reverse flow or loss of triphasic signal; and
- c) where said loss of reverse flow or loss of triphasic signal is present concluding that there is disease in said limb.

According to an alternative aspect of the invention there is therefore provided a method for screening for peripheral limb disease comprising:

exposing vascular peripheral tissue to a selected wave energy and performing Doppler analysis thereon in order to determine the nature of fluid flow in, or through, said vascular tissue whereby an indicator showing loss of reverse flow or loss of triphasic signal is indicative of disease in said limb.

In a preferred method of invention the peripheral limb is a lower limb such as a foot and, more preferably still, the indicator is indicative of arterial disease in said limb.

It will be apparent to those skilled in the art that the said Doppler analysis can be undertaken in either a qualitative or quantitative fashion. In the former instance, visual interpretation of an image of a waveform, representing blood flow in said tissue i.e. an image showing forward and, if present, reverse flow, can be used to judge the nature of the flow in, or through, said vascular tissue.

Alternatively, or additionally, quantitative analysis of the said waveform may be undertaken. In this instance, at least one index of said waveform is analysed such as, without limitation, the pulsatility index, resistance index or spectral broadening index may be used.

Additionally or alternative, the following indices may be used. The monophasic, biphasic or triphasic profiles of said vascular tissue.

Reference herein to monophasic, biphasic or triphasic profiles includes reference to the waveforms described in reference 13 wherein a monophasic profile (or waveform) is indicative of a single forward flow, a biphasic profile (or waveform) is indicative of 2 forward flows and a triphasic profile (or waveform) is indicative of a forward, reverse, forward flow. These waveforms are further illustrated in Figure 1.

In a preferred method of the invention said selected wave energy is ultrasound and most preferably at a frequency between 3 and 10 MHz and most typically at a frequency of between 5 and 8 MHz.

According to a further aspect of the invention there is provided an

apparatus for use in determining peripheral limb disease wherein said device comprises: a Doppler waveform generating device which can be applied to a limb to be investigated, or held in close proximity thereto, in order to generate Doppler information relating to fluid flow in said limb; and a display device to which said Doppler waveform generating device is operationally coupled, said display device including an image generating device whereby visual images produced by said image generating device of waveforms produced by said Doppler generating device can be displayed for the purpose of enabling at least qualitative analysis thereof.

According to a further aspect of the invention there is provided a device, most preferably a hand-held device, for use in determining peripheral limb disease, wherein said device comprises a hand held Doppler waveform device operationally coupled to a display device whereby visual images of waveforms produced by said device are displayed in conventional manner, on said display device for the purpose of enabling at least qualitative analysis thereof by a user.

According to a further aspect of the invention there is provided the new use of an existing piece of equipment wherein a hand-held Doppler analysis device can be routinely and reliably used in order to determine peripheral limb disease, and, more specifically, lower limb or foot disease in diabetes where more preferably, the device is used to determine arterial disease in diabetes. Ideally this existing piece of equipment is operationally coupled to a display device or screen whereby at least a qualitative assessment of visual images representing waveforms of fluid flow in peripheral limbs can be made.

Without being limited to any scientific explanation, we believe that our

methodology is a reliable predictor of peripheral limb disease because occlusions are detected by a lack of reverse flow following contraction of the heart, i.e. during the systolic phase.

An embodiment of the invention will now be described by way of example only with reference to the following figures wherein:

Figure 1 is a diagram showing the characteristics of monophasic, biphasic and triphasic flow patterns through peripheral limb tissue;

Figure 2 represents a chart showing the ABPI index for a variety of subjects. Horizontal lines represent ABPI values of 1.15 and 0.9. V represents the control subjects with arterial disease; D represents diabetics; DN represents diabetics with neuropathy; C represents control subjects; DV represents diabetics with arterial disease; DNV represents diabetics with neuropathy and arterial disease;

Figure 3 shows the ABPI and TBI indices for a variety of subjects. Horizontal lines represent an ABPI value of 0.9 and a TBI value of 0.75. V represents control subjects with arterial disease; D represents diabetics; DN represents diabetics with neuropathy; C represents control subjects; DV represents diabetics with arterial disease; DNV represents diabetics with neuropathy and arterial disease.

Figure 4 is a diagrammatic representation of a hand held Doppler device adapted for use in accordance with the invention.

