Factors affecting assessment of cerebral autoregulation using the transient hyperaemic response test†

G. CAVILL, E. J. SIMPSON AND R. P. MAHAJAN

Summary
The transient hyperaemic response in the middle cerebral artery blood flow velocity on the release of brief compression of the ipsilateral common carotid artery has been validated as an indicator of cerebral autoregulation. We evaluated, in three stages, the effect of experimental factors such as duration of compression of the common carotid artery and magnitude of the decrease in blood flow velocity during common carotid artery compression on the transient hyperaemic response. In stage 1, 13 healthy volunteers underwent six transient hyperaemic response tests each; two tests each for either 3, 6 or 10 s duration of compression of the common carotid artery. In stage 2, 10 volunteers underwent four transient hyperaemic response tests each; two tests each for either 10 or 15 s duration of compression of the common carotid artery. In stage 3, data from the transient hyperaemic response tests using 10 s compression from the 23 volunteers who participated in stages 1 and 2 were analysed to evaluate the relationship between magnitude of decrease in blood flow velocity at the onset of compression and the transient hyperaemic response. The transient hyperaemic response ratio (blood flow velocity after the release of compression/baseline blood flow velocity) increased significantly when the duration of common carotid artery compression increased from 3 to 6 s, or from 6 to 10 s (stage 1); increase in the duration from 10 to 15 s did not have any significant effect (stage 2). The transient hyperaemic response ratio correlated significantly with the magnitude of decrease in blood flow velocity after compression, up to the values of the compression ratio (percent decrease in blood flow velocity at the onset of compression) of 40% but not more (stage 3). We conclude that experimental factors such as duration of common carotid artery compression and magnitude of the decrease in blood flow velocity during common carotid artery compression can significantly influence the transient hyperaemic response. These factors should be controlled if the transient hyperaemic response test is used for a comparison between repeated measurements. A compression time of 10 s and a compression ratio of 40% or more, allow maximum expression of the hyperaemic response in healthy volunteers. (Br. J. Anaesth. 1998; 81: 317–321.)

Keywords: brain, blood flow; measurement techniques, Doppler ultrasonography

Introduction of transcranial Doppler ultrasonography has prompted the development of non-invasive techniques of assessing cerebral autoregulation.1–3 These techniques use different methods of modulating cerebral perfusion pressure, including the use of vasoactive agents,1 cuffs around the thigh2 and short-lasting compression of the common carotid artery.3 For the purpose of research in anaesthesia, the technique should be simple, reproducible, quantifiable and preferably devoid of the use of vasoactive agents.

The transient hyperaemic response test involves the use of transcranial Doppler ultrasonography to establish a continuous record of blood flow velocity in the middle cerebral artery and then briefly compressing the ipsilateral common carotid artery. If autoregulation is effective, the reduction in middle cerebral arterial pressure after common carotid artery compression should cause vasodilatation in the arterioles distal to the middle cerebral artery. Therefore, release of the compression would result in a transient increase in cerebral blood flow (CBF), and thus middle cerebral artery blood flow velocity (fig. 1).3–5 This technique is simple and does not involve the use of vasoactive agents and, therefore, may prove to be a useful research tool.

Smielewski and colleagues6 have shown that the transient hyperaemic response ratio (THRR: ratio of hyperaemic blood flow velocity after release of compression to baseline blood flow velocity) is a valid index of cerebral autoregulation and has similar sensitivity to the leg-cuff method, as described by Aaslid and colleagues,2 in detecting the changes in cerebral autoregulation produced by different systemic carbon dioxide concentrations. In theory, both the duration of common carotid artery compression and magnitude of the decrease in blood flow velocity at the onset of compression can affect the transient hyperaemic response.4–7 To date there are insufficient data examining the effect of these experimental factors on THRR. In this study, we have evaluated the effects of duration of compression and the magnitude of the decrease in blood flow velocity at the onset of compression on THRR.

GWENDA CAVILL, FRCA, RAVI P. MAHAJAN, MD, FFARCS(I) (University Department of Anaesthesia); ELIZABETH J. SIMPSON, BSc (Department of Physiology and Pharmacology); Queen’s Medical Centre and City Hospital NHS Trust, Nottingham NG7 2UH. Accepted for publication: March 30, 1998. Correspondence to R. P. M.
Subjects and methods

The study was approved by the Medical School Ethics Committee. All volunteers were healthy non-smokers and free from systemic or vascular problems. Bilateral carotid artery sonograms were performed in each volunteer to exclude atheromatous disease.

