Evaluation of the cerebral hemodynamic response to rhythmic handgrip

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Giller, Cole A., Angela M. Giller, Christopher R. Cooper, and Mustapha R. Hatab. Evaluation of the cerebral hemodynamic response to rhythmic handgrip. J Appl Physiol 88: 2205–2213, 2000.—The response of the cerebral circulation to exercise has been studied with transcranial Doppler ultrasound (TCD) because this modality provides continuous measurements of blood velocity and is well suited for the exercise environment. The use of TCD as an index of cerebral blood flow, however, requires the assumption that the diameter of the insonated vessel is constant. Here, we examine this assumption for rhythmic handgrip using a spectral index designed to measure trends in vessel flow. Nineteen normal subjects were studied during 5 min of volitional maximum rhythmic right handgrip at 1 Hz. TCD velocities from both middle arteries (left and right), blood pressure, and end-tidal PCO2 were recorded every 10 s. A spectral weighted sum was also calculated as a flow index (FI). Averages were computed from the last 2 min of handgrip. Relative changes in velocity, FI, and pressure were calculated. The validity of FI was tested by comparing the change in diameter derived from equations relating flow and diameter. Mean blood pressure increased 23.8 ± 17.8% (SD), and velocity increased 13.3 ± 9.8% (left) and 9.6 ± 8.3% (right). Although the mean change in FI was small [2.0 ± 18.2% (left) and 4.7 ± 29.7% (right)], the variation was high: some subjects showed a significant increase in FI and others a significant decrease. Diameter estimates from two equations relating flow and luminal area were not significantly different. Decreases in FI were associated with estimated diameter decreases of 10%. Our data suggest that the cerebral blood flow (CBF) response to rhythmic handgrip is heterogeneous and that middle cerebral artery flow can decrease in some subjects. In agreement with prior studies using the Kety-Schmidt technique, we speculate that the velocity increase is due to sympathetically mediated vasoconstriction rather than a ubiquitous flow increase. Our data suggest that the use of ordinary TCD velocities to interpret the CBF response during exercise may be invalid.

digam can dramatically alter the hemodynamic response, so that conclusions from particular studies cannot be generalized (40, 51, 52, 67). The cerebral hemodynamic response to exercise is not stable in time, and factors that can evoke dynamic changes during the exercise period include changes in the CO2 response, temperature, blood pressure, sympathetic response, regional activation, and cerebral autoregulation (39, 43).

Unfortunately, many of the measurement techniques such as positron emission tomography (PET) and single photon-emission computed tomography (SPECT) used in previous studies have poor temporal resolution compared with the complex temporal heterogeneity of the cerebral response to exercise. Furthermore, the demands of these techniques have limited the number of exercise paradigms that can be studied in detail, and the techniques themselves are problematic in the mobile environments of human exercise. The technique of functional magnetic resonance imaging (fMRI) has high temporal resolution and therefore holds great promise for the study of exercise. However, few systematic studies have been reported, and the type of exercise attainable in the MRI framework is limited.

These constraints have motivated some groups to use transcranial Doppler ultrasound (TCD) (29, 30, 32, 34–36, 40, 42, 51, 52, 54). The TCD method provides continuous measurements of blood velocity in the cerebral arteries, and its restriction to the middle cerebral artery (MCA) has been used to provide an index of the cerebral response (45). The method is completely noninvasive, the equipment is portable, and the temporal resolution is in excess of that required for the study of exercise. Furthermore, several studies have shown that the velocity increase in the MCA during cycling and rhythmic handgrip (34–36) is similar to that of simultaneously measured regional cerebral blood flow (rCBF). These encouraging results have fostered the belief that not only are TCD methods convenient for the study of exercise but that velocity measurements faithfully replicate the rCBF response.

We have been concerned, however, that limitations of the TCD method prevent full support of these conclusions. For example, MCA flow does not precisely represent either global flow or flow to any specific cortical area, and its distribution is not identical from subject to subject (70). Of central importance, however, is the fact that TCD methods measure blood velocity and not flow.

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Although the assumption that vessel diameter remains constant would imply that velocity is proportional to flow, the constancy of diameter has not been established during exercise and may possibly be altered by such factors as sympathetic activation and changes in blood pressure. Significant diameter changes would destroy the proportionality between velocity and flow, negating the interpretation of the observed velocity as an index of the rCBF response.