Parameters for the investigation

The following investigation was undertaken by making a comparison with the, conventionally used, gold standard non-invasive assessment, CDI. It was

estimated that analysis of 120 limbs would be required to facilitate valid comparisons of the efficacy of the modalities in individuals with and without arterial disease based on pragmatic factors related to feasibility of recruitment, study duration and participant burden. The study was given ethical approval by the local ethics committee and all subjects gave written informed consent.

Research Design and Methods

No individuals had active foot disease, rest pain or signs suggestive of lower limb critical ischaemia. Individuals without diabetes, with and without arterial disease were used as controls. Patients with Types 1 and 2 diabetes were confirmed as having diabetes in their medical records. Subjects were grouped according to the presence or absence of diabetes, peripheral neuropathy and peripheral vascular disease on CDI. Neuropathy was tested using 10g monofilament, 128Hz tuning fork and proprioception at the 1st Metatarsophalangeal joint, using ICDF guidelines. Loss of sensation of any modality was indicative of peripheral neuropathy.

The study was performed over a period of eight months. All tests were performed at one visit. All individuals had capillary blood sugar measurements and arterial CDI performed at the end of each attendance.

Exclusion criteria included smoking, other causes of peripheral neuropathy, history of reconstructive vascular surgery, other causes of peripheral vascular disease, skin changes associated with venous disease, pyrexia and significant cardio-respiratory and/or renal disease. All patients (with two exceptions of serum creatinine $\sim 0.3\text{mmol/l}$), had serum creatinine less

than 0.2mmol/l and haemoglobin values no lower than 11g/dl.

Room temperature was maintained at 24°C to 25°C. Individuals were rested reclining at approximately 20 degrees to the horizontal and acclimatised for 20 minutes. Foot skin temperatures were measured until a steady state was achieved.

Foot pulses of individuals with diabetes and/or peripheral vascular disease were palpated by at least two examiners and classified as present or absent. Absence of one or both foot pulses was used as an indicator of arterial disease. Toe pressures were measured by the photoplethysmographic (PPG) method, employing an infrared sensor placed on the hallux, (Dopplex Assist, Huntleigh Healthcare, Cardiff, UK). Both brachial pressures were measured using PPG and hand held Doppler (Huntleigh Healthcare, Cardiff, UK), the higher value used in calculating the ABPI and TBI. Toe pressures were taken at three, five-minute intervals and a mean calculated. Ankle pressures were then measured using PPG and hand-held Doppler. ABPI values <0.9 and TBI <0.75 were used as indicators of significant Peripheral Arterial Occlusive Disease (PAOD). Both qualitative and quantitative Doppler waveform analysis was performed on the dorsalis pedis and posterior tibial arteries using the Dopplex Assist, employing an 8MHz Doppler probe. Qualitative waveform analysis was performed by visual interpretation of displayed waveforms. Loss of reverse flow (loss of triphasic signal) was used as an indicator of significant arterial disease. Quantitative waveform analyses were performed simultaneously by the Dopplex Assist. Three indices, the pulsatility index, resistance index (Pourcelot) and spectral broadening index were recorded for each artery.

CDI was performed at the end of each session using a Toshiba SSH-140A ultra-sound system (Toshiba Medical Systems, Crawley, UK) with two probes, a 5-MHz linear array probe (PLF-503NT), and a 3.75-MHz curvilinear probe (PVF-375MT). All individuals were scanned from the common femoral artery to the distal third of the tibial and peroneal arteries. Arterial disease on CDI was deemed significant when occlusions, single or multiple stenoses, or diffuse stenotic disease in the femoropopliteal segments, individually or collectively, caused significant velocity change and flow disturbance locally and resulted in loss of reverse flow distally. Occlusions of below-knee arteries were also recorded. Quality control was assured by acquiring a second CDI scan of 10 individuals with and without arterial disease within 1 month of the original scan. The repeat scan was performed by medical physicists at the local teaching hospital. Statistical analysis was performed using SPSS version 10 software (Chicaggo, IL).

Results

Demographics

A total of 130 limbs were studied on 68 volunteer subjects.

All subjects were white Caucasian, predominantly male (74%) in the diabetes groups. The groups were matched for age ($F_5, 74=0.783, p=0.565$), with means ranging from 63 to 69 years, and body mass index ($F_5, 74=2.04, p=0.083$). All groups with diabetes had mean body mass indices greater than 25, the group with neuropathy greater than 30. Type 2 diabetes accounted for 85% of the total number of subjects with diabetes and was evenly distributed through all groups except group five. Duration of diabetes was similar for all groups ($F_3,$

52=2.08, $p=0.115$), with means ranging from 11 to 24 years. Repeat CDI demonstrated complete agreement on the presence or absence of significant arterial disease. The strong association between detectable peripheral neuropathy and arterial disease meant that group five (arterial disease but no neuropathy) was relatively small and contained the limbs of individuals with type 2 diabetes only.