Volunteers were studied in the supine position with the head resting on a pillow. The left middle cerebral artery was identified by recognition of the characteristic waveform, typical flow velocity profile and depth of insonation using a 2-MHz pulsed transcranial Doppler probe (SciMed PCDop 842). After establishing a stable and continuous record of blood flow velocity in the middle cerebral artery, the position of the transcranial Doppler probe was fixed using a headband. Transcranial Doppler measurements were recorded on a DAT tape for subsequent analysis using specific software (SciMed PCDop 842). Simultaneous continuous measurements of finger arterial pressure and heart rate were made using an automated pressure cuff (Finapres, Ohmeda 2300). Changes in arterial pressure or heart rate were considered significant if at any stage during the transient hyperaemic response test their value was outside the normal range recorded during any stage during the transient hyperaemic response.

STAGE I

We studied 13 volunteers (seven men, aged 21–39 yr). Six transient hyperaemic response tests were performed in each; two tests each for either 3, 6 or 10 s duration of compression of the common carotid artery. At least 2 min were allowed between tests and the duration of compression was selected randomly.

STAGE 2

Ten volunteers (six men, aged 23–33 yr) underwent four transient hyperaemic response tests each; two tests each for either 10 or 15 s duration of common carotid artery compression. At least 2 min were allowed between tests and the duration of compression was selected randomly.

STAGE 3

A transient hyperaemic response test was accepted only: (a) when onset of compression resulted in a sudden and maximal decrease in blood flow velocity; (b) when conditions remained stable during compression; and (c) when flow transients after release of compression (associated with inertial or volume compliance) were not obvious. If any of these confounding factors were detected, the test was repeated 2 min later. In stage 3, the data collected from stages 1 and 2 were used. Transient hyperaemic response tests, which were performed with 10 s of common carotid artery compression in all the volunteers who participated in stages 1 and 2, were selected for analysis. The magnitude of the decrease in blood flow velocity at the onset of compression was correlated with the transient hyperaemic response.

DATA HANDLING AND STATISTICAL ANALYSIS

For the analysis, the middle cerebral artery waveform just preceding common carotid artery compression (F1), the first waveform after the onset of common carotid artery compression (F2) and the first waveform after release of common carotid artery compression (F3) were selected. PCDop has analogue outputs of flow velocity maximum (emax), determined using the upper envelope of the velocity power spectrums. The time averaged mean of emax was used for analysis.

THRR was calculated using the formula:

\[
THRR = \frac{F3}{F1}
\]  

(1)

As a measure of the magnitude of the decrease in blood flow velocity during compression, the compression ratio (CR) was calculated using the formula:

\[
CR(\%) = \frac{(F1 - F2) \times 100}{F1}
\]  

(2)

The mean of the two measurements at each duration of compression was used. For stage 1, the Kruskal–Wallis test was applied to THRR, CR and baseline values of blood flow velocity, heart rate and mean arterial pressure recorded during the transient hyperaemic response tests with different durations of compression. The Wilcoxon signed rank test was used to compare THRR after a duration of compression of 3 s vs 6 s and 6 s vs 10 s in stage 1, and 10 s vs 15 s in stage 2. For stage 3, Pearson correlation and regression analysis between CR and THRR were applied to the data from transient hyperaemic response tests of 10 s duration of compression from stages 1 and 2.

Results

MAP and heart rate did not change significantly during any transient hyperaemic response test.

STAGES 1 AND 2

Baseline values for heart rate, mean arterial pressure, blood flow velocity and CR were comparable at different durations of common carotid artery compression (table 1). In stage 1, duration of compression had a significant effect on THRR (P = 0.002, Kruskal–Wallis). This index increased significantly as the duration of compression was increased from 3 to 6 s (P = 0.008, Wilcoxon signed rank test), or from 6 to 10 s (P = 0.004, Wilcoxon signed rank test) (fig. 2, table 1). In stage 2, increasing the duration from 10
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Table 1  Median (25–75% quartiles) heart rate (HR), mean arterial pressure (MAP), compression ratio (CR), baseline middle cerebral artery flow velocity (FV) and the transient hyperaemic response ratio (THRR). Wilcoxon signed-rank test: **P<0.01 compared with 3 s of compression; ††P<0.01 compared with 6 s of compression

