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The Sit-to-Stand Technique for the Measurement of Dynamic Cerebral Autoregulation

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Abstract

Measurement of cerebral autoregulation is important for the evaluation and management of a number of clinical disorders that affect cerebral blood flow. We currently lack simple bedside measures that mimic common physiologic stresses. Therefore, we evaluated a new sit-to-stand technique as an alternative method to the frequently used thigh-cuff technique in healthy volunteers. Continuous middle cerebral artery (MCA) blood flow velocities (BFV) and arterial blood pressure (ABP) were measured in response to standing from a sitting position, or rapid thigh-cuff deflation in 24 healthy subjects (50 ± 22 years). Autoregulatory Index (ARI) was calculated as the BFV response for step changes in ABP using a second-order differential equation with a set of parameters that can be used to grade the performance of autoregulation. Of these 24 subjects, 30% could tolerate only two thigh-cuffs and refused to proceed with the third cuff, while none of our subjects had any difficulty with performing the three sit-to-stand trials. The two techniques produced similar changes in mean arterial blood pressure (ABP), but the times to nadir of the blood pressure and BFV were significantly faster for the thigh-cuff. The mean group ARIs were similar between the two techniques. While between subjects variability was higher for sit-to-stand ARIs, the within subject sit-to-stand ARI variability was small. Thus, for the assessment of cerebral autoregulation, the sit-to-stand procedure is well tolerated and produces ARI values that have low within subject variability. The sit-to-stand technique appears to be a suitable measure of individual ARI values for inferring dynamic cerebral autoregulation.

Keywords

Dynamic Cerebral Autoregulation; Sit-To-Stand Procedure; Transcranial Doppler Ultrasound

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INTRODUCTION AND LITERATURE

Cerebral autoregulation is an important regulatory process that maintains a relatively constant cerebral blood flow (CBF) in response to changes in arterial blood pressure (ABP). Abnormalities in cerebral autoregulation are thought to occur in a number of clinical disorders such as cerebral microvascular disease, stroke, subarachnoid hemorrhage, postpartum angiopathy, eclampsia, syncope, and traumatic brain injury. While in some of these disorders such as traumatic head injury (Matz and Pitts 1997; Lee et al. 2001), stroke (Eames et al. 2002), subarachnoid hemorrhage (Aaslid 1999; Ratsep and Asser 2001) and eclampsia (Oehm et al. 2003), abnormal measures of autoregulation have been demonstrated, the role of cerebral autoregulation in the other common disorders such as syncope and cerebral microvascular disease, has not been well defined. In syncope numerous studies using various techniques have been used, but the results are conflicting (for a brief review see (Folino 2006)). Studies of cerebral autoregulation in cerebral microvascular disease have been limited to one study in diabetes (Novak et al. 2006) and one study using near-infrared spectroscopy to examine spontaneous oscillations in the visual cortex of elderly subjects with cerebral microangiopathy (Schroeter et al. 2005). Since cerebral autoregulation may play a role in the pathophysiology of all these disorders, methods that can assess cerebral autoregulation rapidly, reliably, and non-invasively will significantly advance our understanding of these cerebrovascular conditions, particularly syncope and microvascular disease, where we still need more information.

Early investigations of cerebral blood flow regulation were limited to the steady-state behavior of cerebral blood flow. However, CBF regulation is a dynamic process, constantly changing cerebrovascular resistance to optimize CBF. With the introduction of transcranial Doppler ultrasound (TCD) to measure CBF velocity (Aaslid et al. 1982), beat-to-beat changes can be measured during rest and activity. TCD, which can provide continuous measurement of the blood flow velocity in the basal cerebral arteries with a high temporal resolution, has proved to be a powerful tool for non-invasively assessing dynamic CBF responses to various stimuli, including changes in ABP (Panerai 1998).