Although the precise measurement of cerebral vessel flow remains elusive, calculations based on weighted spectral sums derived from the Doppler signal have been used to create indexes proportional to flow and independent from vessel diameter (1, 4, 21, 22, 27, 53, 54, 62). These indexes have been validated in phantom models (4, 27) and approximately predict diameter changes following subarachnoid hemorrhage (21). Diameter changes during visual stimulation (1), spontaneous oscillations of MCA flow (22), and changes in CO₂ (21, 53) have been demonstrated. Poulin and Robbins (54) have recently shown small but definite differences between these indexes and ordinary TCD velocities obtained during cycling.

The purpose of the present study was to evaluate the cerebral response to one form of exercise through the use of weighted spectral sums, with comparison to the response of ordinary TCD velocity. Agreement between the spectral flow index and velocity would establish the validity of velocity as a measure of MCA flow, whereas a difference would suggest the presence of a change in diameter that would negate the use of velocity for these purposes. We chose the commonly used paradigm of rhythmic handgrip because of its relative convenience for the study purposes. We chose the commonly used paradigm of rhythmic handgrip because of its relative convenience to the TCD method and because a unilateral exercise might allow distinction between global bilateral influences and those related to cortical activation.

METHODS

Subjects. Twenty normal subjects without cardiopulmonary disease were studied. The mean age was 33.6 ± 8.3 (SD) yr; thirteen subjects were men. Each subject was studied at most twice. Informed consent was obtained, and the protocol was approved by the Institutional Review Board.

Protocol. TCD velocities were measured (Pioneer, Nicolet, Golden, CO) simultaneously from both the right and left MCA using two probes held to the temporal windows as previously described (2). Depths were chosen to insonate the proximal portion of the MCA just distal to the carotid bifurcation and to approximate values described in ideal cases. The velocity in the vessel lumen (rather than the maximum velocity measured by TCD) was assumed to be the mean FI for that particular 10-s interval.

Blood pressure was measured noninvasively from the left arm using finger cuff plethysmography (Ohmeda 2300 Finapres, Louisville, CO). End-tidal PCO₂ (PETCO₂) was measured continuously (Nellcor Model N-1000, Hayward, CA).

TCD velocities, mean arterial pressure (MAP), and PETCO₂ were recorded every 10 s. The entire TCD waveform appearing every 10 s was also saved for later calculation of spectral sums as previously described (21).

The subjects were kept in a sitting position in a quiet room. Data were first gathered as above during a 10-min baseline period, followed by a 5-min period of right-handed maximal handgrip against resistance at a frequency of 1 Hz. An audible computer-controlled beep at 1 Hz was used to cue the subjects. The subjects were instructed to exert maximal force.

Next, a 5-min (first) recovery period was allowed; this was followed by a second 5-min period of handgrip and then a final 5-min (second) recovery period. The beep used for cues continued throughout the entire study.

Controls. Three studies were performed in an identical fashion in two subjects, except that neck and arm movements were performed instead of handgrip. The data were examined to determine if random movement could lead to a decrease in the weighted spectral sum.

Data analysis. Initially, 34 studies were obtained from the right MCA and 33 from the left MCA in the 20 subjects. Each subject was studied no more than twice. One subject could not tolerate head movement, which produced noticeable TCD artifact, and these four studies were not considered for analysis. An additional four studies were rejected because of extremely fluctuating baseline recordings, leaving 30 studies from the right MCA and 29 studies from the left MCA in 19 subjects for analysis.

The values of each measured variable collected over the last 2 min of each period of the protocol were averaged and taken as representative of that period. Changes (in percent) relative to baseline were calculated for each period. Changes of the second handgrip period relative to the first recovery period were also calculated.

The analysis presented here focuses on the first handgrip period. The results for the second handgrip period may have been altered by the prior exercise.

Flow index. The complete TCD signals saved during each 10-s acquisition were averaged to obtain one waveform, and a weighted spectral sum termed the flow index (FI) was computed as previously described (21). Briefly, the FI at any given point in time is calculated as the sum of each acoustic intensity within the TCD spectrum multiplied by the corresponding velocity (27). Averaging over the entire waveform yields the mean FI for that particular 10-s interval.

