Comparison of two plethysmography systems in assessment of forearm blood flow

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Venous occlusion plethysmography has been used to study forearm blood flow (FBF) for almost 100 years (4). The underlying principle is simple: by obstructing venous outflow, but not arterial inflow, the forearm volume initially increases in proportion to the FBF. The standard technique for the assessment of this change in FBF, using a circumferential mercury-in-Silastic strain gauge as part of a Wheatstone bridge to detect increases in forearm circumference and derive volume changes, has remained essentially unchanged for 50 years (24). A commonly used and well-validated device employing the above principles is the Hokanson EC4 system (HEC4) (5, 7, 10, 17, 20, 22).

Recently, a new device, the Filtrass 2001 system (F2001), has been developed, particularly to measure capillary permeability. However, this device may also be useful for measuring FBF. It is based on similar principles as HEC4 but with some important differences. With the F2001, forearm circumferential measurement is measured by displacement of a freely movable core of a linear variable displacement transducer (LVDT) attached to a circumferential plastic monofilament (Fig. 1). A linear relationship exists over a large range of calibration movements (6). The system is mechanically and electrically calibrated to measure differences of 10 μm and undergoes internal calibration for changes in temperature and tissue compliance at each time point. The potential utility of this device in forearm venous occlusion plethysmography has not previously been assessed.

The aim of this study was to compare the F2001 against the established HEC4 in terms of repeatability, systematic bias, and ease of use. To compare the F2001, subjects underwent simple, noninvasive systemic interventions to reduce or increase FBF. It was assumed that systemic hemodynamic changes would result in similar changes in FBF simultaneously in both arms (9). To assess higher blood flows, postocclusive hyperemia (POH) was used. In this study, the repeatability of each individual device could be assessed when the same device was used on both arms. Comparison of one system against the other on different arms allowed examination for systematic bias between devices.

METHODS

Subjects. Ten healthy subjects (9 men) aged 22–30 yr were recruited for this study, which was undertaken in accordance with the Declaration of Helsinki and with the approval of the local research ethics committee. Written, informed consent was obtained from each subject. All subjects abstained from vasoactive drugs for at least 1 wk, from alcohol and cigarettes for 24 h, and from food and caffeine for at least 3 h before each study visit.

Study design. Volunteers attended for two separate study periods of four visits each. The protocol was similar on each of the first four study days except for the plethysmography device used. The devices were studied in random order using either the HEC4 on both arms, the F2001 on both arms, the HEC4 on the right arm with the F2001 on the left, or the F2001 on the right arm and the HEC4 on the left.

During the second four study visits, POH was employed to cause a decrease in FBF. It was assumed that systemic hemodynamic changes would result in similar changes in FBF simultaneously in both arms (9). To assess higher blood flows, postocclusive hyperemia (POH) was used. In this study, the repeatability of each individual device could be assessed when the same device was used on both arms. Comparison of one system against the other on different arms allowed examination for systematic bias between devices.

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Study protocol. The study visits were performed on different days in a quiet, draft-free, temperature-controlled room (22–24°C). During the low-flow experiments, the volunteer was subjected to either Stroop’s colored word test (SCWT), lower body negative pressure (LBNP), or a rest period. Mean arterial pressure and heart rate were measured during minute 6 and FBF was measured during the last 3 min of each 10-min time period. During the high-flow experiments, volunteers were exposed to 5, 8, and 13 min of arterial occlusion during different control mechanisms than FBF (21, 23, 24). Therefore, the strain gauges were placed around the forearm at the point of greatest circumference.

There were some features unique to each device. HEC4 (D. E. Hokanson, Bellevue, WA) consists of several discrete components: two HEC4 plethysmographs, two Hokanson E20 rapid cuff inflators, a Hokanson AG 101 cuff inflator air resource, strain gauges, and Hokanson wrist and upper arm cuffs. HEC4 uses electrically calibrated mercury-in-Silastic strain gauges, which were calibrated at the beginning of each study. HEC4 occupies a total volume of 1.4 m³.

