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# Pulsatile blood flow asymmetry in paired human legs

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**Summary.** Average leg blood flow has been extensively measured using non-invasive methods, but knowledge concerning pulsatile flow at specific leg cross-sections in normal or vascularly impaired limbs is quite limited. The present study used nuclear magnetic resonance flowmetry to address two fundamental questions; (1) to what extent are pulsatile flow differences present between paired-legs? and (2) is paired-leg flow symmetry affected by the presence of lower extremity arterial disease (LEAD)? Comparisons of left-right leg pulsatile blood flow (ml/min), perfusion (ml/min/100cc), and arterial status index at multiple leg sites showed highly significant correlations between legs ($P<0\cdot001$) in 57 normal and 37 patients with LEAD. To evaluate symmetry, the ratio of lower to higher paired-leg flow parameter values at five below-knee sites were averaged. Results showed all ratios significantly greater in normal subjects ($P<0\cdot001$). These findings establish the distribution and range of leg flow symmetry in vascularly normal individuals and show significant symmetry reductions accompanying bilateral LEAD. Although the cause of the asymmetry is presently unknown, non-uniform disease progression between paired legs may be involved. These initial findings provide a basis for subsequent research regarding the possible use of bilateral flow asymmetry assessment to further clarify the pathophysiological progression process and the possibility of using symmetry-based parameters to develop early markers of sub-clinical peripheral arterial disease progression.

**Key words:** flow symmetry, leg blood flow, magnetic resonance, peripheral arterial disease, pulsatile blood flow, vascular disease.

## Introduction

Methods for the measurement of average blood flow in human legs for physiological and clinical purposes has long been available using minimally invasive (Lassen, 1964) and non-invasive methods (Sumner & Strandness, 1969; Sumner 1993). As clinical tools, such measurements have been used to study resting and hyperemic flow features of limbs that

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have varying degrees of peripheral arterial disease. Due to the temporal resolution limitations of these techniques, our knowledge concerning the pulsatile flow component at specific leg cross-sections in normal or diseased limbs is quite limited. Although dynamic methods for measuring pulsatile flow features in individual leg arteries is available, and is used clinically (Fronek, 1993; Strandness, 1993), total arterial flow is not readily done using these methods. Recent developments and advances in nuclear magnetic resonance flowmetry (Kerr *et al.*, 1991) have shown that it is possible to measure total cross-sectional pulsatile flow non-invasively at multiple leg cross-sections in both normal and diseased limbs (Mayrovitz & Larsen, 1994; Mayrovitz & Larsen, 1996). Data from such studies have revealed significant differences in pulsatile flow magnitude and patterns between normal and diseased limbs (Salles-Cunha & Beebe, 1994). However, basic questions relating to the normal physiological variations of pulsatile flow remain unanswered. The present research study was directed to providing seminal data bearing on two fundamental questions; (1) to what extent are pulsatile flow differences present between paired-legs? and (2) is paired-leg flow symmetry affected by lower extremity arterial disease?

