Effects of norepinephrine and glyceryl trinitrate on cerebral haemodynamics: transcranial Doppler study in healthy volunteers


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Background. The effects of vasoactive substances on cerebral haemodynamics are not fully known. We studied the effects of norepinephrine and glyceryl trinitrate (GTN) on cerebral haemodynamics in healthy volunteers.

Methods. The effects of norepinephrine (n=10) and GTN (n=10) on the middle cerebral artery flow velocity (MCAFV), cerebral autoregulation, reactivity to carbon dioxide, and estimated cerebral perfusion pressure (eCPP) were studied using transcranial Doppler ultrasound. Established methods were used for calculating zero flow pressure (ZFP). Measurements were made at baseline, and after i.v. infusion of the study drug to the endpoints of 25% increase in mean arterial pressure (MAP) for norepinephrine (0.02–0.1 \( \mu g \) kg \( ^{-1} \) min \( ^{-1} \)), or 15% decrease in MAP for GTN (0.5–2.5 \( \mu g \) kg \( ^{-1} \) min \( ^{-1} \)).

Results. The MCAFV remained unchanged with norepinephrine, but decreased slightly with GTN [from [median (inter-quartile range)] 53 (38, 62) to 48 (33, 52) cm s \(^{-1} \)]. Cerebrovascular reactivity did not change significantly with either drug. The eCPP did not change significantly with norepinephrine, but increased significantly with GTN [from 49 (32, 54) to 62 (47, 79) mm Hg]. ZFP increased with norepinephrine [from 39 (28, 48) to 56 (46, 62) mm Hg] and decreased with GTN [from 35 (30, 49) to 12 (–7, 20) mm Hg].

Conclusions. Norepinephrine, despite increasing arterial pressure, did not increase the eCPP. The eCPP increased significantly with GTN, despite decreased MAP. Cerebral vascular tone is an important determinant of CPP during pharmacologically induced changes in arterial pressure.

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Methods
The study was approved by the local ethics committee. Twenty healthy volunteers were recruited. Informed written consent was obtained from all the subjects. The exclusion criteria were as in the following: age <18 or >40 yr, history of hypertension (or measured arterial pressure >140/90 mm Hg), neurological disease, history of migraine, smoking, pregnancy/potential pregnancy, and history of intake of vasoactive drugs (antidepressants, anti-hypertensives).

The subjects were studied in the supine position with their heads resting on a pillow. A 2 MHz pulsed TCD probe (SciMed PCDop 842, SciMed, Bristol, UK) was used to insonate left middle cerebral artery (MCA) using temporal window. The artery was identified using standard criteria. A custom-built head band was used to hold TCD probe in a constant position throughout the study to ensure a constant angle of insonation. The MCAFV waveform was recorded continuously onto digital audiotape for subsequent analysis using specific software (SciMed). All subjects used a nose clip and a mouthpiece to allow accurate derivation of the FV profile. The strength of autoregulation (SA) was calculated as:

\[
SA = \frac{F3 \times P2}{MAP \times F1}
\]

where P2 is the greater value of either the estimated arterial pressure in the MCA at the onset of CCA compression, as calculated by P2 = MAP × F2/F1, or 60 mm Hg (the assumed lower limit of autoregulation). The details of the derivation of these formulae have been published previously. The transient hyperaemic response (THR) test was performed to assess cerebral autoregulation; the details of this test have been described previously. This test involves a 10 s compression of the common carotid artery ipsilateral to the insonated MCA followed by a sudden release. If the autoregulation is intact, a THR is seen at the release of compression. The THR tests were accepted only if they met certain predefined criteria. These criteria were:

(a) a sudden and maximal decrease in flow velocity at the onset of compression;
(b) stable heart rate for the period of compression;
(c) steady Doppler signal for the duration of compression;
(d) absence of flow transients after release of compression.

The strength of autoregulation (SA) was calculated using previously described formulae. Three waveforms from each period of compression were taken for analysis. These were the MCA waveform immediately before compression (F1), the first waveform after compression (F2), and the waveform immediately after the release of compression (F3). The time-averaged mean of the outer envelope of the FV profile was used for performing the analysis. SA was calculated as:

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Cerebral vascular reactivity to carbon dioxide
CRCO2 was calculated as % change of mean MCAFV per mm Hg change in the \( V_{\text{co}_2} \). The changes in MCAFV were recorded at rest (baseline), during induced hypocapnia [voluntary hyperventilation to an \( V_{\text{co}_2} \) of 7.5 mm Hg (1 kPa) below baseline] and hypercapnia [rebreathing through a Mapleson D circuit with oxygen-enriched air to achieve an \( V_{\text{co}_2} \) of 1 kPa (7.5 mm Hg) above baseline]. At baseline and after induced changes in \( V_{\text{co}_2} \), MCAFV was prepared by diluting 100 mg in 100 cc of 0.9% saline and was started to deliver 0.5 \( \mu g \) kg\(^{-1}\) min\(^{-1}\). The rate of infusion was increased gradually to a maximum of 2.5 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) to achieve a predetermined 15% decrease in MAP. Cerebral haemodynamic measurements were repeated after achieving a steady state at the arterial pressure endpoints.