Trends. The slope of the regression line for each data curve was calculated, and the linear trends were removed. Biphase patterns in the FI (i.e., a single peak followed by a decrease in the FI or conversely) within a period were noted.

Correction for CO₂. Values of FI and velocity corrected for changes in PETCO₂ (using the factor of 4%/Torr) (38, 47) were also calculated, and relative changes were calculated as described in Data analysis. Unless explicitly stated, however, the uncorrected values were used for analysis.

Diameter and area calculations. Vessel diameters and areas can be related to FI by two different formulas (46)

\[
FI = \text{velocity} \times \text{vessel cross-sectional area}
\]

\[
MAP = FI \times \text{resistance}
\]

Each of these equations is an approximation applying only to ideal cases. The velocity in Eq. 1 is the average velocity across the vessel lumen (rather than the maximum velocity measured by TCD). Equation 2 becomes Poiussel’s law if we assume that the venous pressure is negligible so that MAP is an approximation of perfusion pressure. Poiussel’s law applies only to steady flow in rigid tubes but has nevertheless been used to approximate the steady-flow component in more complicated systems.

After it was assumed that vessel area is proportional to (diameter)² (i.e., a circular cross section) and that resistance
is proportional to 1/(diameter)^4, each of these equations gives an independent relationship between diameter and FI so that two independent estimates of proportionate diameter changes can be calculated from measured changes in FI, MAP, and velocity [we also assumed that flow was laminar so that the velocity in Eq. 1 was proportional to TCD velocity (46)]. Although the estimates may not agree when these assumptions are invalid, agreement between these diameter estimates would not be expected if our FI measurements were too noisy to be reliable. We therefore compared the multiplicative factors by which the diameters and areas changed from baseline.

Area estimates were compared with the paired t-test, and statistical power was computed at α = 0.05. (Bonferroni corrections were not used.)

For the first handgrip period, estimates of diameter changes were computed separately for the group showing increases or decreases of FI, respectively.

All values are reported as means ± SD.

RESULTS

MAP, FI, and velocity. Table 1 shows percent changes in MAP, FI, and velocity during the two handgrip periods compared with baseline and also shows percent changes in MAP, FI, and velocity of the second handgrip period relative to the first recovery period. The mean increase in MAP during the first period was 23.8 ± 17.8%, with a simultaneous velocity increase of 13.3 ± 9.8% on the left and 9.6 ± 8.3% on the right. MAP never decreased during this period for any subject. Velocity increased in all but three studies on the left and in all on the right. The mean change in FI was minimal (2.0 ± 18.2% on the left and 4.7 ± 29.7% on the right), reflecting a large variation in flow changes. This is demonstrated in Fig. 1, which shows the distribution of changes in FI for the first handgrip period. For the left side, velocity decreased in only three studies and each by <10%. There were 11 studies in which FI increased by more than 10% and 7 in which FI decreased by more than 10% (ratio = 11:7 = 1.6). On the right, velocity never decreased. There were 9 studies in which FI increased more than 10% and 11 studies in which FI decreased more than 10% (ratio = 9/11 = 0.82).

The velocity values clustered so that 24 studies on the left and 25 on the right showed velocity changes between 0 and 20%.

Table 2 shows changes in velocity and FI when corrected for $P_{ETCO_2}$. The values for the first handgrip period are similar to the uncorrected values from Table 1.

Sample data for FI, velocity, and MAP are shown in Fig. 2.

![Fig. 1. Histogram showing number of studies in each percentile group of change in flow index (FI). Right and left refer to right and left middle cerebral artery.](http://jap.physiology.org/)

Estimates of changes in diameter and area. On the left side, for the first handgrip period, the area computed from Eq. 1 differed from baseline by a factor of 0.90 and the factor from Eq. 2 was 0.91. On the right, the factors were 0.96 and 0.92 for Eqs. 1 and 2, respectively. The differences were not significant (P = 0.05), suggesting that our FI data were not simply noise. For the right side, at α = 0.05, the power of detecting a difference of 0.15 (representing an area change of 15%) was 83% for the first handgrip period, 98% for the second handgrip period, and 98% for the second handgrip period relative to the first recovery period. For the left side, the corresponding powers were 98%, 99.8%, and 95%.

