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Letter to the Editors

Blood pressure-lowering effects of propofol or sevoflurane anaesthesia are not due to enhanced nitric oxide formation or bioavailability

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Blood pressure (BP) reduction is a common pharmacodynamic feature of propofol, sevoflurane and other drugs used in general anaesthesia. The mechanisms by which propofol induces anaesthesia have been discussed [1, 2]. During total intravenous anaesthesia with propofol and sevoflurane anaesthesia, systolic and diastolic BP decreased by ~30% [3–5]. The underlying BP-lowering mechanisms of propofol and other anaesthetics are incompletely understood. Propofol is likely to induce hypotension by inhibiting the sympathetic nervous system and by impairing baroreflex regulatory mechanisms [5]. Additional mechanisms may involve endogenous vasoactive species, including the vasoconstrictor thromboxane A_2 (TxA_2) and the vasodilatator nitric oxide (NO). During total intravenous anaesthesia with propofol in surgical patients, platelet-derived TxA_2 was inhibited *ex vivo*, whereas the plasma concentrations of nitrite and nitrate, the major metabolites of NO [6], increased by 37% [7]. As TxA_2 is a potent vasoconstrictor and NO a potent vasodilatator, the BP-lowering actions of propofol could be related to TxA_2 inhibition in platelets and concurrent enhancement of NO synthesis [7]. *In vitro*, propofol inhibited TxA_2 in human platelets while inducing inositol-1,4,5-trisphosphate formation, suggesting that propofol may both enhance and inhibit human platelet function, presumably depending upon its concentration [8]. We observed that during general anaesthesia in patients undergoing elective spinal surgery, the plasma concentration of the endocannabinoid anandamide, an arachidonic acid derivative, rapidly decreased [9]. Yet, in the same study we also observed a comparable decrease in plasma anandamide in thiopental–sevoflurane anaesthesia [9]. Furthermore, anandamide is considered not to decrease BP on its own [10]. Taking these findings together, BP lowering during anaesthesia may obey mechanisms that are not related to endogenous vasoactive substances, such as TxA_2 and NO.

During total intravenous anaesthesia with propofol in surgical patients, plasma nitrite and nitrate concentrations ranged between 1 and 15 μmol l^{-1}, with the majority of the concentrations being lower than 5 μmol l^{-1} [7]. This interval is much too low compared with the vast majority of reported data [6], and presumably resulted from the use of the Griess assay, with its analytical shortcomings [11].

We aimed to measure nitrite and nitrate concentrations in plasma samples obtained in a previously reported clinical study [9]. We applied a fully validated and clinically proven gas chromatography–mass spectrometry method [12]. This assay uses the stable-isotope-labelled analogues of nitrite and nitrate, i.e. ^{15}N-nitrite and ^{15}N-nitrate, as internal standards.

As reported earlier [9], all patients received standard doses of midazolam, atracurium and fentanyl/remifentanil. Induction of anaesthesia was achieved with either propofol or with thiopental plus sevoflurane. Blood samples were collected in EDTA-containing tubes before injection of propofol or thiopental (0 min) and 10, 30 and 60 min after induction. Vacutainers were immediately cooled and centrifuged at 4°C (10 min, 3500***g***). Plasma was then quickly separated from blood cells and kept on ice until storage at −80°C. In the present study, nitrite and nitrate were measured in nonhaemolytic plasma samples of 32 patients who had undergone propofol (n = 18) or thiopental–sevoflurane anaesthesia (n = 14). In brief, nitrite and nitrate were determined simultaneously in 100 μl aliquots of thawed plasma samples using ^{15}N-nitrite and ^{15}N-nitrate at added final plasma concentrations of 4 and 40 μmol l^{-1}, respectively. Study samples were analysed by the same experimenter within five runs alongside quality control samples as reported elsewhere [12]. Accuracy and imprecision (relative standard deviation) were (mean ± SD) 108.3 ± 5.4% and 1.75 ± 1.85% for plasma nitrite, and 105.9 ± 3.4% and 3.64 ± 4.03% for plasma nitrate, respectively,