## Methods

### SUBJECTS AND SCREENING PROCEDURE

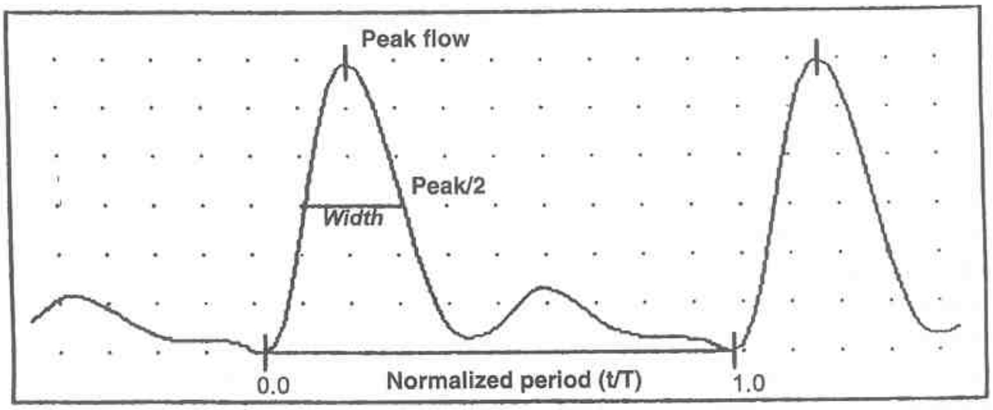
A total of 91 participants (182 legs) were recruited and evaluated in the present study after each participant signed an Institutional Review Board approved informed consent. Subjects without history or symptoms of lower extremity arterial disease (LEAD) were recruited from hospital staff and other sources. Patients screened as potential LEAD participants were recruited from patients referred to the vascular diagnostic laboratory with symptoms of intermittent claudication. During the participants first visit to the laboratory (subjects and patients) bilateral ankle-brachial systolic pressure indices (ABI) were determined after a supine rest interval of 20 min. If the ABI was $<0{\cdot}9$ in both legs of either a patient or subject, and if recent vascular diagnostic tests confirming the presence of bilateral LEAD were not available in the patient's chart, the presence of LEAD was tested for and confirmed (or ruled out) using either or both bilateral pulse volume recordings and duplex color flow imaging. If subjects and patients satisfied the criteria of bilateral ABI $<0{\cdot}9$ and a LEAD diagnosis was confirmed by one or more of the noninvasive diagnostic tests, they were assigned to the LEAD group ($n=34$). Patients with claudication symptoms who had bilateral ABI$\leq 0{\cdot}95$ were also evaluated using the above standard vascular laboratory tests to rule out LEAD. Patients confirmed free of haemodynamically significant LEAD and normal subjects free of symptoms, with no history of vascular disease having bilateral ABI$\geq 0{\cdot}95$ were assigned to the normal group, NORM ($n=57$). Patients with rest pain, ischemic ulcers and diabetic patients or subjects with an ABI in either leg $>1{\cdot}25$ were not included in the study. Average participant age was 60·4 years (25-88 years, sd=16·5); 62 (68%) were male. Diabetes mellitus was present in 41 subjects with a mean duration of 16·8 years (5-43 years, sd=10·8 years).

LEG BLOOD FLOW MEASUREMENT

On a follow-up visit (within one week of screening) eligible participants returned to the laboratory whereupon pulsatile blood flow was evaluated in each leg under resting, supine conditions using the method of nuclear magnetic resonance flowmetry (NMRF). With this method the participant is placed on a moveable table which is advanced by an operator so as to position a specific leg site within the center of a tubular measurement section of the NMRF system (Metriflow AFM100, Milwaukee). Within the measurement section a fixed magnet (0·1 Tesla) causes the hydrogen nuclei of the fluids within the leg to precess at a very precise frequency, and an NMR sensor detects the amount of precession. The main NMR signal detected and processed is due to precession of hydrogen nuclei associated with intravascular water. As the precession frequency is very specific, it is possible to finely tune the detection processor to optimally detect the amount of hydrogen precession within the vascular compartment of the leg which is exposed to the magnetic field. The magnitude of the detected signal is proportional to the number of precessing hydrogen nuclei and is, thus, proportional to the amount of vascular water flowing into and out of the measurement section. Non-pulsatile flow (e.g. tissue water, venous flow) produces small contributions which, in any case, are filtered out by the system. Calibration to obtain absolute blood flow is accomplished using a pulsatile flow pump which drives water, doped with a paramagnetic solute to simulate the NMR characteristics of blood, through a phantom limb composed of simulated vessels which is positioned within the NMRF measurement region. The pump pulsatile flow is registered using an electromagnetic sensor and a range of calibration flows are used (0-120 ml/min) to obtain a calibration curve. The calibration is done each day prior to patient use and a calibration factor relating actual pulsatile flow to NMR magnitude is automatically determined by the system software. Further technical details and theoretical aspects regarding the NMRF may be found in the literature (Battocletti, 1986; Kerr *et al.*, 1991; Kofler *et al.*, 1991; Rice, 1994; Salles-Cunha & Beebe, 1994).