Assessment of dynamic cerebral autoregulation is based on transient changes in cerebral blood flow induced by sudden changes in ABP. Although a “gold standard” for this assessment is not available (Panerai 1998), a commonly used technique to induce a significant rapid change in ABP has been the sudden deflation of bilateral thigh-cuffs (Aaslid et al. 1989). However, the thigh-cuff approach cannot always be used in clinical assessment. The inherent variability in the magnitude of the ABP decline during each inflation/deflation cycle, necessitates a minimum of 3–8 cycles of inflation/deflation to obtain an averaged response (Mahony et al. 2000). Moreover, inflation of the thigh-cuffs can be painful, making subjects unwilling to undergo repeated trials, particularly those who are elderly and frail. Finally, the thigh-cuff deflation may not be representative of the physiologic stresses of everyday life that threaten cerebral perfusion, such as posture change or medication intake.

To overcome the technical limitations of the thigh-cuff technique, several other dynamic methods have been developed. These include the Valsalva Maneuver (Greenfield et al. 1984; Tiecks et al. 1995; Tiecks et al. 1996), Transient Hyperemic Response test (Giller 1991; Ratsep and Asser 2001), and Transfer Function analysis (Birch et al. 1995; Diehl et al. 1995; Panerai et al. 1999) using induced or spontaneous oscillations in ABP. While each of these methods may be more suitable for different patient populations, transfer function analysis has so far been the most practical approach. However, it depends on adequate spectral power and coherence between pressure and flow in the auto-regulatory frequencies; two conditions that many not be met in many subjects.

One method that we have developed uses a simple sit to stand procedure to produce a transient decrease in blood pressure (Lipsitz et al. 2000). We have previously shown that this method can be effectively performed in elderly subjects and produces consistent results with transfer function analysis (Serrador et al. 2005). The aim of this study was to assess the sit-to-stand protocol as an alternative to the thigh-cuff technique to measure dynamic cerebral autoregulation. The test is simple, well tolerated by ambulatory subjects and closely mimics a physiological stimulus experienced during activities of daily living.

MATERIALS AND METHODS

Subjects

Twenty-four healthy subjects (50 ± 1 years, range 24 to 81 years old) volunteered to participate in the study. Subjects were recruited from among laboratory personnel and members of the Harvard Cooperative Program on Aging subject registry. All subjects were carefully screened with a medical history, physical examination, and electrocardiogram to exclude any acute or chronic medical conditions. Subjects were nonsmokers and refrained from alcohol for at least 12 hours. The study was reviewed and approved by the Hebrew SeniorLife institutional review board, and followed institutional guidelines in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects gave their informed consent prior to their inclusion in the study.

Experimental Protocol

Instrumentation

Subjects were studied in the cardiovascular laboratory in the post-absorptive state, ≥ 2 hours after their last meal. Subjects were instrumented for heart rate (HR electrocardiogram) and beat-to-beat mean arterial pressure monitoring (ABP, Finapres, Ohmeda Monitoring Systems, Englewood, CO) as previously described (Sorond et al. 2005). End-tidal CO_2 was measured using a Vacumed CO_2 Analyzer (Ventura, CA). Thigh-cuff inflation/deflation was achieved with the Hokanson Rapid Cuff Deflator (Bellevue, WA).

TCD ultrasonography (MultiDop X4, DWL-Transcranial Doppler Systems Inc., Sterling, VA) was used to measure simultaneous changes in MCA mean blood flow velocity (BFV) in response to: 1) blood pressure changes during a sit-to-stand protocol and 2) blood pressure changes during thigh-cuff inflation/deflation. The MCA signal was identified according to the criteria of Aaslid et al (Aaslid et al. 1982) and recorded at a depth of 50 to 60 mm. A Mueller-Moll probe fixation device was used to stabilize the Doppler probe for the duration of the study. The envelope of the velocity waveform, derived from a fast-Fourier analysis of the Doppler frequency signal, was digitized at 500 Hz, displayed simultaneously with the ABP, ECG, and end-tidal CO_2 signals, and stored for later off-line analysis.