For the first handgrip period, estimates of changes in diameter for the group in which FI increased were close to 1.0 (1.0 ± 0.06 and 1.06 ± 0.12 on the right, 0.98 ± 0.02 and 0.99 ± 0.04 on the left), indicating relative constancy of diameter. For the group in which FI decreased, the estimates of percent diameter decrease were lower (0.91 ± 0.04 and 0.90 ± 0.05 on the right, 0.90 ± 0.06, 0.86 ± 0.05 on the left), indicating an ~10% decrease in diameter. A decrease in flow was therefore accompanied by a diameter decrease.

Trends. Seven studies from the right MCA and four studies from the left MCA showed a biphasic pattern.

Controls. No consistent decrease in FI was found during periods of neck and arm movement performed without handgrip.

Correlation with blood pressure. Figure 3 shows plots of velocity and FI vs. MAP (one outlier with a very high

![Graph showing number of studies for each percentile group of change in flow index (FI). Right and left refer to right and left middle cerebral artery.](http://jap.physiology.org/)
The correlation between MAP and FI was not significant for the right or the left side ($R^2 = 0.003$ on the left, $R^2 = 0.04$ on the right). The correlation between MAP and velocity was significant for both sides ($R^2 = 0.16$ and $P < 0.034$ on the left, $R^2 = 0.26$ and $P < 0.005$ on the right, $F$ test).

**DISCUSSION**

The data presented here document the increases in blood pressure and TCD velocity (by $\sim 20\%$ and $15\%$, respectively) during rhythmic handgrip as previously reported by other authors (18, 32, 39, 40, 42, 44, 47, 51, 52). The new finding is the behavior of a weighted spectral sum, FI, during rhythmic handgrip. The average change of FI was small, with a large variation reflected by a significant number of studies showing either relatively large increases or decreases in FI. FI, however, is known to be sensitive to TCD probe movement and potentially other sources of artifact (27). The question of whether the high variance in FI represents new hemodynamic behavior not detected by ordinary TCD velocities or is simply the product of artifact is relevant, and we will give this considerable attention.

Distribution of CBF changes in prior studies. Prior studies of CBF during exercise have shown in general that global CBF changes minimally whereas rCBF increases. Although the high variance seen in FI would appear to contradict these data, examination of these studies will show otherwise.

Most studies showing a minimal change in global CBF (23, 28, 57) report only group averages rather than individual changes. In fact, our average change in FI was also minimal, consistent with these previous studies. In one of the few studies reporting individual changes in CBF, Madsen et al. (42) measured global CBF in humans during cycling by the Kety-Schmidt technique. Although their mean change in CBF was minimal, some subjects showed large increases and some showed large decreases, in agreement with our FI measurements. TCD velocities were also simultaneously measured: a consistent velocity rise of $22\%$ was documented. The authors interpreted this discrepancy between flow and velocity as evidence of vasoconstriction of the insonated MCA segment.

It is important to note that changes in global CBF can be minimal even if rCBF increases significantly because the volume of the activated region is often small compared with the entire brain. Furthermore, it is likely that the activation response is heterogeneous and that some areas may experience decreases in rCBF. Seitz et al. and Roland et al. (58, 63, 64) have documented this phenomenon during finger exercise, reporting an exhaustive list of cerebral regions and their volumes and degrees of activation as found using PET. Many areas showed decreases as well as increases in rCBF. When their data were added over the MCA distribution, the flow increased by $6\%$ on the left and by

$\begin{array}{c|c|c|c|c}
\text{Table 2. Percent changes in FI and velocity when corrected for } & \text{Velocity} & \text{FI} \\
& \text{Left} & \text{Right} & \text{Left} & \text{Right} \\
\hline
\text{First handgrip period (relative to baseline)} & 13.9 \pm 10 & 9.5 \pm 8 & 2.5 \pm 18 & 4.6 \pm 31 \\
\text{Second handgrip period (relative to baseline)} & 10.1 \pm 8 & 5.2 \pm 9 & 3.8 \pm 17 & -0.9 \pm 26 \\
\text{Second handgrip period (relative to first recovery period)} & 6.9 \pm 7 & 5.2 \pm 9 & 9.1 \pm 21 & 0.8 \pm 27 \\
\end{array}$

Values are means $\pm$ SD.

