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Intra-tester and inter-tester reliability of post-occlusive reactive hyperaemia measurement at the hallux

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ABSTRACT

Background: Post-occlusive reactive hyperaemia (PORH) is a measurement of the vasodilatory capacity of the microvasculature that is associated with cardiovascular disease, peripheral arterial disease and foot ulceration. The reliability of its measurement in the hallux (great toe) for clinical and research purposes has not been adequately assessed. This study assesses both the intra-tester reliability and inter-tester reliability of four methods of assessing PORH in the hallux.

Methods and results: A within-subject repeated measures design was used. Forty-two participants underwent PORH testing using four methods: pressure measurement with photoplethysmography; an automated laser Doppler technique with local heating; an automated laser Doppler technique without local heating; and a manual laser Doppler technique. Participants underwent testing on two occasions with a three to 14 day interval. Laser Doppler measurement with a heating probe was found to be the most reliable method of PORH measurement. The index of the area under the curve pre- and post-occlusion and peak perfusion as a percentage of baseline were the most reliable variables.

Conclusions: PORH can be reliably measured using laser Doppler when combined with a heating probe. Further research is required to determine the clinical utility of photoplethysmography in the measurement of PORH.

Introduction

Post-occlusive reactive hyperaemia (PORH) is a measure of microvascular function characterised by the occurrence of a rapid rise in skin and muscle blood flow (in excess of baseline flow) following a period of proximal arterial occlusion (Cracowski et al., 2006). Typically, arterial occlusion causes shear stress and the release of vasodilators such as nitric oxide from the endothelium, lowering myogenic vascular tone and vessel pressure (de Mul et al., 2005). Once the occlusion is released, the lowered vessel pressure allows for a rapid and excessive increase in skin blood flow until the tone is restored and the flow returns to its resting state (de Mul et al., 2005). Impairment in this reaction is indicative of microvascular dysfunction.

Microvascular dysfunction is associated with atherosclerosis (Sitia et al., 2010), diabetes and diabetic foot disease (Chao and Cheing, 2009), peripheral arterial disease (Brevetti et al., 2008) and kidney disease (Long et al., 2012). An impaired post-occlusive reactive hyperaemia response, specifically, is associated with coronary artery disease (Tibirica et al., 2015), peripheral arterial disease (Morales et al., 2005; Nukada et al., 1998) and diabetes (Gomes et al., 2008; Jorneskog et al., 1995), especially those with poor blood glucose control (Jorneskog et al., 1998). Importantly, it has been shown to precede clinically apparent microvascular dysfunction and atherosclerosis as well as late diabetes complications (Yamamoto-Suganuma and Aso, 2009). Consequently, a valid and reliable measure of assessing PORH is needed for both clinical and research purposes.

Several methods can be used to quantify PORH. Cutaneous microcirculation in the periphery can be measured continuously during the task with laser Doppler technology. This allows for quantification of the response through comparison of baseline flux with post-occlusion flux as well as a selection of variables such as the peak flux during hyperaemia and time to peak. This can be performed with or without local heating. Reliability data is available for PORH measurement with laser Doppler in the upper limb in non-pathological populations (Agarwal et al., 2010; Binggeli et al., 2003; Boignard et al., 2005; Roustit et al., 2010; Tew et al., 2011; Yvonne-Tee et al., 2005); however, data for the lower limb in at-risk populations is lacking.

Laser Doppler flowmetry requires expensive equipment that is not widely available to primary care clinicians. As an alternative technique, blood pressure in the small vessels can be obtained by using a digital cuff and sphygmomanometer along with a photoplethysmograph (PPG) probe (Bergstrand et al., 2009). A pressure reading pre- and post-occlusion can be used to measure hyperaemia indirectly through

Abbreviations: AUC, area under the curve; BL, baseline; BZ, biological zero; CVC, cutaneous vascular conductance; ICC, intra-class correlation coefficient; LOA, limits of agreement; PORH, post-occlusive reactive hyperaemia; PPG, photoplethysmography; PU, perfusion units.

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vessel pressure comparison before and after occlusion. The reliability of this technique is yet to be determined. This study will investigate the reliability of a PPG method as well as three methods of laser Doppler flowmetry for the measurement of PORH.

Materials and methods

Participants

Participants were recruited from podiatry clinics on a volunteer basis. All participants met the current guidelines for regular screening for peripheral arterial disease i.e. over the age of 65 years or those who are over 50 years of age who have other risk factors for peripheral arterial disease (Rooke et al., 2011). None were confirmed as having peripheral arterial disease. Exclusion criteria included: the presence of ulceration, injury or infection of the hallux or foot that prevented measurements being taken, amputation of both halluces, severe lymphoedema, connective tissue diseases, vasospastic conditions, and any condition precluding supine lying. The study was approved by the University of Newcastle Human Research Ethics Committee and all participants gave their informed consent to participate.

Equipment and measurement

Participants were asked to refrain from nicotine, caffeine and exercise for 2 h before testing. Room temperature was maintained at 23–24 °C for the duration of testing. Participants were placed in a supine lying position with feet at heart level for 10 min prior to testing and asked to avoid coughing, talking, yawning and moving for the duration of the tests.