Each subject underwent 3 thigh-cuff and 3 sit-to-stand trials. Subjects who did not have at least 2 thigh-cuff and 2 sit-to-stand trials for analysis were excluded. Sit-to-stand and thigh-cuff trials were excluded (technically inadequate) if the drop in ABP was less than 10 mmHg, the blood flow and/or blood pressure signal was lost during the procedure, or the tracings were noisy and therefore, uninterpretable. Subjects with APB drops of less than 10 mmHg were excluded to make sure each method induced a similarly robust BP stimulus.

Standing Protocol

The active sit-to-stand procedure, which produces immediate orthostatic hypotension without altering the spatial or gravitational relation between the Doppler probe and the insonated vessels, was developed in our laboratory and previously described in detail (Lipsitz et al.

2000). After instrumentation, subjects sat in a straight-backed chair with their legs elevated at 90 degrees in front of them on a stool. For each of 3 active stands, subjects rested in the sitting position for 5 minutes, then stood upright for 1 minute. The initiation of standing was timed from the moment both feet touched the floor. Data were collected continuously during the final 1 minute of sitting and 1 minute of standing. The autoregulatory response to transient orthostatic hypotension was assessed by the Autoregulatory Index (ARI) using Tieck's method (Tiecks et al. 1995), as well as by determining the absolute and percent changes in cerebrovascular resistance ($CVR=ABP/BFV$) for the MCA from the sitting position (average of 50 seconds data) to the BP nadir during standing (average of 5 values).

ARI was calculated as a coefficient graded from 0 (absence of autoregulation) to 9 (strongest autoregulation), describing a dynamic model of autoregulation first proposed by Tieck (Tiecks et al. 1995).

Thigh-cuff Protocol

The thigh-cuff procedure, which produces immediate transient step decreases in BP, has been extensively described (Aaslid et al. 1989; Mahony et al. 2000). Recordings were made with the subjects in the supine position. Bilateral large thigh-cuffs were inflated 20 mmHg above the systolic BP as measured by the Finapres for each subject. Occlusion was maintained for 2 minutes and a transient MAP drop was induced by rapid cuff deflation using the Hokanson Rapid Cuff Deflator. The procedure was repeated three times in each subject. The autoregulatory response to the transient BP decline was assessed by the Autoregulatory Index (ARI) using Tieck's method (Tiecks et al. 1995), as well as by determining the absolute and percent changes in cerebrovascular resistance ($CVR=ABP/BFV$) for the MCA during thigh-cuff deflation.

Data Processing

All data were displayed and digitized in real time at 500 Hz with commercially available data acquisition software (Windaq, Dataq Instruments). BFV, ABP and CO_2 waveforms were re-sampled at 1Hz using a MATLAB program. Beat-to-beat R-R interval, ABP and BFV were determined from the R wave of the ECG and the maximum and minimum of the arterial pressure or BFV waveforms. Individual responses were averaged across trials and individuals to obtain group waveforms for ABP, BFV, CVR and end-tidal CO_2 .

Beat-to-beat values for the mean BFV and mean ABP during the sit-to-stand protocol were analyzed across each trial for each individual. Cerebrovascular resistance (CVR) was calculated as the ratio of ABP to BFV. To compare group responses, percent change in BFV, CVR and ABP were calculated as the difference between standing and sitting values, divided by sitting values. Data were processed in the same manner for the thigh-cuff with the exception that percent changes were calculated as the difference between deflated and inflated cuff values, divided by the inflated cuff values. Individual percent changes were then averaged to obtain percent changes in BFV, CVR and ABP for each group.

Statistical Analysis

Individual ARIs were compared using one-way analysis of variance (ANOVA), where subject was the single factor in the model. Intraclass correlation coefficients (ICC) were calculated as the difference of between and within subject mean squared deviations divided by between subject mean squared deviations $[(BMS-WMS)/BMS]$ (Shrout 1995). To compare the ICC values between the sit-to-stand and thigh-cuff methods, we ran 1000 bootstrap samples (sampling persons) to obtain interval estimates for the ICCs and the difference between the ICCs for the two methods.