PROTOCOL AND BLOOD FLOW PARAMETERS

For the present study, the measurement protocol started with a 15 min supine acclimation interval after which pulsatile leg blood flow (Q, ml/min; see Fig. 1 for example) was measured bilaterally at five below-knee sites. This measurement includes the sum of all pulsatile arterial flow passing peripherally through the leg cross-section within an axial segment five cm in length. The flow measuring sites were standardized for all participants by first measuring the length (L) between the medial malleolus and the tibial tubercle at the knee. Five leg sites located at 10, 25, 50, 75 and 90% of L as measured from the malleolus were then marked. Leg circumference measurements at each site were used




**Flow = (Area under flow-time curve) x Heart Rate**

**Perfusion = Flow/(Limb volume distal to measured site)**

**ASI = Perfusion/Width**

**Fig. 1.** Flow parameter definitions illustrated for an actual flow-pulse measured in a normal subject. Flow is denoted by the symbol Q and perfusion by the symbol Q" elsewhere in the text and in the following figures.

together with an algorithm incorporated in the AFM100 system to calculate blood perfusion (Q") expressed as ml/min/100 cc of distal tissue volume. Figure 1 shows a typical flow-pulse waveform as recorded at the 75% site in a normal subject. From such waveforms (ensemble averaged over at least 20 beats) a derived parameter known as arterial status index (ASI), which is sensitive to both perfusion and flow-pulse width, was calculated. The ASI value is obtained by first determining the width of the flow-pulse at its half-maximum amplitude. The width determined using this method is expressed as a fraction of the cardiac period (e.g. a flow-pulse width of 0·25 s at a heart rate of 80 beats/min would be expressed 0·25 s/0·75 s=0·33 s). The ASI value is then calculated as the ratio of the blood perfusion divided by the flow-pulse width. The leg average of the five measured sites was used to characterize the ASI of each leg. The degree of blood flow symmetry between legs at corresponding anatomical sites was assessed using paired-leg flow parameter ratios; the leg having the higher flow parameter value always being in the denominator e.g (lower flow/higher flow). Defined in this manner, the ratio lies between zero and unity with maximum symmetry when paired flows are exactly equal.

## ANALYSIS AND STATISTICS

Bivariate regression analyses were used to test for relationships of parameters between paired legs. Statistical significance was accepted at the $P<0{\cdot}01$ level. Relationships of specific parameters were tested similarly using individual leg values ($n=182$). Symmetry at each of the five measurement sites was compared between NORM and LEAD groups,

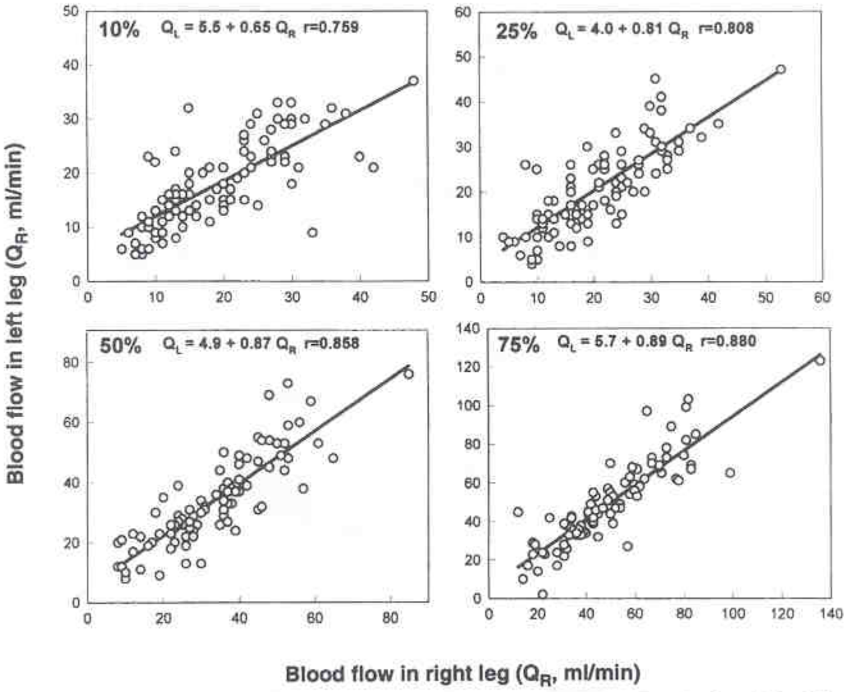



**Fig. 2.** Blood flow relations between paired legs at different anatomical sites. Panels show left-right pulsatile flows (circles) at the 10%, 25%, 50% and 75% leg sites for 91 subjects. The 10% site is closest to the ankle. Solid lines are linear regression lines for data with equations and parameters as shown in each individual panel. All regressions are highly significant ($P<0{\cdot}001$). A slight increase in the correlation value ($r$) is noted from ankle toward knee.

overall leg comparisons between groups were made on a site-by-site basis and overall leg values were tested using the non-parametric Mann-Whitney *U*-test.

