Transcranial Doppler and anesthetics

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Transcranial Doppler (TCD) is widely used to investigate the effects of anesthetic drugs on cerebral blood flow. Its repeatability and non-invasivity makes it an ideal, first choice method. Anesthesia providers are required to be conscious of the cerebral hemodynamic effects of drugs given in their practice, especially in neurosurgery and in subjects with impaired brain functions. The purpose of this review is to present the basic concepts of the TCD technique and the effects on cerebral hemodynamics of the most popular anesthetic drugs evaluated using TCD ultrasonography.

Accepted for publication 12 April 2007

Key words: Transcranial Doppler; cerebral blood flow; anesthetic drugs.

Transcranial Doppler

The basic concepts

Transcranial Doppler (TCD) ultrasonography is a non-invasive technique which allows us to observe velocity, direction and properties of blood flow in the cerebral arteries by means of a pulsed ultrasonic beam (1–3).

It is based on the Doppler effect of ultrasounds (4) concerning frequency variations in sound waves as a result of relative motion between source and signal receiver. In TCD, the ultrasonic beam, with a frequency of about 2 MHz, crosses the intact skull at points known as ‘windows’ and is reflected back from the moving erythrocytes in their path. Thus, the frequency of the transmitted signal is different from that of the received signal and this difference, called the ‘Doppler Shift’, can be expressed by the formula (5):

\[
\text{Doppler Shift} = \frac{2 \times V_f \times F_{\text{sec}} \times \cos(\alpha)}{V},
\]

where \(V_f\) is the velocity of blood flow, \(F_{\text{sec}}\) is the transmitted frequency source, \(V\) is the speed of sound in soft tissue (1540 m/s) and \(\alpha\) is the angle of insonation (angle between transmitted ultrasonic beam and blood flow direction). Considering that in TCD frequency and speed of sound in soft tissue remain constant, the frequency shift depends mainly on the angle of insonation and the velocity of blood flow.

Within a vessel, therefore, erythrocytes move at different speeds and the Doppler signal obtained is composed of a group of different frequency components. Spectral analysis is used from TCD devices to present these data (three-dimensional) in a bi-dimensional format where frequency shift (or velocity) is represented on the vertical scale, time on the horizontal scale and signal intensity is represented as the relative brightness or color (Fig. 1).

The velocity of flow is calculated through the creation of a ‘spectral envelope’ corresponding to the maximum signal throughout the cardiac cycle. Once this outline is created, the spectral detail is largely ignored and different parameters (systolic, diastolic and mean flow velocity) are measured from the spectral envelope (5, 6).

Methodology of examinations

TCD is performed through ‘ultrasonic windows’, points where ultrasounds can reach the cerebral arteries as a result of the presence of either a thin cranial theca or a natural hole.

The ‘trans-temporal window’, found above the zygomatic arch, is most frequently used and allows us to insonate the arteries in the Circle of Willis (anterior, middle and posterior cerebral arteries). The ‘trans-foraminal window’, instead, takes advantage of the presence of the foramen magnum and is used to measure the blood flow in vertebral and basic arteries. Finally, the ‘trans-orbital window’ allows us to insonate the ophthalmic artery and carotid siphon while an ultrasonic beam passes through the orbital structures.
For each particular window, the identification of an artery is carried out by means of the same criteria: sample depth, flow direction, angle between beam and skin surface, and the response of the TCD signal to compression tests of the ipsilateral internal carotid on the neck. The basic technique of the transcranial Doppler examination has been widely reported (7).

Once the vessel has been identified – the middle cerebral artery (MCA) – the examiner attempts to follow it toward the bifurcation of the internal carotid artery (ICA) into the MCA and anterior cerebral artery (ACA), at a depth of 55–75 mm.

At this point, the Doppler signal has flow velocity (FV) pulse wave images above and below the zero line of reference (Fig. 2), representing the flow
directions towards (MCA) and away from (ACA), respectively.

The anterior and posterior cerebral arteries can also be examined through the trans-temporal window: the first at a depth of 55–75 mm with the flow going away from the probe; the second at a depth of 65–70 mm with blood flow direction like the MCA (towards the probe).

Finally, every recorded signal is verified by means of an ipsilateral or a contralateral carotid compression test (Table 1) (7).

Information obtained using TCD

The blood flow velocity is used as an indirect measure of blood flow, provided that the diameter of the insonated vessel is unchanged and the angle constant. A study with TCD is composed of two main steps: abnormal pattern recognition and interpretation, in the light of the clinical data, for confirming or excluding a diagnosis.