RESULTS

Subject Characteristics

Demographic and baseline data for all the subjects (24 subjects enrolled and 17 subjects analyzed) studied are summarized in Table 1. Seven subjects were excluded from further analysis because they did not have at least 2 trials for each of the thigh-cuff and sit-to-stand procedures. Of these 7 subjects, 6 were excluded because they did not have at least 2 acceptable thigh-cuffs and 1 was excluded because they did not have at least 2 acceptable sit-to-stands. Significantly more subjects ($p < 0.05$ by Chi Square) had to be eliminated because they did not have at least 2 adequate thigh-cuffs. Of the 24 subjects enrolled, eight subjects refused the third thigh-cuff because it was too painful, 5 subjects had at least one technically inadequate thigh-cuff, while 8 subjects had at least one technically inadequate sit-to-stand and in 3 subjects the last sit-to-stand could not be performed because of time limitation. These three subjects were randomized to get the thigh-cuff first and were three of the 8 subjects who refused the third thigh-cuff trial because of pain. In these three subjects we spent a significant amount of time between each thigh-cuff so as to minimize discomfort and allow them to complete the three thigh-cuff trials. As a result, we did not have time to complete the third sit-to-stand.

Baseline MAP, BFV and HR for the sit-to stand (taken sitting) and the thigh-cuff (taken supine) were not significantly different between the two methods.

Cerebral Blood Flow Responses to Step Drops in Blood Pressure

Table 2 summarizes the group hemodynamic changes for each procedure. For the 17 subjects whose data were analyzed, there were no significant differences in the percent change in blood pressure between the two procedures. However, the time to the nadir of the blood pressure was significantly faster for the thigh-cuff than the sit-to-stand technique (6.2 ± 2.3 vs. 7.8 ± 1.5 sec, $p = 0.03$). There was a significantly larger, but slower decline in BFV during the sit-to-stand procedure. The ARI and percent change in the cerebrovascular resistance (pcCVR) were not significantly different between the two procedures.

Group average responses in BFV and end-tidal CO_2 to a drop in ABP with the sit-to-stand and thigh-cuff methods are shown in Figure 1. The slower ABP and BFV responses of the sit-to-stand can also be observed in these group-averaged data. Both procedures are also associated with a small decline in end-tidal CO_2 , which is more pronounced for the sit-to-stand method, but similar at the time BFV reaches its nadir. Despite a slower decline in ABP during the sit-to-stand procedure, the recovery is much faster and more complete as compared to the thigh-cuff.

Measurement Reliability

Table 3 displays the raw data for both the sit-to-stand and thigh-cuff protocols for the seventeen subjects studied. Also shown are the results of a one-way ANOVA of the ARI using subject as the single factor in the model. As can be seen, there is good agreement between both techniques, which generate similar ARI values. Both techniques have a high between subject variability, with the larger variability corresponding to the sit-to-stand method (the total variance of sit-to-stand is 8.46, the variance of the thigh-cuff is 2.69). However, despite a larger between subject variability, the sit-to-stand technique produces ARI measures with a low within subject variability. To measure the reliability of the ARI measures we calculated the intraclass correlation coefficient (ICC) for the sit-to-stand and thigh-cuff technique ARIs. Intraclass correlation coefficients provide a reliability index for measurements used in behavioral and physical sciences (Nunnally and Bernstein 1994; Shrout 1995). The ICC (reliability) for the sit-to-stand ARI data was 0.88, very close to the 0.9 threshold that identifies measures suitable for inferences about individuals (Nunnally and Bernstein 1994; Shrout

1995), and the ICC for the thigh-cuff procedure was 0.13. The 95% Confidence Region for different assessment method ICC's are 0.72 – 0.96 for the sit-to-stand and –1.3 – 0.60 for the thigh-cuff method. The 95% Confidence Region for the difference in the ICCs is 0.26 – 2.19. Thus, ICC was significantly larger for the sit-to-stand method.