## Results

### OVERALL PAIRED LEG RELATIONSHIPS

Figure 2 illustrates the relationship of left to right leg blood flow at four of the measured sites. Significant correlations ($P<0{\cdot}001$) are present at all sites, but a trend for a decrease in the correlation ($r$-value) from knee toward ankle may be noted. Figure 3 shows the relationship between paired values for leg averaged parameters. Highly significant direct correlations for each are demonstrated with associated regression equations as shown in the figure. For all legs evaluated ($n=182$) flow, perfusion and ASI were found to correlate with ABI in a nonlinear fashion and best fitted in each case with exponential regressions as shown in Fig. 4.

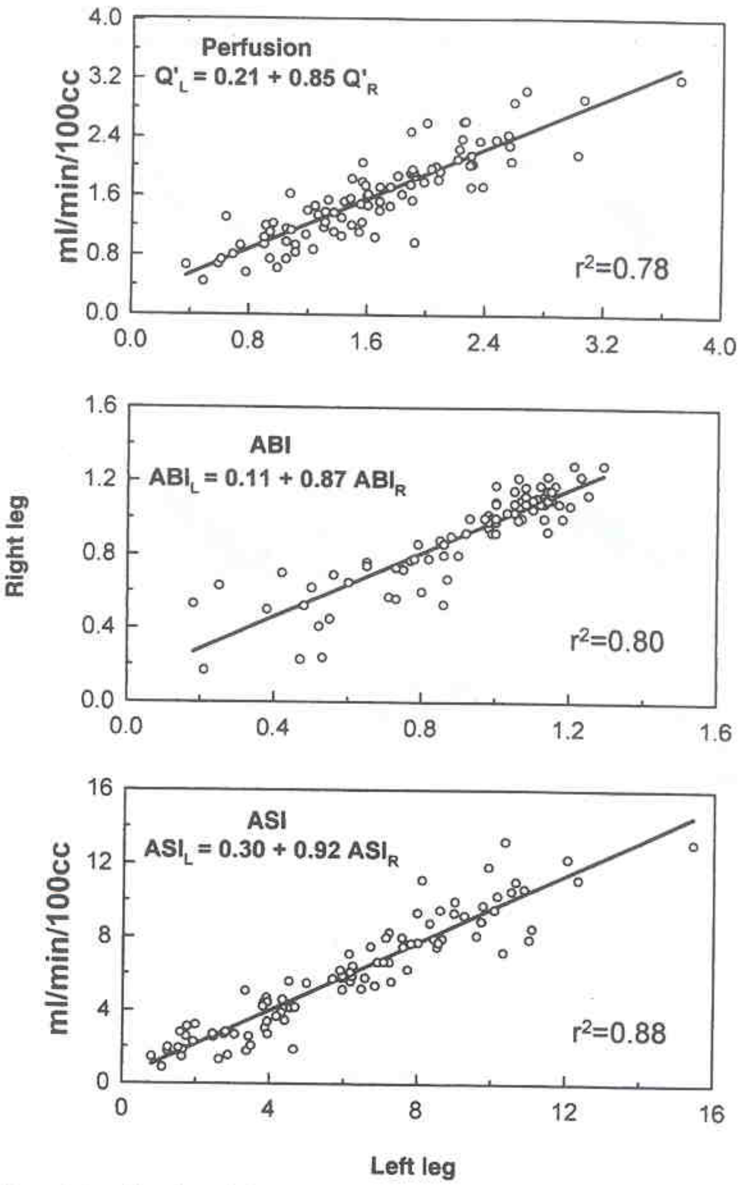



**Fig. 3.** Paired-leg relationships for whole leg parameters. Perfusion and ASI are the below-knee blood perfusion and arterial status index, respectively, obtained by averaging each of the five measured sites; ABI is the ankle brachial pressure index (mmHg/mmHg). Data is for $n=91$ subjets; solid lines are linear regressions with equations and parameters given in the figure. The strongest left-right correlation is noted for the ASI parameter.