Foot pulses

The absence of one or more pulses was common in all groups, making this test prone to a high false positive rate and poor specificity. Both foot pulses were palpable in some individuals with significant arterial disease. In the groups with arterial disease, the absence of one or more pulses in the control group was a more sensitive test than in the groups with diabetes, where almost 20% of limbs had both pulses present.

Ankle brachial pressure index

There was a strong positive correlation between Doppler and PPG ankle pressure measurement, ($n=125$, $r=0.954$, $P<0.001$), Hand-held Doppler consistently gave marginally higher readings.

In the control groups, all limbs without arterial disease had ABPI values >0.9 . Employing Doppler, four of fourteen limbs with arterial disease had values >0.9 (29% false negative rate). Employing PPG, only two values were >0.9 (14% false negative rate).

In the presence of diabetes, there were several ABPI values >1.3 , in individuals with and without arterial disease (Figure 1). Three limbs with no arterial disease had values >0.9 . Using Doppler, twelve out of 23 limbs with

significant arterial disease had ABPI values >0.9 (53% false negative rate). Employing PPG reduced the false negative rate to 32%. There was an association between elevated ABPI values and neuropathy. Mean ABPI values in limbs with no arterial disease but detectable peripheral neuropathy were higher than those with no neuropathy (1.21 vs. 1.06 $t=2.39$, $df=64$, $p=0.02$).

All seven ABPI values >0.9 identified in the groups with diabetes and arterial disease were associated with detectable peripheral neuropathy. This reflected in a false negative rate and poor sensitivity (Table 2). No values >0.9 were identified in those with arterial disease but no neuropathy using PPG. Using ICDF guidelines on ABPI measurement, limiting the upper range to 1.15, would still have resulted in a false negative rate of 6 of 16 (38%) employing Doppler and 5 of 15 (33%) employing PPG, in the group with peripheral neuropathy and arterial disease.

Toe brachial pressure index

Comparatively lower toe pressures reflected in TBI values that were universally lower than ABPI values across all groups ($t=10.7$, $df=123$, $p<0.001$). TBI did reflect the presence of arterial disease in all groups (F_5 , $121=13.56$, $p<0.001$; Figure 2).

In individuals with diabetes and arterial disease, there were 15 limbs with neuropathy vs. 7 without. Mean TBI values were 0.49 and 0.58 respectively ($t=1.32$, $df=20$, $p=0.27$). In the groups with no arterial disease, there 41 limbs with neuropathy and 25 without. Mean TBI values were 0.85 and 0.82 respectively ($t=0.438$, $df=64$, $p=0.628$). These results demonstrated that peripheral neuropathy did not influence TBI values in this study.

In the control group, TBI identified all 13 limbs with arterial disease, but 5 of 21 control limbs with no disease had values <0.75 (Table 2.)

Of the 22 limbs in the groups with diabetes and arterial disease, but 5 or 21 control limbs with no disease had values <0.75 (Table 2.)

5 Of the 22 limbs in the groups with diabetes and arterial disease, only 2 false negatives were identified (10%). Analysis of the 66 limbs of individuals with diabetes but no arterial disease, demonstrated 23 false positive results (35%).

Continuous waveform analysis

10 *Qualitative waveform analysis*

Two from 14 control limbs with arterial disease had triphasic profiles in both foot vessels, (false negative rate=15%). One of the two limbs had a monophasic signal in one tibial vessel on CDI and no proximal disease. Of 27 limbs in the control group with no arterial disease, one had an absent flow in a
15 single vessel (false positive rate=4%).

In diabetes, of those limbs with no detectable peripheral neuropathy or arterial disease (n=25 limbs), two limbs had absent flow in a single vessel. Where flow was detected, all signals were triphasic (false positive=8%). However, in those limbs with no arterial disease but detectable peripheral
20 neuropathy (n=41 limbs), 12 limbs had at least one waveform with loss of reverse flow and two had undetectable flows (False positive rate=34%). In the presence of arterial disease, there was a zero false negative rate when any vessel waveform anomaly was regarded as indicative of the presence of arterial disease in the absence of neuropathy (n=7). Where neuropathy was present

(n=16), one limb had two triphasic signals, but had diffuse atherosclerotic disease on CDI (False negative rate of 6%).