DISCUSSION AND SUMMARY

The sit-to-stand and the thigh-cuff techniques can both be used to assess cerebral autoregulation by inducing a transient drop in blood pressure and monitoring the cerebral blood flow response to this transient fall in cerebral perfusion pressure. We have shown that: (1) the sit-to-stand procedure is better tolerated than the thigh-cuff, (2) both the thigh-cuff and sit-to-stand methods produce similar group ARI values, and (3) in response to a similar drop in ABP, the CBF response in the sit-to-stand method was larger and slower than the thigh-cuff. Since these two mechanisms provoke the transient drop in blood pressure by fundamentally different mechanisms, using them both in future studies provides a unique opportunity to examine cerebral blood flow regulation under diverse physiological states. Our results, which are discussed in the context of each method, address several important differences and similarities between these two techniques.

Methodological Considerations

The active sit-to-stand procedure is known to be associated with an immediate increase in HR, a pronounced increase in cardiac output (for detailed review see (Wieling et al. 2007)) and a simultaneous fall in systemic vascular resistance, resulting in a transient fall in ABP. This initial ABP response to the upright position, which is exclusively associated with active rising and not seen in passive tilting, has been proposed to be the underlying cause for initial orthostatic hypotension (Wieling et al. 2007). Therefore, the etiology of the transient fall in ABP is a temporal mismatch between cardiac output (rate of blood volume entering the arterial vasculature) and vascular resistance (rate of blood volume leaving the arterial vasculature). Studies have shown that this mismatch results from a reduction in peripheral resistance (Wieling et al. 2007) and not cardiac output. Active rising leads to a decrease in vascular resistance attributed to vasodilation in the working muscles through local mechanisms. This vasodilation peaks at 4 seconds and then returns to normal over the next 10–20 seconds (Wieling et al. 2007). In addition, standing up causes an initial increase in venous return through the effects of contraction of leg and abdominal muscles. The consequent sudden increase in right atrial pressure activates cardiopulmonary receptors resulting in a decrease in systemic sympathetic vasoconstrictor tone and total systemic vascular resistance lasting 6–8 seconds.

Inflating and holding thigh-cuff pressures above systolic pressure occludes blood flow to the lower limb and during this occlusion local vasodilation occurs. Rapid thigh-cuff deflation following three minutes of suprasystolic inflation is associated with a massive inflow of blood into the low resistance lower limbs, immediately lowering the central arterial pressure. This is accompanied by pooling of blood in the lower limb venous system which reduces the venous return to the heart, further reducing central arterial pressure. Thigh-cuff deflation typically reduces central artery blood pressure by 15–20% and restoration of normal pressure is not usually complete for at least 20 seconds. Given that the inflation of the thigh-cuffs can be painful, there is a concern for sympathetic activation (Panerai 1998) during the thigh-cuff procedure.

Most studies of cerebral autoregulation have examined the relationship between mean CBF and mean ABP without considering the time course of changes in flow following changes in pressure. Studies using the thigh-cuff technique have shown that the cerebral blood flow response to a sudden drop in ABP starts in approximately 2 seconds and the transient response is usually complete within 10–15 seconds (Aaslid et al. 1989; Panerai 1998). The blood flow

response to the sudden drop in ABP during the sit-to-stand procedure follows a slower time course, with a time to nadir of the blood flow almost 4 times longer than the thigh-cuff. One possible explanation for the slower time course of the sit-to-stand ABP and BFV responses may be relative hypocapnia. However, as one can observe from the time courses of the response in Figure 1, there is not a significant difference between the magnitude of the end-tidal CO₂, before the BFV response to the ABP stimulus is completed. The most significant difference in end-tidal CO₂ occurs at a time when BFV has recovered and autoregulation is completed. An alternative possibility may be the effect of sympathetic activation, discussed below. The sit-to-stand method is more likely associated with decreased sympathetic tone, where as the painful nature of the thigh-cuff procedure is most likely associated with increased sympathetic tone (Panarai 1998).