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  A: \%change in FI in 1 subject. Bar indicates period of rhythmic handgrip. Note decrease at end of handgrip period.
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  B: \%change in velocity in same subject.
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\begin{subfigure}{.3\textwidth}
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  C: \%change in mean blood pressure in same subject.
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\caption{A: \%change in FI in 1 subject. Bar indicates period of rhythmic handgrip. Note decrease at end of handgrip period. B: \%change in velocity in same subject. C: \%change in mean blood pressure in same subject.}
\end{figure}$
1% on the right. Their data elegantly demonstrate how global flow changes may be minimal even in the presence of significant cortical activation due to other regions showing simultaneous decreases in flow.

Other examples of heterogeneous activation have been reported during psychogenic activation, in which regions of increasing and decreasing rCBF were detected with PET studies during application of psychological stress (13, 15, 16, 73). Animal studies have also demonstrated heterogeneous activation during exercise using microsphere techniques (14, 24, 49). We speculate that these heterogeneous patterns may arise from the balance of factors affecting rCBF during exercise listed earlier and that a shift in these patterns gives rise to individuals with increasing or decreasing changes in global CBF or rCBF.

The existence of heterogeneous activation patterns, in which rCBF decreases in some regions, is therefore firmly established. Because the actual distribution of MCA flow is highly variable between subjects (70), this heterogeneity may explain the cases of FI decrease seen in our subjects and CBF decrease seen in those of Madsen et al. (42).

Other studies have shown consistent increases in rCBF during exercise (34–36, 40), again in apparent contradiction to our data. To resolve this conflict, one must note that the cerebral regions addressed in these rCBF studies do not coincide with the MCA distribution for several reasons. First, the MCA territory is quite variable between subjects (70) so that the use of standard templates to delineate this territory is in fact crude. Second, for studies that used 133Xe with external detectors (23, 31, 34, 36, 47, 68), the region beneath the detectors may only coarsely overlap with the true MCA territory as mentioned above. Furthermore, the portion of the MCA territory that is subcortical is significant [in fact, using templates of MCA territories (5), we have calculated that the superficial 2 cm represents only 65% of the total MCA distribution]. Moreover, it has been clearly documented that the rCBF of these subcortical areas can increase or decrease by as much as 30% during exercise or movement (13, 15, 16, 58, 63, 64, 73). Because these 133Xe techniques emphasize the more superficial layers (8, 25, 47, 50, 55, 59, 60), the representation of the MCA distribution by a region detected using these 133Xe techniques is further eroded.

Other studies have found a similar activation of ~20% using PET or SPECT techniques (12, 17, 18, 74, 75), again concluding that the velocity activation of similar magnitude must represent changes in flow. However, none of these studies reported quantitative data from the entire brain, and all were limited to two or three selected slices. Studies (58, 63, 64) have shown that activation occurs throughout the brain so that the reported changes in rCBF do not represent those seen globally or in the MCA distribution.

One cannot conclude, therefore, that these reported rCBF change values, which match those in velocity, are, in fact, changes in true MCA flow. The Kety-Schmidt method used by Madsen et al. (42) and our FI may more accurately reflect MCA flow and suggest a high variability. Why then, are TCD velocities found to be consis-

Fig. 3. A and B: %changes in left (A) and right (B) FI vs. %changes in mean blood pressure during first period of handgrip. C and D: %change in left (C) and right (D) middle cerebral artery velocity vs. %changes in mean blood pressure during first period of handgrip.
RHYTHMIC HANDGRIFF

The exact role of autonomic activity on CBF regulation remains uncertain (41), but it is clear that sympathetic activation can produce constriction in some large vessels (3) and likely that it does so in the MCA. Sympathetic activity may prevent MCA dilation during autoregulation (6), stellate blocks lead to a 10% rise in rCBF (69), and sympathetic stimulation has been shown in animals to produce a decrease in ipsilateral rCBF (7, 44). MCA velocities recorded during endoscopic sympathectomy in humans indicate a diameter increase of 5% (33). Sympathetic stimulation in humans during operation was shown by Wahlgren et al. (72) to elevate ipsilateral MCA velocity. Contrary to the conclusions reported, careful inspection of their data shows evidence of MCA vasoconstriction because part of the velocity rise was not secondary by passive means to blood pressure.