The usual parameters evaluated are ‘the velocities of flow’ – systolic, diastolic and time-averaged mean values can be calculated from the flow velocity waveform (but the mean flow velocity is commonly considered the best indicator) – and ‘the pulsatility index’ (PI), used to estimate the cerebrovascular resistance, and defined by Gosling and King (8) as the ratio between the difference in systolic velocity and diastolic and the mean flow velocity.

\[
\text{PI} = \frac{(FVs - FVd)}{FVmean}.
\]

As a ratio, with a normal range from 0.85 to 1.10, PI is not affected by the angle of insonation, but it may be influenced by a large number of factors including arterial pressure, vascular compliance and PaCO2 (8).

Finally, TCD can also be used to evaluate the state of cerebral autoregulation, or the ability of the cerebral vascular bed to undergo constriction or dilatation, in response to various modifications of the cerebral perfusion pressure (CPP), to keep the cerebral blood flow (CBF) constant (9–11). The test essentially consists of assessing the changes of the flow velocity in MCA to changes in CPP. Several methods can be used to obtain artificial variations of the CPP: the transient hyperemic response (THR) test is most commonly used. Described for the first time by Giller (9–11), the test consists of measuring the response of MCA blood flow velocity after a brief compression (5–9 s) of the ipsilateral common carotid artery. This produces a reduction in the flow velocity of MCA and perfusion pressure. If autoregulation is intact, this provokes vasodilatation in the area of the MCA and a transient increase in the MCA flow velocity is seen on release of compression (Fig. 3A). If autoregulation is damaged, the flow velocity goes back to the pre-compression basic values without episodes of hyperemia (Fig. 3A,B).

The transient hyperemic response ratio is commonly used as a quantitative index to evaluate the autoregulation state. It is defined as the ratio between the systolic flow velocity (FV1) – calculated using the mean value of systolic peaks from five heart cycles, ending with the one preceding compression – and the hyperemic response (FV3), calculated using the mean systolic value of two heart cycles after compression, with exception of the very first cycle (Fig. 3A,B) (12, 13).

Anesthetic agents

Volatile anesthetic agents

The effect of a volatile anesthetic on CBF depends on the balance between the agent’s intrinsic vasodilatory action and the vasoconstriction as a result of flow-metabolism coupling (Table 2) (14, 15). Sevoflurane is widely used in neuroanesthesia. In common with other volatile anesthetics, but in a less evident manner, sevoflurane shows an intrinsic dose-dependent cerebral vasodilatory effect (14, 16). Several studies, in fact, have demonstrated how it increases the cerebral blood flow velocity (CBFV) and decreases the cerebrovascular resistance (CVR) in

| Table 1 |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Vessel direction | Probe (mm)      | Depth of flow   | Direction compression | Ipsilateral carotid compression | Contralateral carotid compression |
| ACA             | Anterior        | 55–75           | Away                | Flow reversal          | Increased velocity               |
| MCA             | Perpendicular  | 35–60           | Toward              | Reduced velocity       | No change                        |
| PCA             | Posterior       | 65–70           | Toward              | No change or increased velocity | No change                        |

ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.
a dose-dependent manner (13, 17, 18). The reduction of CVR could cause an impairment of cerebrovascular autoregulation mechanisms but different transient hyperemic response tests, carried out on adults and children, showed that cerebral autoregulation is well preserved during anesthesia, with up to 2.0 MAC sevoflurane (19, 20). These data are also confirmed by a recent study demonstrating that, at higher doses (2.0 MAC) and deep anesthesia level (Bispectral index = 35), sevoflurane exhibits a certain degree of uncoupling flow-metabolism (12). Finally, also cerebrovascular CO$_2$ reactivity is preserved during sevoflurane anesthesia (21, 22).

Desflurane is a volatile anesthetic agent with a low blood/gas solubility coefficient that allows rapid changes in anesthesia depth (23, 24).

Nevertheless, several studies, carried out on the effects of this agent on cerebral hemodynamics, showed how also desflurane has an intrinsic dose-related cerebral vasodilatory effect (25–27). CBFVs and heart rate (HR), in fact, increase significantly with increasing concentration of desflurane, while arterial pressure remains unchanged, suggesting that the cerebrovascular effect of this drug is independent of its systemic vascular action (26–29).

When in anesthetized children, propofol is substituted with desflurane to avoid delayed recovery from anesthesia, CBFV increases, but not when isoflurane is changed to desflurane (24). This cerebral vasodilatory effect may have important implications in the neurosurgical setting.