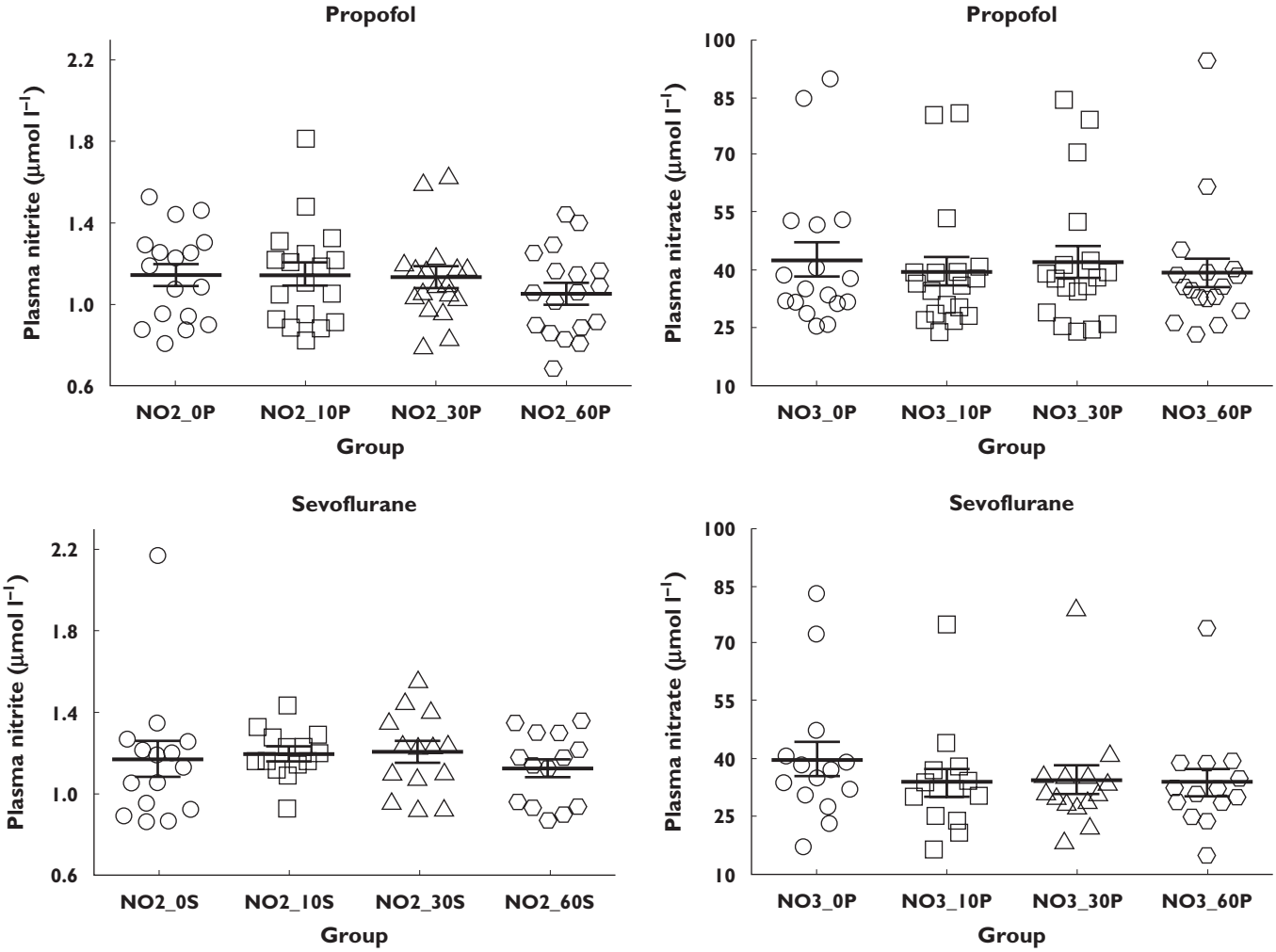

Figure 1

Nitrite (NO2) and nitrate (NO3) plasma concentrations during the first hour (0, 10, 30 and 60 min) of general anaesthesia with either propofol (P, $n = 18$) or thiopental/sevoflurane (S, $n = 14$). Data are shown as mean values ± SEM. Two-tailed Mann–Whitney *U*-test was used to test statistical significance. None of the comparisons yielded statistical significance between the groups ($P > 0.05$)

indicating the reliability of the nitrite and nitrate plasma concentrations measured in the study samples.

The results of the present study are depicted in Figure 1. Plasma nitrite and nitrate concentrations measured in the study were of the same order of magnitude reported by us and others (for a review see Tsikas *et al*. [6]). Plasma nitrite and nitrate concentrations measured 10, 30 and 60 min after the start of anaesthesia did not differ from those measured at time zero, i.e. immediately before starting anaesthesia, in both groups. Also, we observed no statistical difference between the propofol and thiopental–sevoflurane groups. These findings suggest that the BP-lowering actions of propofol and sevoflurane in human subjects during anaesthesia cannot be attributed to an enhancement of NO synthesis (sum of nitrite and nitrate) or NO bioavailability (nitrite).

Isoflurane, another anaesthetic of the flurane group, and pentobarbital, but not ketamine, have been very recently shown to lower BP and to protect the heart in a rat model of stress-induced cardiomyopathy (takotsubo cardiomyopathy) [13]. Thus, interaction of fluranes with adrenergic signalling and inhibition of catecholamine-induced increase in contractility may explain both the BP-lowering and the cardioprotective effects of sevoflurane. Hypotension during propofol or sevoflurane anaesthesia may result from several different mechanisms. Taking into consideration that anaesthetics such as propofol may alter the pharmacokinetics of other co-administered drugs, such as midazolam, may help in the design of mechanistic studies to provide better understanding of the pharmacodynamic effects resulting from drug–drug interactions [14]. Ultimately, anaesthetics such