Cerebral haemodynamics
Cerebral autoregulation
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averaged more than 12 s to include at least two complete respiratory cycles.

Estimated cerebral perfusion pressure and zero flow pressure
The method described by Belfort and colleagues was used to calculate eCPP and ZFP. Taking simultaneous measurements of arterial pressure and TCD velocities at steady state, the following formulae were used:

\[
eCPP = \left( \frac{\text{MFV}}{\text{MFV} - \text{DFV}} \right) \times (\text{MAP} - \text{DAP})
\]

where MAP and DAP are mean and diastolic arterial pressures, and MFV and DFV are mean and diastolic MCA flow velocities.

\[
\text{ZFP} = \text{MAP} - eCPP
\]

Statistics
The calculated range for SA in healthy volunteers is 0.88–1.12 with a coefficient of variation of <10% on repetitive measurements within the same subject. We calculated that 10 subjects would be required to detect an absolute difference of 0.15 in SA with a power of 0.8 and \(\alpha\) of 0.05. This is a clinically relevant change of similar magnitude to that seen with impairment of autoregulation with inhalational anaesthetics. On the basis of the previous studies, similar sample size would also be sufficient to determine significant changes in ZFP.

Data were analysed for normal distribution using Anderson–Darling test. Since some data were not distributed normally, cerebrovascular and cardiovascular variables were analysed using non-parametric tests; Wilcoxon signed rank test was used to analyse within-group changes before and after drug infusions; Mann–Whitney U-test was used for comparing corresponding values between the two groups.

Results
Seven males and three females received norepinephrine, and six males and four females received GTN. The subjects were aged between 22 and 38 yr. The endpoints of increase or decrease in MAP were reached in all subjects (Table 1). The oxygen saturation was greater than or equal to 98% for all subjects throughout the study. The median dose (range) of norepinephrine required to achieve endpoint was 0.06 (0.04–0.1), and that for GTN was 2 (1.5–2.5) \(\mu\)g kg\(^{-1}\) min\(^{-1}\). The median (range) time to reach steady state was 15 (11–33) min for norepinephrine and 20 (15–24) min for GTN. There were no adverse events with either of the agents. Some subjects reported increased awareness of their heart beat with GTN.

The heart rate decreased significantly with norepinephrine and it increased significantly with GTN (Table 1). The MCAFV remained unchanged with norepinephrine and it decreased by a small but significant amount with GTN. The CRCO\(_2\) and SA remained unchanged with both the drugs.

In the subjects who received norepinephrine, despite significant increases in MAP, the eCPP did not change significantly, and there was an associated significant increase in ZFP. On the other hand, with GTN, despite significant decreases in MAP, eCPP increased significantly with an associated significant decrease in ZFP.

Discussion
We have shown that neither norepinephrine nor GTN have significant effects on SA or CRCO\(_2\). In addition, we have shown that despite having significantly increased MAP, norepinephrine did not increase eCPP, and was associated with significant increases in ZFP. This is consistent with the hypothesis that ZFP is a function of the tone of cerebral vasculature. Cerebrovascular tone increases in response to the increase in MAP. GTN had the opposite effect; despite significant decreases in MAP, eCPP increased, and was associated with significant decreases in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Norepinephrine</th>
<th>Glyceryl trinitrate</th>
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<tbody>
<tr>
<td>Control</td>
<td>Drug</td>
<td>Wilcoxon signed-rank test</td>
</tr>
<tr>
<td>HR (beats min(^{-1}))</td>
<td>67 (55, 80)</td>
<td>56 (47, 60)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>85 (82, 91)</td>
<td>104 (101–107)</td>
</tr>
<tr>
<td>(\text{eCO}_2) (kPa)</td>
<td>5.4 (5.0, 5.6)</td>
<td>5.2 (4.5, 5.3)</td>
</tr>
<tr>
<td>MCAFV (cms(^{-1}))</td>
<td>53 (47, 66)</td>
<td>54 (46, 64)</td>
</tr>
<tr>
<td>CRCO(_2) (%/kPa)</td>
<td>39 (37, 43)</td>
<td>38 (33, 42)</td>
</tr>
<tr>
<td>SA</td>
<td>1.14 (1.04, 1.23)</td>
<td>1.18 (0.9, 1.29)</td>
</tr>
<tr>
<td>eCPP (mm Hg)</td>
<td>45 (38, 58)</td>
<td>49 (40, 55)</td>
</tr>
<tr>
<td>ZFP (mm Hg)</td>
<td>39 (28, 50)</td>
<td>56 (46, 62)</td>
</tr>
</tbody>
</table>
ZFP, suggesting a decrease in the tone of cerebral vasculature in response to the decrease in MAP. The study shows that in awake subjects with no neurological disorder, simply increasing MAP with norepinephrine may not achieve an increase in CPP. Equally importantly, it also shows that reducing cerebral vascular tone may be an effective strategy to significantly increase eCPP, despite a moderate decrease in systemic arterial pressure.