The F2001 LVDT (DOMED Medizintechnik, Munich, Germany) was positioned on the forearm skin at a similar position to the mercury-in-Silastic strain gauges and fixed to the forearm with adhesive tape. The plastic monofilament component surrounding the forearm was supported on the skin by a “zigzag band” (Fig. 1). Before the start of measurements, the surface of the monofilament was coated with synthetic oil (DOMED Medizintechnik) to reduce friction and then inserted into the main body of the LVDT. The LVDT was calibrated at the beginning of each study, and the resting tension on the monofilament was adjusted automatically at each time point. The F2001 is a smaller, more compact device than the HEC4, with all components contained within a single housing with a volume of 0.22 m³.

LBNP. The lower body of the subject was placed in an airtight steel chamber and sealed with a pneumatic belt around the waist. Suction was applied by a low-pressure vacuum device, and the negative pressure within the chamber was kept constant by a servomechanical pressure regulator (Department of Medical Physics, Western General Hospital, Edinburgh, UK). LBNP (15 mmHg) was applied for 10 min to reduce FBF. LBNP caused venous pooling, which, via baroreceptor unloading and selective activation of elements of the sympathetic nervous system, results in an increase in systemic vascular resistance and forearm vascular resistance and thus a reduction in FBF. Previous work (13) has shown that there is no effect on mean arterial pressure or heart rate at this level of negative pressure.

SCWT. SCWT consists of several pages of the words “blue,” “red,” “yellow,” and “green,” each printed in different colors of ink (blue, red, yellow, and green) in a random order. The subject is asked to state the color of the ink in which the word is printed not the printed word. Mental conflict arises because the learned response is to read the word rather than report the color. This task was performed at a steady rate of ~100 words/min with a metronome and observer acting as a guide to encourage volunteers to keep to the pace. To induce reproducible mental stress in our subjects, we applied the SCWT for 10 min. Responses to the SCWT include a decrease in forearm vascular resistance and a marked increase in FBF (14). SCWT also causes an increase in mean arterial pressure, heart rate, and cardiac output and a fall in systemic vascular resistance. Increases in FBF are stable and reproducible after 9 min (8). However, forearm vasodilator responses to SCWT may become diminished with repeated exposure (11) and, to cause a range of FBF changes, three 10-min exposures to SCWT were performed at each study visit.

POH. Postocclusive hyperemia (POH) can cause marked increases in FBF (16). Brachial artery occlusion was applied by manually inflating an upper arm cuff to at least 60 mmHg above systolic pressure. POH of the forearm resulted after the occlusion was released. A range of occlusion times (5, 8, and 13 min) were used to assess the devices over a range of FBF.

Data acquisition and statistical analysis. FBF was obtained from the mean of the last five consecutive recordings of each period. Both systems allow the manual rejection of curves if rendered unsuitable for analysis by movement artifact. Each slope recording was taken from the steep linear part of the response curve. In the high-flow experiments, the plateau phase was reached more quickly, but the steep linear portion of the curve was still easily identified and assessed over three or more heartbeats. Data obtained from the Hokanson plethysmograph were stored on a Macintosh computer using the Chart version 3.3 software (MacLab, ADInstruments). Data from the F2001 were analyzed in a similar manner using a PC-based automatic analysis program, which fits a curve to the measured slope and produces a mean value for FBF.

There is no “gold standard” for the noninvasive measurement of FBF. Repeatability of the devices was quantified by the average difference between the changes in FBF from the preceding rest period. In response to stimuli, measured FBF by the same device when used simultaneously on left and right arms (HEC4 on both arms or the F2001 on both arms). Therefore, assuming stimuli will affect the FBF in each arm to a similar degree, the closer to zero the difference in
FFB between each arm and the smaller the standard deviation of results, the more repeatable the device. Systematic bias between devices was determined by the average of the differences from the mean when different devices were simultaneously used to measure the changes in FBF (HEC4 on the right arm with the F2001 on the left arm or F2001 on the right arm and the HEC4 on the left arm) and presented as Bland-Altman plots (3).

The effects of the SCWT, LBNP, and POH on FBF were assessed using all data from both devices on left and right arms and expressed as mean percentage changes from baseline ± SE. Mean differences were assessed by using Student’s t-test. Statistical significance was taken at the 5% level. The study had 80% power to show a 7.5% difference between the devices, assuming a 15% standard deviation in FBF measurement.