The magnitude of MCA vasoconstriction can be estimated from the findings of Duckworth et al. (11) in which sympathetic stimulation produced a diameter decrease of 20% of the maximum attainable decrease in isolated MCA preparations. Because an estimate of this maximal contraction is given by the common observation of MCA diameter reductions of as much as 50% during neurosurgery due to mechanical factors (37), the resulting MCA diameter decrease is 10%. This is an agreement with our estimates of MCA diameter changes calculated using the FI in the group showing an FI decrease.

A 10% decrease in diameter represents a relatively small degree of MCA vasoconstriction, which is not, however, responsible for a decrease in flow. We speculate instead that rhythmic handgrip evokes a similar degree of vasoconstriction in the other portions of the vascular bed, which is fully capable of decreasing flow.

Sympathetic activation has been associated with several paradigms for exercise (41), and there is evidence for its presence during rhythmic handgrip. Total peripheral resistance increases during rhythmic handgrip (39), and serum epinephrine increases (26, 51). Although one study found a minimal effect of rhythmic handgrip on sympathetic activity of the tibial nerve (61), the handgrip strength was limited to 10% of maximum and the associated elevation in blood pressure was relatively small. Likewise, the minimal muscle sympathetic nerve activity (MSNA) during rhythmic handgrip found in one study (52) can be explained by a handgrip strength limited to 20% of maximum. Victor and Seals (71) found an increase of MSNA during moderate but not mild levels of rhythmic handgrip from a total activity of 311–590 bursts·min⁻¹·mean burst amplitude⁻¹. Silber et al. (65) also found an increase in MSNA and skin sympathetic nerve activity during rhythmic handgrip. These studies offer compelling evidence that maximum rhythmic handgrip evokes a sympathetic response. Because our protocol called for maximal effort and produced a consistent MAP elevation of 23.8% during the first handgrip period, we believe that a sympathetic response was evoked that was responsible for much of the measured rise in velocity.

Although static exercise does not induce an increase in global CBF (17, 34, 57), Jorgensen et al. (34–36) found that MCA velocity is unchanged during static leg extension. A similar finding of constant MCA velocity during static handgrip would challenge the interpretation of elevated velocity during rhythmic handgrip as arising from sympathetic vasoconstriction, since static handgrip is associated with a sympathetic activation (39, 65, 67). The response of MCA velocity to static handgrip, however, has been thoroughly studied by Sohn (66), who found an increase in mean MCA velocity of 11 ± 12% (SD) after 1 min of static handgrip at 30% maximum effort and an increase of 36 ± 19% after 5 min. These increases were seen bilaterally and support the presence of a sympathetic vasoconstriction of the MCA. The discrepancy with Jorgensen’s results may be due to differences in the exercise paradigm or intensities.

Our data support the presence of MCA vasoconstriction, predicting a 10% decrease in MCA diameter whenever FI decreased and a minimal diameter change when blood pressure and FI increased. MCA vasoconstriction was also the conclusion of Madsen et al. (42), which was made from comparison of changes in CBF and velocity. We cannot unequivocally determine from our data whether the origin of the vasoconstriction was indeed sympathetically mediated.

Effects of blood pressure. Effective cerebral autoregulation acts to hold flow constant when blood pressure varies and, hence, acts to reduce any correlation between these quantities. Therefore, the lack of correlation (10) between blood pressure and FI (Fig. 3) suggests that autoregulation is intact and that FI reflects flow. The good correlation between blood pressure and velocity (Fig. 3) is consistent with a sympathetic vasoconstriction giving rise to the increase in both velocity and blood pressure. The opposite interpretation (that velocity represents flow, autoregulation is impaired, and FI measurements are artifact) is not likely because global CBF is relatively unchanged during the pressure variation seen during exercise (42).