<table>
<thead>
<tr>
<th>Duration of compression</th>
<th>Stage 1, n=13</th>
<th>Stage 2, n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 s</td>
<td>6 s</td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>70.0 (67.0–77.5)</td>
<td>72.0 (66.0–74.5)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>94.0 (87.5–98.0)</td>
<td>92.0 (88.5–94.5)</td>
</tr>
<tr>
<td>FV (cm s⁻¹)</td>
<td>54.0 (52.5–60.5)</td>
<td>57.0 (50.5–59.0)</td>
</tr>
<tr>
<td>CR (%)</td>
<td>34.0 (25.5–55.0)</td>
<td>35.0 (24.0–51.0)</td>
</tr>
<tr>
<td>THRR</td>
<td>1.17 (1.11–1.23)</td>
<td>1.23** (1.17–1.28)</td>
</tr>
</tbody>
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Figure 2  Effect of duration of compression of the common carotid artery on the transient hyperaemic response ratio (THRR) in stage 1. Dotted lines represent individual subjects; solid line represents median change.

Figure 3  Effect of duration of compression of the common carotid artery on the transient hyperaemic response ratio (THRR) in stage 2. Dotted lines represent individual subjects; solid line represents median change.

to 15 s did not have any significant effect on THRR (fig. 3, table 1).

Stage 3

A total of 23 volunteers underwent transient hyperaemic response tests with a 10 s duration of common carotid artery compression. CR was 14–75% and THRR 1.10–1.46. Both variables showed a significant positive correlation ($r^2 = 0.7$, $P<0.001$) (fig. 4). However, the increase in THRR tended to plateau as the value of CR approached 40%. Pearson correlation analysis on the subsets of data showed a significant correlation ($r^2 = 0.9$, $n=10$, $P<0.001$) between THRR and CR <40% but not between THRR and CR >40% ($n=13$, $r^2 = 0.1$, $P=0.29$).

Discussion

Giller described the transient hyperaemic response test as a bedside investigation for assessment of cerebral autoregulation. Subsequently, a modelling study was published followed by a clinical study involving a large number of patients with neurological disorders, further demonstrating the usefulness of this test in a clinical setting. Only recently have Smielewski and colleagues validated THRR as an index of cerebral autoregulation compared with the autoregulatory index obtained by the leg-cuff method described by Aaslid and colleagues. They have shown this test to be simple, sensitive, reproducible and therefore potentially an attractive research tool.

Our results showed that both duration of compression and the magnitude of the decrease in blood flow velocity during compression affected THRR. These findings have important implications because control of these factors would be necessary if the test is used to compare cerebral autoregulation between different individuals or between repeated measurements in an individual.

Duration of Compression

Cerebral autoregulation is a complex process involving several mechanisms which operate at different rates. Experiments have shown an initial fast component of cerebral autoregulation. Transcranial Doppler studies have confirmed the presence of fast autoregulation which occurs within 5–8 s of a step decrease in arterial pressure.

A modelling study of the transient hyperaemic response has suggested that compression should be maintained for longer than the inherent autoregulation delay (5–8 s) in order to generate a constant response. Our results support this theoretical suggestion and show that a compression time of 10 s...
would fulfil the criteria. Our study has not shown any advantage of increasing the duration of compression from 10 s to 15 s. Smielewski and colleagues attempted to evaluate the effect of duration of compression on the transient hyperaemic response. They concluded that the result of the transient hyperaemic response test is independent of compression time, providing the compression lasts for at least 5 s. Our results indicate that a compression time of 5 s may not be sufficient for complete expression of the transient hyperaemic response, and in fact Smielewski and colleagues showed an increased response after up to 7 s of compression which was not significant, probably because of increased variability. In addition, our results showed that the inherent autoregulatory delay in human volunteers may last 6–10 s, and that a compression time of 10 s would ensure maximal response.

Potentially, changes in resting arterial pressure, CR (see below) and end-tidal carbon dioxide concentration can confound the results obtained by a transient hyperaemic response test. In stages 1 and 2, resting arterial pressure and CR did not change significantly during different durations of compressions within an individual (table 1). Although we did not measure end-tidal carbon dioxide concentration in our volunteers, it is highly unlikely that it would have changed significantly between different tests as all tests were performed under the same resting conditions. We allowed 2 min between successive measurements. This decision was based on a preliminary study which had shown that the results of the transient hyperaemic response test were reproducible even if 10 repeated measurements at 2-min intervals were made. Measurement of THRR and CR is based on single pulse wave tracings before, during and after compression. In order to avoid artefacts we accepted the transient hyperaemic response test for analysis only when it met strict criteria, such as absence of flow transients and unchanged reflected Doppler power during die test.