Quantitative waveform analysis

Generally, the Resistance Index was the more accurate indicator of arterial disease than the Pulsatility or Spectral Broadening Indices. However, this modality's major limitation in this study was its inability to perform accurate analyses in the presence of low amplitude and/or low intensity signals, often allocating normal index values to qualitatively abnormal waveforms. This was most evident in the group with diabetes and arterial disease, where 14 of 46 analyses (30%) were erroneous.

Conclusions

In the clinical assessment of lower limbs for arterial disease, palpation of foot pulses is mandatory. However, the test is subjective and is influenced by many factors (12). In our assessment, the absence of one or both foot pulses was found to be a sensitive test in individuals without diabetes. In subjects with diabetes, its sensitivity was reduced, detecting four out of five limbs with arterial disease in the presence of detectable peripheral neuropathy. However, the frequent absence of one or both foot pulses in subjects with no arterial disease resulted in a notable loss of specificity the poor specificity of foot pulses in diabetes reduced its overall accuracy.

ABPI accurately reflected underlying arterial disease in the limbs of individuals without diabetes and those with diabetes but no detectable peripheral neuropathy. However, a mean ABPI >0.9 in the group with arterial disease and detectable peripheral neuropathy reflected a considerable loss of sensitivity.

ABPI demonstrated the highest specificity and positive predictor value of all the tests across all groups (Table 2), low values being highly indicative of arterial disease. However, this inability to detect arterial disease in the presence of detectable peripheral neuropathy resulted in false negative results in 1/3 of limbs. This finding is probably due to the influence of arterial calcification. ABPI was less sensitive than palpation of foot pulses in screening for arterial disease in diabetes in the presence of detectable peripheral neuropathy.

TBI did not improve on the screening offered by pulses and ABPI in limbs without neuropathy, but was superior to ABPI in screening for arterial disease in limbs with neuropathy, with a normal TBI effectively excluding the presence of significant arterial disease in limbs with neuropathy. TBI maintained its sensitivity through all the diabetes groups. Its specificity did however reduce in the presence of peripheral neuropathy and this reflected in a reduced accuracy (Table 2). TBI was demonstrated to be an effective screening tool in diabetes, both in limbs with and without detectable peripheral neuropathy and appears therefore to be less influenced by arterial calcification than ABPI.

Qualitative waveform analysis in diabetes was as sensitive and specific in limbs without detectable neuropathy as pulses and ABPI. The modality was as sensitive as TBI in the presence of detectable peripheral neuropathy. Although specificity was reduced in diabetes, this was less than that demonstrated by TBI. The presence of a triphasic waveform with reverse flow in both foot arteries was demonstrated to effectively exclude significant arterial disease in over 90% of limbs with neuropathy. Monophasic or biphasic flow (with loss of reverse flow) in either foot artery was highly suggestive of haemodynamically significant arterial

disease.

Quantitative waveform analysis in this study was a very poor screening modality. The high frequency of erroneous results demonstrated on our equipment excludes it as a screening tool.

5 Further analysis of the 14 limbs that had no arterial disease on CDI but loss of reverse flow in one foot artery on qualitative waveform analysis, demonstrated that all but one occurred in the presence of detectable peripheral neuropathy. These limbs also had reduced TBI ($r=0.409$, $p=0.008$) and absent foot pulses ($r=0.495$, $p<0.001$), suggesting that CDI may have been less
10 sensitive than waveform analysis and TBI in detecting significant arterial disease in these individuals.

Qualitative waveform analysis was the most effective screening tool of all the methods tested in this study. In the absence of neuropathy it performed as well as ABPI and pulses, but in neuropathic limbs was clearly superior to pulses
15 and ABPI with comparable sensitivity and marginally better specificity than TBI. Our findings demonstrate that in screening for lower limb arterial disease in diabetes, qualitative waveform analysis is preferred.

Accordingly, Figure 4 shows a representation of a hand held Doppler device for use in the method of the invention. The device comprises a Doppler
20 Probe 1, of conventional nature, which is operationally and releasably coupled to an audio/visual display means 2. Display means 2 comprises a screen 3 and speaker 4. Waveforms indicative of fluid or blood flow in tissue under examination are represented, in conventional manner and using conventional equipment, on screen 3 +/- or via sounds emanating from speaker 4. A user of

the equipment is therefore able to use Doppler Probe 1 to visualise blood flow in selected tissue and using conventional skill and judgement perform a qualitative analysis of the images +/- sounds presented on screen 3 or emanating from speaker 4. In this way the invention can be straight forwardly practised by those skilled in the art with a view to efficiently and reliably diagnosing vascular disease, particularly in lower limbs.