Sympathetic Nervous System

The effect of sympathetic activation on cerebral blood flow regulation is not clear. It has been suggested that under normal conditions sympathetic tone is minimal and only when the cerebrovascular system is stressed, activation of the sympathetic nervous system plays a protective effect by shifting the static autoregulatory curve to the right (Panarai et al. 2001). In their study of cerebral autoregulation in response to induced and spontaneous sudden changes in arterial blood pressure using various methods, Panarai et al., (Panarai et al. 2001) reported that they were unable to detect a significant difference in the BFV-ABP relationship in response to various degrees of sympathetic activation resulting from different maneuvers. Therefore, it is unlikely that the differences in levels of sympathetic activation between the thigh-cuff and sit-to-stand, had a significant effect on the slower sit-to-stand cerebral blood flow response or the ARI measures and BFV-ABP relationship in our study.

Effect of Age on ARI

Results from previous studies using the thigh-cuff technique have reported ARI values for the thigh-cuff that are lower than those we found in our subjects. Mahoney et al., studied 16 volunteer subjects (mean age, 31.8±8.5 years; range, 23 to 51 years) with 6 thigh-cuff iterations and reported a mean ARI of 4.98±1.06 for the group (Mahoney et al. 2000). In the study by Tiecks et al., (Tiecks et al. 1995) the mean value of ARI was 4.8±1.0 in a group of 10 subjects 35±10 years under propofol anesthesia for elective orthopedic surgery. Junger et al. (Junger et al. 1997) quoted a mean ARI of 4.7±1.0 in a group of 29 normal volunteers aged 22±5 years. In contrast, White and Markus (White and Markus 1997) quoted a mean ARI of 6.3±1.1 in a group of 21 normal control subjects with the mean age of 67.8±7.8 years, significantly older than the previous studies mentioned. Similarly, we report an ARI value of 7.0 ± 1.1 for our 17 healthy volunteers 51±23 years. Thus it may be possible that the higher ARI values in our subjects are related to the greater age, similar to White and Markus. Our population includes data on 8 elderly subjects, mean age 73±5; a group older than those previously studied. In fact, the mean ARI value was 7.4 ± 0.8 for our older subjects (those = 70 year) and 6.6 ± 1.2 for our younger subjects, suggesting that the larger ARI values are driven by our older subjects.

Summary

Assessment of cerebral autoregulation is critical to our understanding and evaluation of cerebrovascular physiology. Research on human cerebral autoregulation has been classically viewed as an “all or nothing” phenomenon using widely different criteria (Panarai 1998). Given that autoregulation is a dynamic process that cannot be reduced to a single measurable property, previous investigations have proposed that it be regarded as a continuum of stages dependent on the feedback gain of the multiple mechanisms involved (Panarai 1998). Until a single method can be regarded as the “gold standard”, assessment of cerebral autoregulation in

research and clinical practice should use multiple methods or perform comparisons between methods.

Our analysis demonstrates that both the thigh-cuff and sit-to-stand methods produce similar group ARI values. The sit-to-stand stimulus has a favorable consistency with low within subject variability. This consistent response in combination with the minimal discomfort and ease of the procedure support its use for assessing autoregulation in many populations, including the elderly where disorders of cerebrovascular function are more prevalent. The slower response of the sit-to-stand technique also provides us with the opportunity to study the dynamic properties of cerebral autoregulation over a different time course than that available with the thigh-cuff using a quantitatively similar hypotensive stimulus. The physiological nature of the sit-to-stand procedure is an additional favorable feature of this technique, allowing one to assess autoregulation during a maneuver that has realistic implications for activities of daily living. This technique could be used in conditions such as: syncope; cerebral microvascular disease (cerebral white matter disease); vertigo; multiple system atrophy and autonomic failure; Parkinson's disease and sleep apnea.

