

Sympathetic Nervous System Activation and Hyperdynamic Circulation Associated with Desflurane: Not All Isomers Are Created Equal

The search for better, safer inhalation anesthetics has continued despite the excellence of presently available drugs. Molecular medicinal chemists are able to tailor compounds for specific desirable traits. Thus, halothane was supplanted by enflurane and isoflurane, each associated with definable differences, advantages, and disadvantages. Recently, desflurane, an isomer of isoflurane with a solubility in blood similar to that of nitrous oxide and extraordinarily high physical stability, was introduced into clinical practice in the United States after a broad range of meticulous studies.¹ It was anticipated that desflurane would have many properties in common with isoflurane because of the similarity in molecular structure. However, one unexpected finding described initially by Helman *et al.* was the occurrence of hypertension and tachycardia during induction of anesthesia.²

In an article in the present issue of ANESTHESIOLOGY, Ebert and Muzi, following up on the findings of Helman *et al.*, compared hemodynamics during induction of anesthesia, during steady-state anesthesia, and during an abruptly increased concentration of isoflurane to equipotent concentrations of desflurane.³ They measured systemic arterial blood pressure, heart rate, peroneal sympathetic nerve activity, and forearm blood flow in subjects who had first received thiopental and vecuronium. At steady-state equivalent minimum alveolar concentrations, heart rate, mean arterial pressure, forearm vascular resistance, and sympathetic nerve activity were similar between isoflurane and desflurane, confirming observations of previous observers.⁴⁻⁶

On the other hand, the contrast between the effects of these two isomers immediately following their introduction during induction and when inspired concentration was increased abruptly after a period of stability was dramatic in several respects. Introduction of increasing concentrations of desflurane into the circuit

2 min after induction with thiopental and neuromuscular blockade with vecuronium was accompanied by tachycardia, hypertension, and enhanced sympathetic nerve activity, whereas this was not true with isoflurane administered similarly. Abruptly increasing the inspired concentration of desflurane from 1.0 to 1.5 MAC after a period of stability was associated with similar sympathetic nervous system and circulatory hyperdynamic responses. Such changes also did not occur with similar abrupt elevations of inspired isoflurane.

The observations by Ebert and Muzi inevitably raise at least three questions, including: (1) Why were these properties not recognized during the initial studies before Food and Drug Administration approval despite apparently comprehensive studies? (2) What are the mechanism(s) leading to the changes? (3) Can they be predictably avoided?

The answer to the first question is that, as noted above, similar observations were made but their potential importance not widely acknowledged. In an induction protocol similar to that of Ebert and Muzi's in patients with coronary artery disease who were premedicated with morphine and midazolam, Helman *et al.* observed increases of systemic artery, pulmonary artery, and pulmonary capillary wedge pressures and increased heart rate during induction.² The hemodynamic changes were treated promptly with esmolol (56% of patients during induction; 32% during the remainder of the prebypass period) or vasodilators, and the duration of the changes was not defined. Nine percent (9/99) of patients demonstrated electrocardiographic changes consistent with myocardial ischemia during induction. In three patients, electrocardiographic changes were preceded by hemodynamic changes by 5 or 10 min. The investigators did not study isoflurane with the same protocol.

In a more recent preliminary report, Ostapovich *et al.* reported greater changes with desflurane than with isoflurane in heart rate and blood pressure in patients undergoing peripheral surgery or neurosurgery in whom anesthesia was induced with thiopental, either with or without vecuronium-induced neuromuscular blockade and with or without nitrous oxide.⁷ An ad-

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ditional preliminary report by the same group demonstrated increases in heart rate and systemic arterial pressure with abrupt increase of desflurane but not isoflurane from 1.0 to 1.5 MAC in patients anesthetized with thiopental and paralyzed with vecuronium.⁸

Thus, Ebert and Muzi's hemodynamic data are consistent with the findings of others. Their steady-state data are also compatible with other reports emphasizing the similarity of the hemodynamic associates of equivalent minimum alveolar concentrations of isoflurane and desflurane under steady-state conditions.⁴⁻⁶

In contrast to the lack of hemodynamic changes in patients receiving isoflurane in the study by Ebert and Muzi are data recently reported by Yli-Hankala *et al.* in patients receiving steady-state 1 MAC (1.3%) isoflurane.⁹ When the inspired isoflurane concentration was increased suddenly to 5%, hemodynamic changes remarkably similar to those reported by Ebert and Muzi occurred. Anesthesia in these patients was induced with propofol/vecuronium after benzodiazepine premedication. These data impute a property for isoflurane similar to that of desflurane but with a dose-response curve shifted to the right for isoflurane, since 1.5 MAC inspired isoflurane does not elicit this response³ but 5.0% inhaled concentration (~ 3.5 MAC) does.⁹ This, again, is compatible with the similarities in molecular structure. The difference in the dose-response curve may be responsible for the late recognition of this syndrome with isoflurane. It is noteworthy, however, that Yli-Hankala *et al.* initiated their studies on the basis of clinical observations leading them to suspect that rapid increases of inspired isoflurane concentration were associated with a hyperdynamic circulation.

It is tempting to speculate that something in the protocols and methods of administration of the anesthetic predisposed to these changes, particularly since Weiskopf *et al.* did not report similar changes in their initial studies in which anesthesia was induced by inhalation of desflurane.⁴ The reports cited above, however, include volunteers and patients, the elderly and the young, patients premedicated with benzodiazepine and/or morphine, induction with thiopental and propofol, and presence or absence of nitrous oxide. Thus, the changes have been documented in a variety of circumstances, adding credence to the observations.^{2,4-9}

The proximate mechanism for the changes appears to be stimulation of the sympathetic nervous system. An increase in the mixed venous plasma norepinephrine concentration and a correlation of mixed venous

plasma epinephrine and heart rate changes were documented by Yli-Hankala *et al.*⁹ Ebert and Muzi convincingly demonstrated sympathetic nervous system activation.³ The possible role of respiratory tract irritation as the stimulus, as suggested by Ebert and Muzi and by Yli-Hankala *et al.*, deserves further investigation. The case for involvement of the baroreceptors in this syndrome is not convincing at present, because the tachycardia is associated with an increase rather than a decrease in blood pressure.

The question of whether the changes can be avoided, and at what cost, is important. Some have suggested that the presence *versus* absence of opioids is responsible for the disparity of the reported responses. The evidence for this is lacking. Surely, the issue will be the topic of intense investigation.

It would be ironic if a most attractive property, low blood gas solubility leading to the ability to increase anesthetic blood level and depth rapidly, turned out for desflurane to be associated with another property causing hemodynamic changes potentially hazardous to selected patients. Ebert and Muzi have forcefully enabled us to recognize that desflurane, when administered in a fashion heretofore considered appropriate, is predictably capable of inducing activation of the sympathetic nervous system with its associated potentially adverse consequences. Further studies are required to define the precise circumstances, mechanisms, and possible methods to avoid this syndrome.

One of the privileges, frustrations, and rewards of participating in scientific endeavor is the recognition, documentation, and elucidation of the mechanism of unanticipated responses. By their careful studies clearly demonstrating a previously poorly appreciated property of desflurane, Ebert and Muzi have added to the safety of anesthetic practice.

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