The effects of different vasoactive substances on cerebral haemodynamics are not well documented. The cerebral vasculature is known to be abundantly innervated by sympathetic nerves. We have recently reported the effects of norepinephrine and phenylephrine on cerebral haemodynamics using a study protocol similar to the present study. We concluded that neither of these agents significantly affected MCA flow velocity, SA, CRCO₂, or eCPP. These agents are predominantly β-sympathomimetics, although norepinephrine can also have significant α-agonistic effect. On the other hand, phenylephrine is predominantly an α-agonist. However, the present study shows that its effects on cerebral haemodynamics are similar to those reported earlier for norepinephrine or dobutamine. Streb and colleagues have reported the effects of norepinephrine and phenylephrine on anaesthetised individuals. The increase in arterial pressure with these agents was associated with increases in MCA flow velocity, indicating disturbed autoregulation. These authors believed this to be the effects of anaesthetics rather than the vasoactive agents. We chose to study the effects in awake volunteers so as to avoid the confounding effects of anaesthetics. Our results with norepinephrine, when interpreted along with the findings of previous study with norepinephrine and dobutamine, suggest that an increase in MAP with these agents is also associated with an increase in ZFP so that eCPP remains unchanged.

Assessment of ZFP using TCD is indirect since cerebral blood flow is not measured directly. Rather, blood flow velocity is measured. However, the original work on ZFP was performed using directly cannulated vessels in animals allowing direct measurement of flow and pressure throughout the cardiac cycle. Subsequent indirect work in both placental and cerebral flow has been consistent with the original studies. Changes in MCA flow velocity are only directly proportional to cerebral blood flow if the diameter of the insonated vessel does not change. There is no evidence that α-agonists affect directly the diameter of basal cerebral arteries. α-Adrenoceptors are scarce on basal cerebral arteries and phenylephrine appeared to have no effect when the vessels were viewed directly. Various studies have suggested, however, that GTN acts as a vaso-dilator of the MCA leading to reduced flow velocities but maintained or increased cerebral blood flow secondary to intracranial vasodilatation. In this study, we did not measure cerebral blood flow directly, although given that the doses used were similar to previous studies, we assume in the present study, a slight decrease in MCA flow velocity with GTN reflects slight dilatation on the MCA, rather than a decrease in cerebral blood flow. The calculations of various cerebral haemodynamic variables such as CRCO₂ and SA are determined by the per cent change in flow velocity after a stimulus, and that of eCPP is determined by the ratio of pulsatility of arterial pressure and flow velocity, and not the absolute values of flow velocity. Hence, dilatation of MCA per se is unlikely to influence the values of these variables.

The increase in eCPP after GTN is consistent with its effects on cerebral vessels leading to a reduction in tone, similar to that seen during hypercapnia, or inhalation of nitrous oxide. However, in contrast to hypercapnia and inhalation of nitrous oxide, which are known to impair cerebral autoregulation, GTN infusion in this study was not associated with impairment of cerebral autoregulation. This is consistent with previous work investigating the effect of GTN which also found no effect on autoregulation.

The concept of estimating ZFP using TCD has been published previously, supporting its use and validity both in vivo and in vitro. We used Belfort’s method of calculating ZFP. Previously, we have shown that this method is sensitive in calculating changes in ZFP, despite variability in individual measurements. However, so far these studies have been performed in healthy volunteers without evidence of cerebrovascular disease. Further clinical studies will be required to determine the effect of vasoactive substances in the presence of intracranial pathology, particularly reduced intracranial compliance.

This is a volunteer study in young subjects without overt cardiovascular or cerebral disease. Willmot and colleagues found that in patients with ischaemic stroke, despite reductions in systemic arterial pressure, GTN did not decrease cerebral blood flow. Previous workers have found that GTN may be beneficial in vasospasm after subarachnoid haemorrhage. Our study provides support to the concept that the effects of vasodilators on cerebrovascular tone (effective downstream pressure or ZFP) are important determinants of maintenance of adequate eCPP, despite reductions in systemic arterial pressure. In summary, we have demonstrated that during infusion of vasoactive drugs, changes in cerebrovascular tone play an important role in determining eCPP. Changes in systemic arterial pressure do not necessarily equate with changes in CPP.

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Association of Anaesthetists of Great Britain and Ireland.

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