Study Limitations

Transcranial Doppler ultrasound cannot provide an absolute measurement of cerebral blood flow, and BFV is assumed to represent blood flow through the MCA because it is assumed that the diameter of the MCA remains constant during manoeuvres that change cerebral blood flow. Using the thigh-cuff test, Newell et al. (Newell et al. 1994) have shown that the absolute flow in the carotid artery showed a relative change and time course similar to velocity in the MCA. More recently, Serrador et al. reported that during CO₂ manipulation or lower body negative pressure up to 40 mmHg suction there were no changes detected in the diameter of MCA (Serrador et al. 2000). Studies using a variety of techniques (¹³³Xe, SPECT, MRI) have confirmed that relative changes in CBF velocity are representative of changes in CBF (Bishop et al. 1986; Sorteberg et al. 1989; Dahl et al. 1992; Vorstrup et al. 1992; Larsen et al. 1994; Larsen et al. 1995; Sugimori et al. 1995; Ulrich et al. 1995; Clark et al. 1996). Despite the lack of evidence about changes in the MCA diameter, this possibility cannot be eliminated and has to be acknowledged.

The critical closing pressure (CCP) of the cerebral circulation (the value of ABP at which cerebral blood flow approaches zero) is another important consideration. CCP may be different between the two procedures and not constant during the sit-to-stand because changes in intrathoracic pressure as well as head position may all influence the critical closing pressure (CCP). Dawson et al. showed that the Valsalva maneuver was associated with a large increase in CCP during phase I to III, followed by a sudden reduction at the beginning of phase IV (Dawson et al. 1999). The Valsalva maneuver results in a large change in the intrathoracic pressure during phase I-III, similar to active standing and it has been suggested that the changes in CCP may be a result of the intrathoracic pressure modulating venous return and ICP (Panerai 2003). Given that the active standing is associated with increased venous return, but not associated with increased ICP, it is less likely that the active standing is associated with a significant change in CCP as a result of changes in ICP. It is important to note that since true CCP cannot be directly measured in humans, it is not possible to be certain that the CCP values are not significantly different between the two procedures.

Finally, the technical limitations related to these TCD-based methods for the assessment of cerebral autoregulation should be acknowledged. First, large population based studies have shown that in about 35% of the population, an adequate temporal window cannot be found (Bakker et al. 2004). Second, both the methods described in this paper also suffer from technical limitations, where 7 out of the 51 sit-to-stand and 4 out of the 51 thigh-cuff trials were

technically inadequate. Therefore, demonstrating the need for multiple iterations in the same individual.

In conclusion, we compared the sit-to-stand procedure to the thigh-cuff method for assessing cerebral autoregulation and found that the sit-to-stand procedure is much better tolerated and produces ARI values that have low within subject variability. The sit-to-stand technique appears to be a suitable measure of dynamic cerebral autoregulation for inferring individual ARI values.

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Figure 1.

Grouped average response for ABP (expressed as mean arterial pressure), BFV (expressed as mean flow velocity), CVR (cerebrovascular resistance) and end-tidal CO₂ (P_{ET}CO₂) during the sit-to-stand and thigh-cuff protocols. The three dotted lines across the graphs demarcate the time of stand/thigh-cuff release, the time of flow reversal and the time when flow returns to baseline, respectively from right to left.

Table 1
Subjects Characteristics

	ABP (mmHg)	BFV (cm/sec)	CVR (mmHg*sec/cm)	HR (beats/min)
Sit-to-stand				
24 subjects	88 (13)	63 (13)	1.5 (0.5)	64 (10)
17 Subjects	88 (10)	60 (11)	1.5 (0.4)	63 (9)
Thigh-cuff				
24 Subjects	86 (13)	68 (17)	1.4 (0.4)	63 (9)
17 Subjects	87 (13)	66 (15)	1.4 (0.5)	63 (9)

All values are mean (SD).