Table 1. Group distribution and characteristics

Group No.	Groups (abbreviation)	Number of limbs
1	Controls with arterial disease (V)	14
2	Diabetes (D)	25
3	Diabetes with neuropathy (DN)	41
4	Controls C	27
5	Diabetes with arterial disease (DV)	7
6	Diabetes with neuropathy & arterial disease (DNV)	16
	Total	130

Table 2. Validation table – all groups. ABPI measured using hand held Doppler.

Groups	Control				Diabetes No Neuropathy				Diabetes Neuropathy			
Analysis (%)	Pulse/ABPI/TBI/Wave				Pulse/ABPI/TBI/Wave				Pulse/ABPI/TBI/Wave			
Sensitivity	93	83	100	86	87	100	91	100	81	53	100	94
Specificity	70	100	81	96	53	88	65	92	56	95	61	66
Positive Predictor Value	62	100	72	92	39	70	42	78	42	80	48	52
Accuracy	78	95	87	3	62	91	72	94	63	84	71	74

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CLAIMS

1. A method for screening for peripheral limb disease comprising:

a) exposing vascular peripheral tissue to a selected wave energy and
5 performing Doppler analysis thereon in order to generate data indicative of the nature of fluid flow in, or through, said vascular tissue;

b) examining said data for reverse flow or loss of triphasic signal; and

c) where said loss of reverse flow or loss of triphasic signal is present
concluding that there is disease in said limb.

10 2. A method according to claim 1 wherein part c) involves concluding that there is arterial disease in said limb.

3. A method according to claims 1 or 2 wherein the limb is a lower limb such as a foot.

4. A method according to any preceding claim wherein said Doppler
15 analysis is undertaken in either a qualitative or a quantitative fashion.

5. A method according to claim 4 wherein said qualitative analysis involves visual interpretation of an image waveform wherein the waveform represents blood flow in said tissue.

6. A method according to claim 5 wherein said visual interpretation involves
20 an image waveform that represents blood flow in said tissue and the waveform is fashioned to show either forward and/or reverse flow.

7. A method according to claim 4 wherein said analysis is quantitative and therefore at least one of the following indices are analysed in order to determine reverse flow or loss of triphasic signal; pulsatility index, resistance index or

spectral broadening index.

8. A method according to claim 7 wherein, additionally or alternatively, the following indices are analysed: monophasic index, biphasic index or triphasic index.

5 9. A method according to any preceding claim wherein said selected wave energy comprises ultrasound at a frequency of between 3-10MHz.

10. An apparatus for use in determining peripheral limb disease wherein said device comprises: a Doppler waveform generating device which can be applied to a limb to be investigated, or held in close proximity thereto, in order to
10 generate Doppler information relating to fluid flow in said limb; and a display device to which said Doppler waveform generating device is operationally coupled, said display device including an image generating device whereby visual images produced by said image generating device of waveforms produced by said Doppler generating device can be displayed for the purpose of
15 enabling at least qualitative analysis thereof.

11. An apparatus according to claim 10 wherein said apparatus is hand held.

12. An apparatus according to claims 10 or 11 wherein an image analysis device is also provided for quantitatively analysing either said Doppler information or said waveforms in order to provide information on the fluid flow
20 through said limb.

13. An apparatus according to claims 10 to 12 wherein said device provides visual or quantitative data indicative of any loss of reverse flow or triphasic signal.

14. The use of a Doppler waveform device to determine peripheral limb

disease.