NORMAL *vs* LEAD COMPARISONS

The (low leg/high leg) comparison ratios along with pertinent demographics are summarized in Table 1. The leg averaged flow parameter ratios are each shown to be

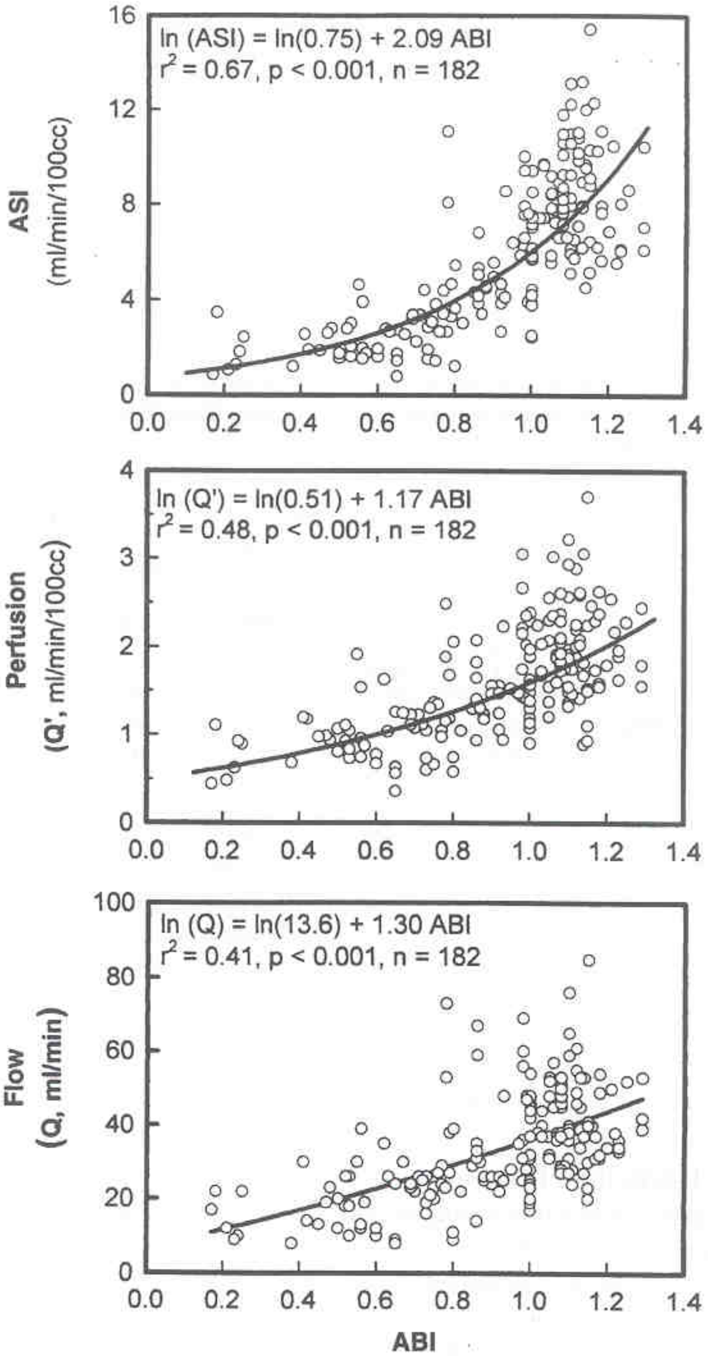



**Fig. 4.** Relationship of blood flow parameters to Ankle-Brachial Index. The perfusion and ASI are below-knee averages and flow is that measured at L =50%. All flow parameters are significantly ($P<0{\cdot}001$) but nonlinearly related to ABI with regression equations and parameters as shown in the figure. The strongest correlation is noted between ASI and ABI.