With regard to cerebral autoregulation, instead, it has been demonstrated that desflurane – at concentrations greater than 1.0 MAC – produces a dose-dependent impairment of the autoregulation mechanisms: at 1.0 MAC, autoregulation appears delayed but preserved, while at 1.5 MAC it is almost abolished (23, 30). Similarly, cerebrovascular CO$_2$ reactivity is maintained at 1.0 MAC (26).

Isoflurane is the most traditional volatile agent used in neuroanesthesia. Like most inhalation anesthetics it shows an intrinsic dose-dependent cerebral vasodilatory effect (16, 25). An isoflurane-based anesthesia induces a significant increase in the CBFV of the MCA (19% and 72–75% at 0.5 and 1.5 MAC isoflurane, respectively) (14, 27). Cerebral autoregulation is also impaired in a dose-related manner (31). In fact, transient hyperemic response ratio values (1.17 ± 0.03, 1.07 ± 0.02 and 1.01 ± 0.01 during baseline, 1.0 and 2.0 MAC, respectively) are attenuated, suggesting that cerebral autoregulation mechanisms are preserved during anesthesia with up to 1.0 MAC isoflurane (20). A previous investigation in other conditions has demonstrated, however, that hypocapnia can be used to restore cerebral autoregulation impaired by isoflurane anesthesia (32). Finally, it has been demonstrated that the cerebrovascular CO$_2$ reactivity, usually markedly influenced by the anesthetic procedure, is not affected by isoflurane – in doses up to 1.0 MAC (33) – in anesthetized, healthy subjects, while it is significantly impaired in patients with diabetes mellitus (34).

Intravenous anesthetic agents
Although adverse effects on cerebral hemodynamics have been reported, intravenous anesthetic and sedative agents are often used in neuroanesthesia.

In healthy subjects, propofol-based anesthesia induces a significant decrease in blood flow velocity in the MCA (35, 36). This suggests a preserved coupling of cerebral blood flow and metabolism. Cerebral autoregulation and carbon dioxide reactivity is
preserved (12, 37–40). The latter is also well preserved in children, and patients with previous stroke (41, 42).

The cerebrovascular effects of propofol on injured patients are different: fast propofol infusion rates impair cerebrovascular autoregulation in subjects with head injury (43), while absolute and relative CO2 reactivity is notably affected by propofol anesthesia in diabetic patients, and this degree of impairment is related to the severity of diabetes mellitus (44).

Used often in total intravenous anesthesia (TIVA) with remifentanil, previous investigations showed how in adult subjects an anesthesia with propofol/ remifentanil induces a dose-dependent flow state with preserved cerebral autoregulation and cerebrovascular CO2 reactivity (12, 45). In children anesthetized with propofol, the addition of remifentanil causes a reduction in mean arterial pressure (MAP) and hearth rate without affecting the CBFV leaving, however, cerebral blood pressure autoregulation and carbon dioxide reactivity unchanged (42, 46).

Nevertheless, there are studies demonstrating that propofol reduces CBF to a greater extent than it reduces cerebral metabolism, indicating that propofol has direct vasoconstricting properties. Jansen et al. (47) found that in patients undergoing brain tumor surgery there was a significantly lower jugular saturation in patients anesthetized with propofol than in a matched group anesthetized with nitrous oxide and isoflurane; Nandate et al. (48) found a significant decrease in jugular bulb saturation 1 h after normothermic cardiopulmonary bypass with propofol anesthesia but not with isoflurane or sevoflurane anesthesia. According to this view, the low-flow state induced by propofol may ameliorate the pressure-flow relationship, but worsen the flow-metabolism ratio, thus creating a disautoregulation instead of a hyperregulatory state.

Ketamine is a general, dissociative anesthetic, with an excitatory effect tending to increase the MCA blood flow velocity that can be reduced by adequate pretreatment (6, 49).

Nevertheless, used generally together with other drugs, ketamine shows controversial effects on cerebral hemodynamics. In combination with isoflurane, for instance, it does not affect MCA blood flow velocity but significantly reduces both absolute and relative cerebrovascular reactivity to CO2 [2.9 ± 0.8 (control) vs. 2.6 ± 1.0 (ketamine) cm/s and 3.5 ± 0.7 (control) vs. 2.8 ± 0.9 (ketamine)%], respectively] (50). If used during propofol-based anesthesia, it does not influence HR, MAP, Vmca nor the cerebrovascular CO2 response (51). Previous investigations, however,
demonstrated how a significant increase in blood flow velocity in the MCA occurs with low-dose ketamine (52, 53) and how similarly, this drug increases the CBF if benzodiazepines are not injected simultaneously (54).