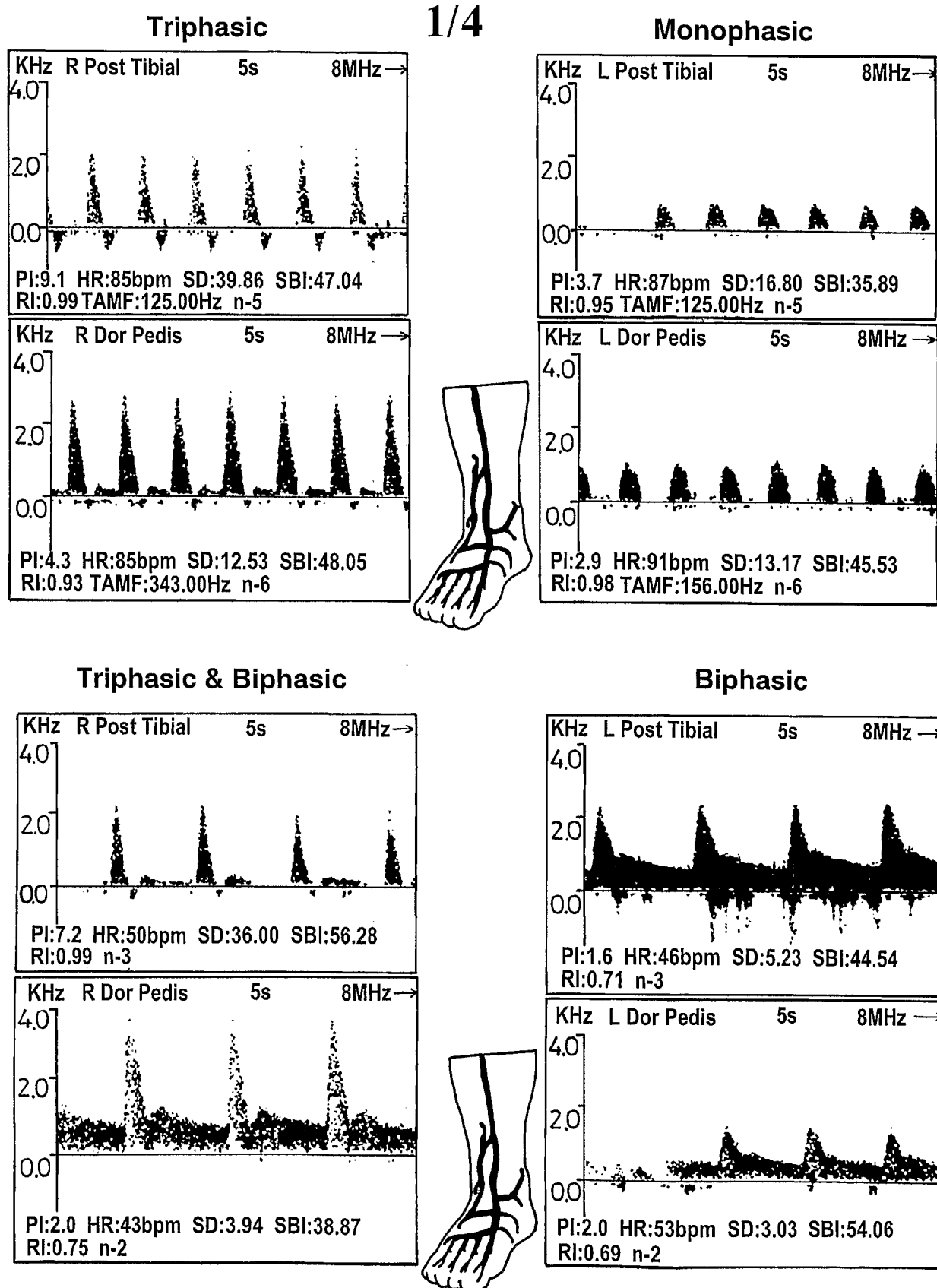
15. Use according to claim 14 wherein said device is used to determine arterial disease in diabetic limbs.

16. Use according to claim 15 wherein said limb is a foot.

5 17. A method for screening for peripheral limb disease as substantially herein described.