**Table 1.** Demographics and paired-leg flow parameter ratios

| Parameter | NORM | LEAD |
|---|---|---|
| $n$ | 57 | 34 |
| Age | 55·0 (10·9) | 69·6 (16·9)* |
| Male | 38 (67%) | 24 [70%] |
| DM | 24 [42%] | 17 [50%] |
| DMYRS | 13·9 (10·1) | 20·9 (10·7)[d] |
| Ratios | | |
| Flow | 0·860 (0·063) | 0·754 (0·112)[a] |
| Perfusion | 0·902 (0·077) | 0·786 (0·120)[a] |
| ASI | 0·904 (0·078) | 0·749 (0·157)[a] |

$n$=number of subjects; DMYRS=duration of diabetes (years); values are mean and (sd); Statistics; Mann-Whitney U-test; [a]=$P<0{\cdot}0001$, [d]=$P<0{\cdot}05$, for NORM *vs* LEAD.

**Table 2.** Pulsatile Blood Flow *vs* Leg Site

| | Flow (ml/min) | | Flow ratio | |
|---|---|---|---|---|
| L | NORM | LEAD | NORM | LEAD |
| 90% | 67·3 | 43·9* | 0·865 | 0·784[d] |
| | (23·7) | (21·1) | (0·100) | (0·192) |
| 75% | 57·7 | 35·4[a] | 0·899 | 0·785[c] |
| | (18·9) | (14·8) | (0·078) | (0·205) |
| 50% | 39·4 | 23·8[a] | 0·886 | 0·742[a] |
| | (11·7) | (12·1) | (0·089) | (0·175) |
| 25% | 24·7 | 14·6[a] | 0·832 | 0·704[b] |
| | (07·3) | (07·6) | (0·120) | (0·161) |
| 10% | 22·2 | 12·6[a] | 0·820 | 0·750[d] |
| | (06·9) | (06·3) | (0·139) | (0·155) |

L is FLOW measurement site expressed as a % of distance between malleolus and knee where L=90% closest to the knee. Flow ratio is (lower flow/higher flow) of leg pairs. Values are mean and (sd). Norm vs Lead Statistics; Mann-Whitney U-test with [a]=$P<0{\cdot}0001$, [b]=$P<0{\cdot}001$, [c]=$P<0{\cdot}001$; for LEAD group $FLOW=0{\cdot}002L^2+0{\cdot}135L+12{\cdot}3$ ml/min, $r^2=0{\cdot}990$, $P<0{\cdot}001$.

significantly less in the LEAD subjects. To determine the possible role of age and diabetes duration on this differential symmetry, two separate subgroup analyses were done. The age factor was addressed by including only subjects whose age was >57 years and comparing the symmetry parameters between NORM and LEAD. The diabetes duration factor was addressed by comparing diabetic subjects matched for duration of diabetes. The results (not shown) reveal that that the similar significant symmetry differences are also present in these sub-groups. Table 2 summarizes the data for flow and the paired leg flow ratios for each leg site. Flow is noted to decrease in both NORM and LEAD groups from knee to ankle in a nonlinear fashion as would be expected from the physiological flow distribution. However, at each site the flow of the LEAD subjects is significantly less than at corresponding sites in the NORM subjects. Separate analyses show that the nonlinear change in site mean flow is well expressed by quadratic regressions as shown in the table legend.

## Discussion

Nuclear magnetic resonance flowmetry is a relatively new technology which has been used for the assessement of various aspects of lower extremity arterial pulsatile blood flow. Kerr and co-workers (Kerr *et al.*, 1991) were among the first to report on the potential, as well as the shortcomings, of the first generation commercially available system used in the present study. Sumner (1991), commenting on the usefulness of this method in a clinical setting, pointed out that, even though the method reliably measures pulsatile flow, its clinical usefulness as compared with other, less expensive and already available non-invasive methods was questionable for a variety of well argued reasons. Contrastingly, several workers have suggested unique applications of NMRF. Salles-Cunha and co-workers (Salles-Cunha *et al.*, 1989) reported that the benificial effects of percutaneous transluminal angioplasty in patients with ABI>0·8 are best demonstrated by comparing pre- and post-angioplasty NMR flows. Serial measurements following femoropopliteal angioplasty may also provide early warning of impending graft failure or developing restenosis (Bendick *et al.*, 1992), although an adequate patient base is not yet available to substantiate this concept. However, when considering the role of NMRF in the diagnostic laboratory, the question of cost benefit is prominent. The system cost is greater but in the neighboorhood of that required for an advanced color flow duplex ultrasound system, with some additional costs asociated with installation. This initial capitalization would need to be reflected against certain positive operational benefits. In our hands, a complete bilateral leg assessment can be done in about 15 min, thus, freeing significant amounts of technician time. The flow data obtained is objective, reliable, independent of operator subjectivity, and is not subject to artifacts associated with segmental pressure measurements in calcified vessels as may be present in patients with diabetes, end-stage renal disease and other conditions. The fact that the flow measurement is non-contact also allows for assessment of flow in patients with leg bandages in place and at sites of open wounds and burns on the lower extremities. These features have been of particular utility in the authors' laboratory. However, the main use of the NMRF technique, in our hands, has been as a clinical/physiological research tool (Mayrovitz & Larsen, 1994; 1996) and the present study is similarly targeted.