CO₂. Measurements of arterial PCO₂ were not available to us in this protocol, and we relied on PETCO₂. The relationship between PETCO₂ and PCO₂, however, is altered with exercise and is difficult to evaluate. Although Robbins et al. (56) found a significant difference between PETCO₂ and PCO₂ during cycling, studies reporting both quantities show smaller and less consistent differences (32, 34–37). Our choice of 4%/Torr as a correction factor was based on studies that used rCBF (48) and TCD (38) but is a gross estimate and represents a reasonable upper bound of the magnitude of changes evoked by alterations in CO₂. We have therefore reported the corrections to velocity and FI based on PETCO₂ in Table 2 but remain unconvinced that these more accurately reflect flow. Our basic findings of variations in FI and velocity increase are unaffected by these corrections.
Validity of F1. Several studies point to the validity of F1 as an indicator of flow change. The theoretical basis for this use of F1 has been demonstrated, and validation of F1 for both flow and diameter has been reported using a phantom model (4, 27). The behavior of F1 during changes in CO2 in humans agrees with known changes of CBF and MCA diameter in this setting and statistically predicts MCA diameter changes seen during vasospasm after subarachnoid hemorrhage (21). Prior investigators have used F1 or other spectral weighted sums to detect cerebral activation to visual stimuli (1), to detect response to anesthetic agents (62), to detect oscillations in MCA flow (22), and to investigate the cerebral response to CO2 and exercise (53, 54).

We are nevertheless concerned that our F1 measurements might contain excessive noise due to the high sensitivity to probe movement or that other factors, such as nonuniformity of the ultrasound beam (19), might denigrate the accuracy of our F1 results as an index of flow. Special precautions and calculations were therefore performed as follows. The subjects were instructed to remain motionless except for the handgrip movement, and this was monitored during the studies. Three extra studies were performed on two subjects who made significant neck and arm movements without handgrip. Neither of these studies produced the commonly observed decrease in F1 seen during handgrip, suggesting that the latter is indeed not simply due to probe movement. The decrease in F1 during the handgrip period always returned toward baseline once the handgrip ended, again suggesting that probe slippage was not the source. Finally, estimated errors because of beam inhomogeneity for cases in which beam width is at least 20% greater than vessel diameter have been shown to be <5% (19).

Calculations of diameter and area changes from Eqs. 1 and 2 were in close agreement, with good statistical power to distinguish significant differences. If F1 reflected a high degree of artifact rather than true changes in flow, this agreement using two different equations would be unlikely. However, Eqs. 1 and 2 apply only to idealized cases of rigid pipes, so that conclusions drawn from them should be regarded as only approximate.

F1 showed an increase more often on the left than on the right side, with, respectively, 11 of 18 studies showing activation by more than 10% compared with 9 of 20. We speculate that this difference is due to left-sided cortical activation arising from the right-sided movements, arguing again that the changes seen in F1 are not simply random.

Conclusion and implications for TCD methods. Results from F1 measured during rhythmic handgrip suggest that changes in MCA flow are heterogeneous, and we speculate that flow can decrease if sympathetic activation is sufficiently intense. The associated increase in velocity is consistent with MCA vasoconstriction, and estimates of the magnitude of diameter change are in agreement with prior work. Our F1 data are in agreement with prior studies that used the Kety-Schmidt method. The different results reported by other authors can be explained by either the failure to include the entire brain in the flow estimate or the use of methods that do not exactly measure MCA flow. Our data, therefore, challenge the traditional interpretation of TCD velocity as a reliable indicator of rCBF in the setting of exercise.

We are somewhat pessimistic, therefore, regarding the utility of ordinary TCD velocities to investigate rhythmic handgrip. Changes in TCD velocity are determined by both changes in MCA flow and diameter, and diameter is affected by the degree of sympathetic activation. Because the magnitude of autonomic activation varies widely between exercise paradigms and individuals, the interpretation of MCA velocity is limited.

Even perfect knowledge of MCA flow is not equivalent to that of either cortical or global activation, and interpretation is more difficult because of the high individual variation in MCA distribution (70) and the likelihood of significant moment-to-moment changes in any particular individual. Although responses to different exercise paradigms can be diverse, we believe similar considerations may apply to any form of exercise and that confirmation of TCD velocity as flow should be mandatory before such interpretation.

REFERENCES

11. Duckworth JW, Wellman GC, Walters CL, and Bevan J A. Aminergic histofluorescence and contractile responses to transmural electrical field stimulation and norepinephrine in human
12. Fink GR, Banss L, Watson JG, Innes JA, Wuyam B, Kobayashi I, Corfield DR, Murphy K, 