RESULTS

None of the subjects were obese. All were right handed with correspondingly larger right forearm circumferences (264 ± 5 vs. 259 ± 5 mm, P < 0.01). However, there was no difference between baseline blood flow between the left and right arms (3.1 ± 0.2 vs. 2.6 ± 0.1 ml·100 ml⁻¹·min⁻¹, P = 0.1). The HEC4 cuff is broader than the F2001 cuff and inflates in <1 s, whereas the F2001 cuff takes 3–4 s to inflate. There did not appear to be any difference in cuff artifacts between the two systems as a result.

LBNP and SCWT caused the expected changes in FBF, which were repeatable within study visits (Fig. 2A). LBNP caused a decrease in FBF (−18.7 ± 0.8%, n = 240, P < 0.0001), and SCWT caused an increase in FBF (24.6 ± 1.5%, n = 240, P < 0.0001). Forearm hyperemia after occlusion times of 5, 8, and 13 min substantially increased FBF by 390 ± 86, 756 ± 217, and 851 ± 132%, respectively (all P < 0.0001) (Fig. 2B).

Comparison between HEC4 and F2001. When used to measure changes in the left and right arm, HEC4 showed no difference in the absolute change in FBF between arms (0.10 ± 2.37 l/min, n = 125, P > 0.05). When used to measure simultaneous changes in the left and right arm, F2001 showed no difference in absolute changes in FBF between arms (−0.47 ± 1.92 l/min, n = 125, P > 0.05). There was no difference between HEC4 and F2001 (0.10 ± 2.37 vs. −0.47 ± 1.92 l/min, n = 125, P > 0.05). There was good correlation between the devices (Fig. 3). Bland-Altman plots reveal no systematic bias between the devices or in relation to flow values when used to measure simultaneous changes in response to the systemic stimuli described above (Fig. 4).

DISCUSSION

FBF measurement is widely used in physiological and pharmacological studies in the clinical laboratory setting (12). Existing mercury-in-Silastic (24) and Dohn air-filled cuffs have been widely used and appropriately validated (18) for measuring baseline and relative changes in blood flow. The present study was designed to assess repeatability and systematic bias using a new device for measuring FBF by venous occlusion plethysmography. This device, the F2001, uses a new and sensitive technique for measuring forearm circumference, is relatively compact, and has been validated for use in assessing capillary permeability (6). The important finding of this study was a demonstration of comparable repeatability, as measured by differences in blood flow between left and right arms, when the F2001 was used compared with a standard mercury-in-Silastic device, the HEC4. In addition, there was no systemic bias between the devices as assessed by Bland-Altman analysis (3).

Stimuli to effect changes in blood flow. To effect small physiological increases and decreases in blood flow in the two arms, we used SCWT and LBNP, respectively. These techniques are well characterized and widely used for this purpose. However, they produced only small changes of blood flow, with generally a <30% change. Because plethysmography techniques are often used to detect much larger changes in blood flow, especially when responses to exogenously administered vasodilators and vasoconstrictors are examined (2, 12), it was necessary to seek an additional stimulus to effect greater increases in blood flow than seen with SCWT. Here, an established ischemia model was used, and the POH response was assessed (16) to graded ischemia. This achieved our aim by producing increases of local FBF of ~800% after 13 min of occlusion, equivalent to responses to potent vasodilator agents in the forearm.

Comparison between arms. In studies with SCWT and LBNP, we compared responses between arms, both for studies of repeatability and systematic bias. This can be justified from many studies showing that the forearm response to systemic stimuli affects both arms equally. Indeed, this is one of the principles underlying the use of the opposite arm as a control in plethysmographic studies (1, 9). Importantly, data from this study confirm the similarity in responses between arms, with only an ~1% difference in percentage change in FBF from
baseline between left and right arms to SCWT and LBNP when measured by HEC4.

In the case of POH, however, the stimulus is local and not systemic, and there may be differences between arms related to hand dominance. Therefore, in this situation, only comparisons within one arm were made in the present study to avoid any risk of obtaining a falsely low measure of repeatability.