**Thiopental** is a rapid-onset, short-acting barbiturate anesthetic agent. It induces – above all in children – a moderate but immediate decrease in MCA blood velocities (55). In young subjects, 1 min after injection, 5 mg/kg thiopental significantly decreases blood flow velocity in the middle cerebral artery (56). There is a prevalent decrease in the cerebral metabolic rate of oxygen (CMRO₂) indicating a preserved coupling of blood flow and metabolism.

**Nitrous oxide**

*Nitrous oxide* (N₂O) has been administered routinely in neurosurgical anesthesia. For a long time it was thought this agent had little effect on cerebral circulation and autoregulation (10, 57). A great number of studies, however, have now demonstrated adverse effects on cerebrovascular hemodynamics, both in humans and animals. When used alone, at concentrations of 30–60%, nitrous oxide significantly increases the CBFV, the intracranial pressure (ICP) and the CMRO₂, while it reduces cerebral autoregulation and leaves cerebrovascular reactivity to acute arterial carbon dioxide (CO₂) changes unaltered (13, 58–60). Nevertheless, these effects can change if N₂O is used, as often happens, together with other anesthetic agents. During anesthesia with desflurane, for instance, neither the addition nor removal of nitrous oxide induces significant changes in MCA blood flow velocity, HR or blood pressure: this is because desflurane has a greater vasodilatory effect (61). The addition of N₂O at lower concentrations of sevoflurane significantly impairs the transient hyperemic response test (62), increases the CBFV (63) and reduces cerebrovascular CO₂ reactivity (64).

On the contrary, the inhalation of N₂O during propofol-based anesthesia has no significant effects on MCA flow velocity (65), cerebral autoregulation (66) and cerebrovascular CO₂ reactivity (67). Finally, in the case of isoflurane, it has been demonstrated how nitrous oxide added to an anesthetic regimen with this volatile agent is a potent vasodilator with non-uniform effects; this last one progressively increases with increasing isoflurane concentration (68). Caution in using N₂O is, hence, suggested.

**Opioids**

Different studies, carried out to investigate the effects of opioids, both alone and in combination with other anesthetic agents, demonstrated how these drugs could affect cerebral hemodynamics with consequent increases in ICP and reduction in CBF (69).

The effects of *fentanyl* on cerebral hemodynamics have been investigated in several studies which demonstrated how an anesthesia based on propofol and fentanyl leaves the autoregulation of CBF unchanged (38). At clinically relevant doses – in the absence of others drugs – the CBFV is usually increased (Vmca changes from 60 ± 10 to 81 ± 12 cm/s) despite the fact that hypocapnia can be used to reverse this potentially undesirable effect: during hypocapnia, in fact, MCA blood flow velocity values are identical (40 ± 7 vs. 40 ± 7 cm/s) before and after fentanyl administration (70). Moreover, in patients with severe head injury, the infusion of fentanyl usually induces a decrease in MAP and CPP, and an increase in ICP at constant PaCO₂ (71). Finally, fentanyl seems to provide a more stable hemodynamic profile than other opioids (remifentanil), above all when it is used – in sevoflurane anesthetized children – during and after laryngoscopy and tracheal intubation (72).

**Remifentanil**, used generally together with propofol, induces in the brain a dose-dependent flow state with preserved cerebral autoregulation (12, 45, 46). Also, cerebrovascular CO₂ reactivity, as previous investigations have showed, is well maintained during high-dose (but not low-dose) remifentanil infusion, while no changes are recorded in HR, MAP and ICP (73, 74).

**Sufentanil** decreases cerebral flow velocity in a dose-related manner: at clinically relevant doses – in absence of other drugs – the infusion of this anesthetic agent is associated with a 27–30% reduction in the CBFV (75) while low sedative doses of sufentanil do not affect the CBFV (76).

No significant effects on MCA blood flow velocity and ICP are, instead, recorded in patients with brain injury, intracranial hypertension and controlled MAP (77). However, transient increases in ICP without changes in middle cerebral artery blood flow velocity may occur concomitant with decreases in MAP suggesting that increases in ICP seen with sufentanil may be due to autoregulatory decreases in cerebral vascular resistance secondary to systemic hypotension (77).

**Conclusions**

Transcranial Doppler is widely used to investigate cerebral blood flow velocity and indirectly, changes in cerebral blood flow. Differences in results, or opposite points of view, should not be considered as a lack of credibility in the technique, but are
essentially related to differences in methodology. Its repeatability and non-invasivity makes it an ideal method for studying cerebral hemodynamics. Anesthesia providers are required to be conscious of the cerebral hemodynamic effects of the drugs used in their practice, especially in neurosurgery or in subjects with impaired brain functions. This review offers an update of the results available today.

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