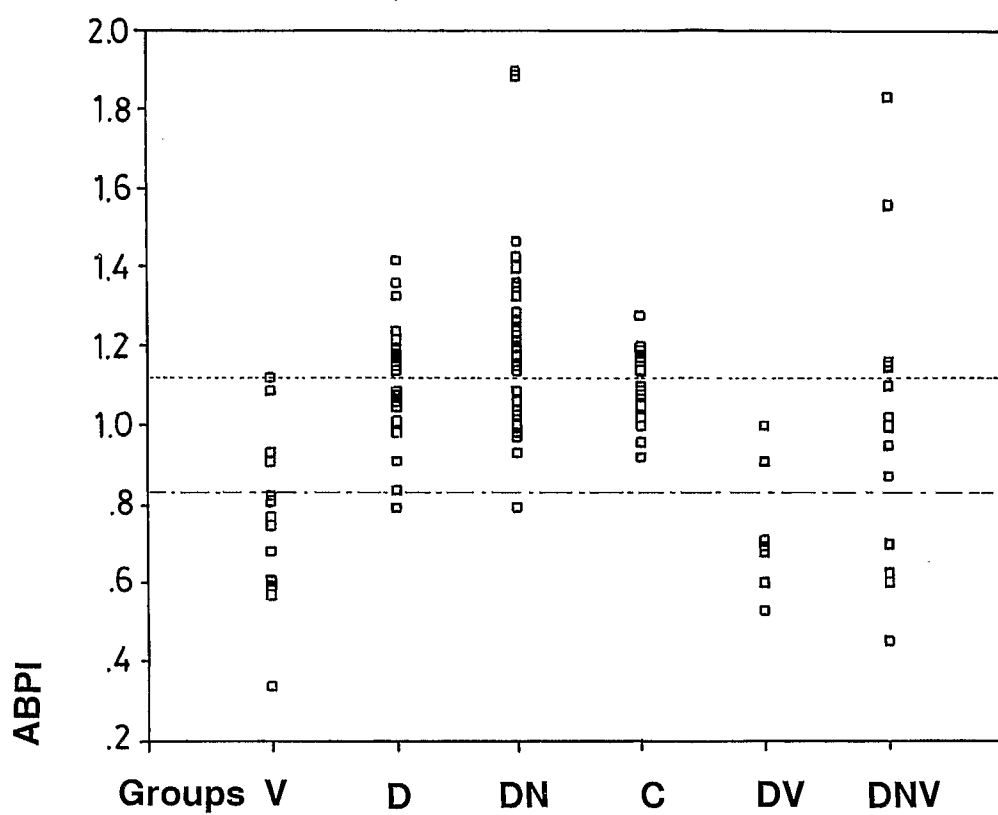
18. A device for determining the existence of peripheral limb disease as substantially herein described.

19. The use of a Doppler analysis device as substantially herein described.

**Fig. 1**

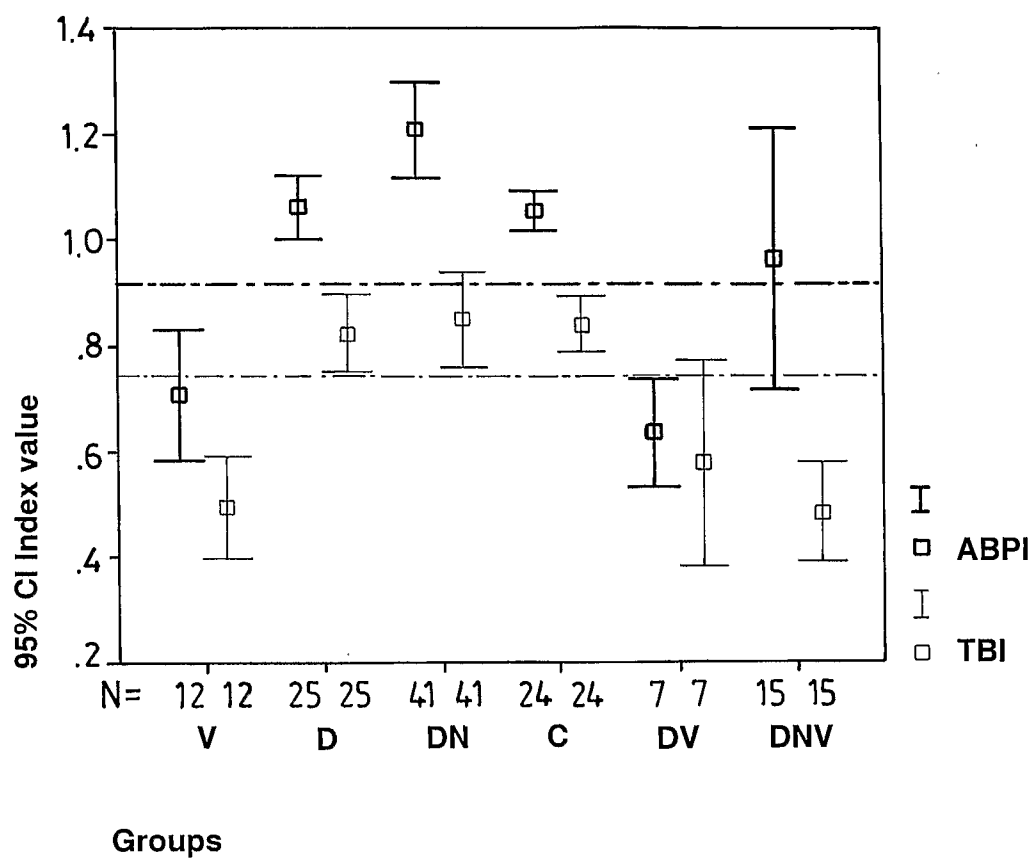
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ABPI employing PPG - all limbs