Fig. 3. Correlation graphs of Hokanson EC4 (right arm) vs. Hokanson EC4 (left arm) (H1 vs. H2; A), Bland-Altman comparison of Filtrass 2001 (right arm) vs. Filtrass 2001 (left arm) (F1 vs. F2; B), Bland-Altman comparison of Filtrass 2001 (right arm) vs. Hokanson EC4 (left arm) (F1 vs. H2; C), and Bland-Altman comparison of Hokanson EC4 (right arm) vs. Filtrass 2001 (left arm) (H1 vs. F2; D).

Fig. 4. Bland-Altman comparison of Hokanson EC4 (right arm) vs. Hokanson EC4 (left arm) (H1 vs. H2; A), Bland-Altman comparison of Filtrass 2001 (right arm) vs. Filtrass 2001 (left arm) (F1 vs. F2; B), Bland-Altman comparison of Filtrass 2001 (right arm) vs. Hokanson EC4 (left arm) (H2 vs. F1; C), and Bland-Altman comparison of Hokanson EC4 (right arm) vs. Filtrass 2001 (left arm) (F2 vs. H1; D). Light dotted lines indicate mean values, and dashed lines indicate 95% confidence limits.
Comparison between devices. The main aim of this study was to explore the comparability between devices for the measurement of blood flow by plethysmography. Because there is no readily usable gold standard for measuring FBF, we chose to compare the F2001 with one of the most widely used devices in current use, the HEC4. Many studies using forearm plethysmography involve multiple measurements of blood flow in the same individual to be performed on separate occasions. Therefore, a high degree of repeatability is required across a wide range of blood flows. LBNP and SCWT could be used to examine small decreases and increases in blood flow, respectively, and POH could be used to examine large increases. The study design allowed within-device as well as between-device comparison of effects of external stimuli on blood flow to assess both repeatability and systematic bias.

The studies show a high level of correlation (>90%) between devices that was similar to that for within-device correlations. More importantly, there was no difference in baseline blood flow or in the response to the various stimuli (LBNP, SCWT, and POH) between devices and no difference between measurements even at the high blood flows associated with POH. Furthermore, Bland-Altman analysis revealed no systematic bias. These data, taken together, show a high level of repeatability that is sufficient to allow either device to be used for plethysmographic studies.

Potential advantages of the F2001. The recently developed F2001 is designed to measure FBF and can also be used to measure capillary permeability. The F2001 device is more compact and portable than the HEC4. This may be of advantage in certain circumstances, such as in intensive care units or if displacement occurred during a critical part of an intervention. In terms of mechanical reliability, one F2001 strain gauge failed during the study (total of 40 study days), whereas there were no failures of the HEC4 strain gauges. The upper cuff air inlet of the F2001 mechanically interfered with the strain gauge on inflation, and the rate of arm and wrist cuff inflations was slower than the HEC4 (3–4 vs. <1 s). Slowly inflating cuffs can result in venous engorgement if arterial occlusion is significantly delayed, which could then cause discomfort and potentially affect results. However, neither of these problems appeared to occur in our study, suggesting the slower rate of cuff inflation is not of practical importance, even at high flows. Although there may be local variations, there was no major cost difference between the two devices. In addition, unlike the HEC4, the F2001 does not use mercury in its construction and, therefore, has the advantage that its use would not be restricted in the future were the use of mercury in medical instruments to be banned (15).

Potential limitations of the study. For ethical reasons, it was not possible to assess intra-arterial responses to vasodilator and constrictor agents directly in these studies. Therefore, postischemic hyperemia was used as the surrogate stimulus for effecting large increases in flow. It is necessary, and probably reasonable, to make the assumption that these observations can be extrapolated to such studies. Similarly, studies here were performed in the forearm circulation, and we cannot be certain that they also apply to the calf, although this again would seem a reasonable assumption.

In summary, the F2001 seems a promising and reliable new addition to the devices available to measure blood flow by strain-gauge plethysmography, with potential advantages in terms of size, mobility, data analysis, and its capacity to be used to measure capillary permeability.

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