The main objective of the present study was to determine the physiological symmetry in pulsatile leg blood flow between paired legs, and secondarily to investigate the effect that lower extremity arterial disease presence might have on that symmetry. The pulsatile component of blood flow perfusing the lower extremities is dependent on multiple factors, but the flow symmetry between paired legs is primarily related to the vascular and haemodynamic differences between legs. Differences in flow to paired organs, even under normal conditions, are expected but the magnitude of the difference in the legs of normal subjects and the impact of vascular disease is unknown. We speculated that in subjects with lower extremity arterial disease, disease progression and its manifestation may tend to be asymmetrical, thereby, causing a haemodynamic asymmetry between paired legs greater than that found in normal limbs. It is clear that flow measurements in all individual arteries of each leg, as may be done using Doppler methods, would be inadequate and inpractical to resolve these issues. The use of NMRF as the primary technique, with its ability to measure total arterial pulsatile flow passing through chosen leg cross sections (including collateral and small vessel flows), is the only practical method available for this purpose. It has been demostrated that the accuracy of the NMRF flow measurement is independent of vessel diameter so long as the maximum velocity is in the physiological range (Kofler *et al.*, 1991). The symmetry of pulsatile blood flow between paired legs was quantified using the ratio of flows and quantities derived from it at multiple leg sites. This approach allowed symmetry to be assessed at multiple sites and the leg as whole. The use of the (lower/higher) ratio has the advantage that it is bounded between 0 and 1, thereby, providing a useful index of symmetry.

The present findings show that there is a high degree of pulsatile flow symmetry in normal legs with an average ratio near 0·9 for all flow parameters. The absolute pulsatile flow was least symmetric among the parameters, this is likely due to slight differences in tissue mass of the paired legs. However, by using the flow perfusion parameter, which takes tissue volume into account, yields a higher symmetry index which is essentially the same as that found with the ASI parameter. When the normal leg flow symmetry parameters are compared with those in legs with vascular disease, clear and significant decreases in symmetry are found to be present in the diseased limbs. This holds true independent of age or diabetes status. The explanation of the larger asymmetry in the LEAD subjects is unclear. Subjects with symptoms (pain on walking) invariably described bilateral involvement, suggesting that symptoms *per se* are not indicative of increased resting pulsatile flow imbalance. The fact that the greatest asymmetry was found in those subjects with the lower ASI values may indicate that the haemodynamic manifestation of disease progression is more rapid in one of the legs. Further, the fact that the highest left-right leg correlation was obtained with the ASI suggests that this parameter may be the best resting indicator of leg flow imbalance when present.

In addition to the new findings regarding flow asymmetry, the present results confirm and extend the findings of others with respect to resting pulsatile leg blood flow. Based on measurements made at 5 cm increments from the malleolus to 30 cm proximal (Kerr *et al.*, 1991), a significant resting blood flow reduction in patients with claudication or resting ischemia as compared with normal subjects was reported. The present results which used subject-by-subject standardized anatomical sites rather than fixed distances confirms this general finding, even though the present study had no subjects with resting ischemia. The relationship between blood flow and anatomical site between the groups was, herein, found to be similar in shape but displaced downward toward lower flows in the LEAD subjects.

In summary, the present findings establish the range and distribution of leg pulsatile blood flow symmetry in vascularly normal individuals and indicate significant reductions in symmetry accompanying bilateral LEAD. These initial findings provide a basis for subsequent research regarding the possible use of bilateral flow asymmetry assessment to further clarify the pathophysiological progression process and the possible use of symmetry-based parameters in the development of early markers of sub-clinical peripheral arterial disease progression.

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