*Fig. 2*

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ABPI vs. TBI - all groups

*Fig. 3*

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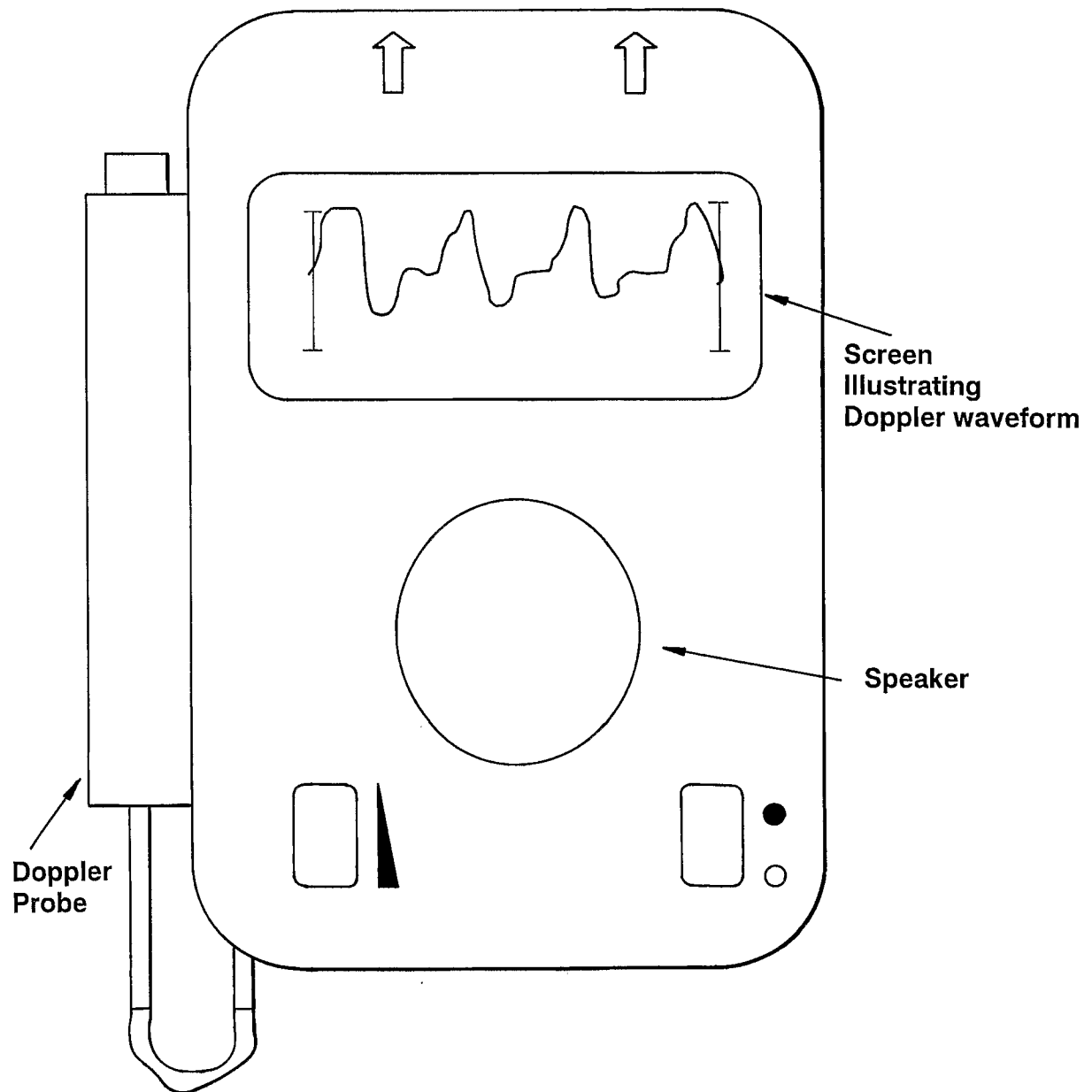


Fig. 4