as propofol and sevoflurane may also alter distribution, metabolism and elimination of endogenously produced compounds, resulting in enhancement or attenuation of their biological activities. The reduction of plasma anandamide during propofol or thiopental–sevoflurane anaesthesia may have arisen from drug-induced increase of the metabolism/elimination of anandamide or redistribution of anandamide between blood and other body compartments [9], presumably depending upon their lipophilicity/hydrophilicity. Propofol altered midazolam pharmacokinetics at plasma concentration of 1.2 mg l^{-1} [14]. In our previous study, the plasma propofol concentration was above this value and did not correlate with plasma anandamide concentration [9]. An explanation for the lack of correlation between plasma anandamide and propofol concentrations may be that plasma propofol concentrations occurring during propofol anaesthesia are sufficient to enhance the metabolism/elimination of the lipophilic, neutral lipid anandamide upon starting anaesthesia, analogous to midazolam [9].

Elevated TxA_2 synthesis [15, 16] and diminished NO synthesis/bioavailability [6] are associated with hypertension. Inhibition of TxA_2 synthesis and elevation of NO synthesis/bioavailability by drugs such as the widely used anaesthetics, including propofol, may lower BP. Published studies do not support the involvement of TxA_2 in anaesthesia-induced hypotension. In the present study, we did not detect influences of propofol or thiopental–sevoflurane on NO synthesis/bioavailability in a sufficiently powered study employing a validated analytical method for measurement of nitrite and nitrate concentrations in human plasma. The BP-lowering effects of propofol or sevoflurane anaesthesia are likely to be mediated through inhibition of the sympathetic nervous system and impairment of baroreflex regulatory mechanisms.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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