Laser Doppler measurements were made with a moorVMS-LDF2 laser Doppler module and a VP1T combined optic and temperature skin probe for the non-heated measurements and a VHP2 digit skin heater probe and needle probe for the heated measurements (Moor Instruments Ltd, Axminster, United Kingdom). Probes were calibrated according to manufacturer instructions.

The laser probe was fixed to the plantar surface of the participant's right hallux using a probe holder and adhesive pad. A 2.5 cm pneumatic cuff (Moor Instruments Ltd) was placed proximal to the probe. The following automated settings were utilised with the moorVMS-PRES pressure module (Moor Instruments Ltd): 3 min of baseline flux recording, inflation of the cuff to 220 mm Hg for 3 min, cuff deflation at maximum speed, and post-occlusive flux recording for a further 4 min. This process was performed with (heated automated method) and without (non-heated automated method) local heating to 33 °C and was repeated using a hand-held a blood pressure gauge (ERKA, Bad Tölz, Germany) and an inflatable digital cuff (Hadeco, Kawasaki, Japan) (manual method). All data were processed with moorVMS recording and analysis software Version 3.1 (Moor Instruments Ltd). All measurements obtained were in arbitrary perfusion units (PU).

Variables obtained manually include: mean (pre-occlusion) flux during 60 s (baseline; BL); mean flux during 60 s of occlusion (biological zero; BZ); highest flux in the 60 s following occlusion (Peak); peak as a percentage of baseline flux (Peak%BL); baseline flux subtracted from the peak (Peak − BL); time from release of occlusion to the peak (TtPeak); and area under the curve (AUC) of 1 min from release of occlusion relative to the AUC of 1 min of baseline flux (Index). Variables obtained automatically by VMS software for the automated method include: mean (pre-occlusion) flux during 180 s (baseline; BL); mean flux during the second half of occlusion (biological zero; BZ); highest flux in the 240 s following occlusion (Peak); peak as a percentage of baseline flux (Peak%BL); baseline flux subtracted from the peak (Peak − BL); time from release of occlusion to the peak (TtPeak); and AUC of 1 min from release of occlusion relative to the area under the curve of 1 min of baseline flux (Index).

Photoplethysmography measurements were made with a Biodop ES-100V3 hand-held Doppler (Hadeco, Kawasaki, Japan), a blood pressure gauge (ERKA, Bad Tölz, Germany) and an inflatable digital cuff (Hadeco, Kawasaki, Japan). A baseline toe pressure was measured by observing the PPG output on a Doppler monitor whilst inflating the digital cuff until the signal fell flat. The cuff was then gradually deflated until the signal reappeared. This was recorded as the systolic toe pressure. After a two minute rest period, the cuff was then inflated to 220 mm Hg for 3 min then rapidly deflated. After 15 s, the toe pressure was taken again. Data were expressed as a ratio of pre-occlusion to post-occlusion systolic pressure.

All measurements were performed by two testers – both podiatrists – trained in the methods described above.

The order of techniques and of the tester was randomised for each participant with a computer generated random allocation function. For each participant, this order and the pre-testing and testing protocol were identical in both sessions taking place between three and 14 days apart at the same time of day. Laser Doppler measurements with heating took place at a separate testing session and repeated three to 14 days later. Testers were blinded to each-other's results and the results of the previous session. Skin temperature was monitored for the duration of testing using a Dermatemp DT-1001RS infrared thermographic scanner (Exergen, Watertown).

Statistics

Statistical analysis was performed in SPSS Version 22 for Windows (SPSS Inc., Chicago, USA). Intra-tester reliability between sessions 1 and 2 and inter-tester reliability between testers 1 and 2 in session 1 were determined with intra-class correlation coefficients (ICCs) and 95% confidence intervals for all four methods. Interpretation of ICCs was in accordance with Portney and Watkins (2000): >0.75 = good, 0.50 to 0.75 = moderate, and <0.50 = poor. T-tests with 95% limits of agreement (LOA) with significance set at $P < 0.05$ (two-tailed test) were also calculated for all four methods to assess agreement.

Results

Forty-two participants at risk of peripheral arterial disease were recruited for the non-heated measurements and thirty-two participants for the heated measurements. Nineteen of the participants took part in both the non-heated and heated measurements. Participant characteristics are shown in Table 1.

ICCs with 95% confidence intervals for intra-rater testers 1 and 2 and intra-rater for session 1 are found in Table 2. Means, standard deviations and 95% LOA for testers 1 and 2 are presented in Table 3. Means, standard deviations and 95% LOA for session 1 are presented in Table 4.

Variables from the non-heated automated method with moderate reliability for both inter-tester and intra-tester were: BL, Peak and Peak − BZ. These were the same for the manual method. Using the automated method with heating, all variables had moderate or good inter-tester reliability. Intra-tester reliability was good for Index and Peak%BL for both testers. Though ICCs were acceptable, LOA for these variables were wide, indicating that a large difference in outcomes would be required to confirm that the change was not due to error.

Table 1
Participant characteristics.

	Heating (n = 32)	No heating (n = 42)
Age (years)	72 ± 7.4	71.5 ± 7.8
Sex distribution (male/female)	17 (53%)/15 (47%)	18 (43%)/24 (57%)
Diabetes present (yes/no)	20 (63%)/12 (37%)	17 (40%)/25 (40%)
Smoker (yes/no)	5 (16%)/27 (84%)	6 (14%)/36 (86%)

Data are presented as mean ± standard deviation.