ABP= arterial blood pressure expressed as mean arterial pressure, BFV= blood flow velocity expressed as mean blood flow velocity, CVR= cerebrovascular resistance, (BFV/ABP), HR= heart rate.

Table 2
Hemodynamic variables

	Sit-to-stand	Thigh-cuff	p
Absolute change			
ABP	-22 (9)	-19 (7)	0.09
BFV	-8 (7)	-4 (4)	0.06
CVR	-0.18 (0.5)	-0.23 (0.16)	0.41
Percent change			
ABP	-25 (10)	-22 (6)	0.12
BFV	-14 (13)	-7 (5)	0.03
CVR	-11(15)	-16(8)	0.19
pcBFV/pcABP	0.63 (0.5)	0.34 (0.3)	0.01
tABP nadir	7.8 (1.5)	6.2 (2.3)	0.03
tBFVnadir	5.5(2.3)	1.4 (0.9)	<0.01
ARI	6.4 (1.9)	7.0 (1.1)	0.19

All values are mean (SD).

Data represent absolute or percent changes in arterial blood pressure (ABP) expressed as mean arterial pressure (mmHg), blood flow velocity (BFV) expressed as mean blood flow velocity (cm/sec), cerebrovascular resistance (CVR) expressed as the ratio of ABP to BFV (mmHg*sec/cm).

pcBFV/pcABP = ratio of percent change in mean blood flow velocity to percent change in mean arterial pressure at the nadir of arterial blood pressure; tABP= time to nadir of the mean arterial pressure (seconds); tBFV= time to nadir of the mean blood flow velocity (seconds); ARI= autoregulatory index.

Table 3
ARI values for each subject during the Sit-to-stand and the Thigh-cuff trials.

Sit-to-stand (STS)				Thigh-cuff (TC)				
Subject	1	2	3	ARI, mean(SD)	1	2	3	ARI, mean(SD)
104	6	7	TL	6.5(0.7)	6	9	Refused	7.5(2.1)
105	8	6	TL	7.0(1.4)	6	7	Refused	6.5(0.7)
106	6	TI	5	5.5(0.7)	5	6	5	5.3(0.6)
107	7	7	8	7.3(0.6)	7	9	7	7.7(1.2)
108	3	3	TI	3.0(0.0)	7	2	Refused	4.5(3.5)
109	6	7	7	6.7(0.6)	9	8	8	8.3(0.6)
110	TI	6	4	5.0(1.4)	7	6	7	6.7(0.6)
111	9	9	TI	9.0(0.0)	5	9	5	6.3(2.3)
112	6	TI	7	6.5(0.7)	6	TI	7	6.5(0.7)
202	9	8	TI	8.5(0.7)	TI	9	9	9.0(0.0)
210	6	8	5	6.3(1.5)	9	6	Refused	7.5(2.1)
214	5	3	5	4.3(1.2)	8	6	TI	7.0(1.4)
216	9	9	TI	9.0(0.0)	TI	8	7	7.5(0.7)
218	9	9	9	9.0(0.0)	6	6	Refused	6.0(0.0)
219	4	4	4	4.0(0.0)	6	9	Refused	7.5(2.1)
224	7	6	TL	6.5(0.7)	9	6	Refused	7.5(2.1)
233	2	4	6	4.0(2.0)	9	6	7	7.3(1.5)
Group Mean				6.4(1.9)	7.0(1.1)			
One-Way Analysis of Variance								
				STS		TC		
Mean Squared (MS) Deviations (df)				3.96 (40)		2.49 (39)		
Between Subject MS Deviations (df)				8.46 (16)		2.69 (16)		
Within Subject MS Deviations (df)				0.97 (24)		2.35 (23)		

TL= technically inadequate, TL= time limited and study had to be cut short after two trials. Refused= Subject refused because the thigh-cuff were too painful. MS= Mean Squared Deviations, BMS= Between Subject MS Deviations, WMS= Within Subject MS Deviations.