EFFECT OF CR

Contrary to our findings, Smielewski and colleagues concluded that CR had no effect on the size of the transient hyperaemic response. The transient hyperaemic response test is based on the principle that brief occlusion of the common carotid artery causes a decrease in blood flow velocity at the ipsilateral circle of Willis which provokes autoregulatory mechanisms. Provided that compression achieves total occlusion of the common carotid artery, the magnitude of the decrease in blood flow velocity in the middle cerebral artery during compression (CR) is dependent on the effectiveness of the collateral circulation at the circle of Willis. Because of the heterogeneity of the anatomy of the circle of Willis, CR is likely to vary between different individuals, and is unlikely to be within the control of the investigator. In theory, the decrease in flow velocity at the onset of compression is accompanied by a proportional decrease in perfusion pressure in the middle cerebral artery. If autoregulation is intact, the magnitude of the decrease in perfusion pressure would affect the magnitude of change in the resistance of the vascular bed distal to the middle cerebral artery. This, in turn, would affect the magnitude of the transient hyperaemic response after release of compression. However, this would hold true only as long as the reduced pressure in the middle cerebral artery is less than the lower limit for autoregulation. If compressions are such that the resultant perfusion pressure in the middle cerebral artery is less than the lower limit for autoregulation, the magnitude of CR is unlikely to be related to the size of the transient hyperaemic response. This is because the vascular bed would be unable to respond to decreases in the perfusion pressure beyond the lower limit for autoregulation.

Values for CR in the study of Smielewski and colleagues were 36–57%. Assuming normal arterial pressure in all volunteers (MAP 90–100 mm Hg), CR values of 36–57% would equate to a reduced middle cerebral arterial pressure of approximately 40–64 mm Hg during compression. This would imply that at the onset of compression almost all volunteers in that study had middle cerebral arterial pressures at or below the lower limit for autoregulation (usually 60 mm Hg). This has been suggested as the reason for the lack of correlation between CR and THRR in that study. It has also been suggested that in order to evaluate the effect of CR on THRR, a study should include data from transient hyperaemic response tests in which CR is such that the resultant perfusion pressure in the middle cerebral artery during compression is greater than the lower limit for autoregulation. This would approximate to a CR value of less than 40% in a normotensive subject. Of the 23 volunteers in our study, 10 had CR values of less than or equal to 40%. We have shown that CR has a significant positive correlation with THRR. Our result supports the theoretical modelling of the transient hyperaemic response although it disagrees with previous work. However, we have found that the relationship between CR and THRR starts to plateau when CR exceeds 40%. We postulate that during a transient hyperaemic response test, a CR value of 40% or more approximates to the point at which the autoregulatory capacity is tested to its maximum in a normotensive human volunteer. However, the exact point is likely to vary with the resting arterial

![Figure 4](image-url) Relationship between the compression ratio (CR) and the transient hyperaemic response ratio (THRR). The increase in THRR tends to plateau as the value of CR reaches 40%. Overall correlation is significant ($r^2=0.7$, $P<0.001$).

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pressure and the individual’s lower limit for autoregulation.

THRR measures the haemodynamic response to an unquantified stimulus. Therefore, previous workers have used the transient hyperaemic response test in a qualitative manner only, with a THRR of less than 1.09 indicating poor autoregulation. Modelling studies have suggested that it is possible to apply this test for the quantitative assessment of autoregulation. This requires control over various factors which can influence the hyperaemic response, especially if the transient hyperaemic response test is applied to make comparative assessments of cerebral autoregulation. Based on the results of our study, we recommend that the duration of compression should be controlled and maintained for 10 s. In addition, the compression ratio should be recorded for each test and its influence on THRR should be taken into consideration, particularly when CR is less than 40%. In theory, resting arterial pressure and the lower limit for autoregulation can also influence the hyperaemic response. Even though the effects of these factors on the transient hyperaemic response have not been studied in experimental or clinical settings, it would seem prudent to achieve a strict control over arterial pressure while making comparisons between different transient hyperaemic response tests.

In summary, we have shown that both the duration of common carotid artery compression and the magnitude of the decrease in blood flow velocity during compression can affect the hyperaemic response. A compression time of 10 s and a CR of more than 40% ensure maximal THRR in normotensive healthy volunteers.

References