

## Automated Anesthesia

### Fact or Fantasy?

IN this issue of ANESTHESIOLOGY, Struys *et al.*<sup>1</sup> provide a challenge to us as anesthesiologists. Can automated closed-loop anesthesia improve patient outcomes? In this small study, they demonstrated that outcomes (as measured by hemodynamic control and initial recovery) were better in the group to which propofol was administered *via* a closed-loop control system than in the group to which propofol was administered by a clinician.

Anesthesiologists often compare themselves to pilots because they have similar work environments and work functions. Automated flight control is standard in professional aviation industry because it reduces workload during busy times and reduces certain types of pilot error. We in anesthesia have been slow or even reluctant to adopt such technology, although the first demonstration of closed-loop anesthesia was described by Bickford in 1950.<sup>2</sup> Comparing automated flight to automated anesthesia is glib; however, making the comparison and then determining how they are different allows one to establish what the challenges are for anesthesia and, from this, to determine how these issues are being resolved.

A generic closed-loop system is shown in figure 1.<sup>3</sup> The set points for flying (speed, altitude, and so forth) are readily defined and measurable. What constitutes anesthesia is still hotly debated, with no sensor able to measure changes in depth of anesthesia. What has been established is that alteration in consciousness is at least a required component of anesthesia. Although consciousness itself may be difficult to define, recent work has demonstrated that derivatives of the electroencephalogram, *i.e.*, Bispectral Index,<sup>4</sup> electroencephalographic entropy,<sup>5</sup> and auditory evoked potentials,<sup>6</sup> can correlate with changes in consciousness. Thus, sensors now exist

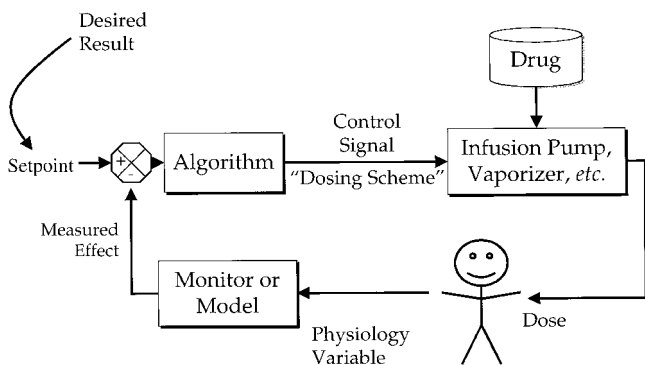
to measure at least one component of the anesthetic, making it amenable to closed-loop control. This has been a major step for developing clinically acceptable closed-loop anesthesia. However, improvements in sensor technology and artifact detection and elimination remain challenges for their routine use in closed-loop anesthesia.<sup>7</sup>

The next objective is to take the step from a drug dose (the control signal for unconsciousness) to the desired set point (*e.g.*, Bispectral Index value). The algorithm is not as simple as delivering  $x$  mg for a given change in Bispectral Index units. The ability to obtain the set point for unconsciousness is dependent on achieving in the brain (biophase) a concentration of the drug that will produce this set point. In turn, the concentration of the drug in the biophase is determined both by the dose administered and by its pharmacokinetics. Innovations in pharmacokinetic modeling have enabled the development of target-controlled delivery systems.<sup>8</sup> They use pharmacokinetic models to calculate the required dosing scheme to achieve a desired concentration. These developments have been crucial in providing closed-loop anesthesia.

Unfortunately, biologic systems have significant variance within a population, and the pharmacokinetic parameters used within the models are likely to result in inaccuracies for any given individual. In addition, there may be up to 10-fold differences in the relation between concentration and effect (pharmacodynamics) among individuals. Pharmacodynamics may also vary over time and during surgery according to the intensity of the applied noxious stimulus. This adds further complexities to the algorithm. To accommodate this, an adaptive control signal is added by which the algorithm is altered or adapted to the individual's unique response. Variability may be caused by pharmacokinetics or pharmacodynamics. One may assume that pharmacodynamics between individuals do not vary and thus any difference in the measured effect is caused by the pharmacokinetic parameters. Alternatively, one may assume that the pharmacokinetic parameters are always correct but that pharmacodynamics vary among individuals. Struys *et al.* have taken the latter approach. During induction, propofol was administered using an open-loop mode (*i.e.*, target concentration rather than target effect was the initial set point). This relation between concentration and effect was used to construct a Hill curve for each individual. In this early stage of development, we need to establish the optimal approach for closed-loop systems used to provide anesthesia. Is the approach of Struys *et al.* better

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**Fig. 1.** The components of a typical automated drug delivery system.

than altering the pharmacokinetic parameters? Did the authors achieve an accurate estimation of the individuals' Hill curves? All subsequent adjustments in drug administration were dependent on the accuracy of this curve. Their system performed well (achieving a median absolute performance error of less than 10%), but this may have been because the system was not fully tested or stressed. Loss of consciousness is only one component of the anesthetic state. Analgesia also plays a significant role. In the study by Struys *et al.*, the patients were all administered a maintenance dose of  $0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  remifentanyl. This dose of remifentanyl is sufficient to produce a maximal reduction in the minimum alveolar concentration of isoflurane.<sup>9</sup> It is likely that during surgery, the required concentration of propofol was only that needed to achieve loss of consciousness. This is confirmed by the small adjustments in propofol concentration that occurred during the study.<sup>1</sup> Would the control algorithm have worked as well if the dose of analgesic administered had been much less, thereby requiring much larger adjustments in propofol concentration? Would the accuracy of the original Hill curve under these circumstances have been adequate, and would the methods proposed for making these adjustments have been sufficient and appropriate for these larger changes in concentration? Would overshoot or undershoot have occurred? Would the responses have been rapid enough for the changing stimuli encountered during surgery with the potential for awareness or movement? It is important that at this stage of development of closed-loop anesthesia, we do not extrapolate any results beyond the narrow confines of the specific study design, especially because of the critical role of analgesia in the performance of the system.

The study design chosen by Struys *et al.* for comparing the two groups may be criticized by some. In the control group, propofol was titrated manually to achieve set points that are commonly used during anesthesia, *i.e.*, blood pressure, heart rate, and sympathetic tone. In contrast, the closed-loop group had as their set point a Bispectral Index value. Thus, they compare two groups

whose anesthetic was adjusted to two very different measures of adequate anesthesia. Is this acceptable? It depends on the question being answered. If the question is "Can a machine titrate propofol to a desired Bispectral Index better than humans?" then the study design is faulted. A more fundamental question is "Does closed-loop anesthesia titrated to a set point of unconsciousness provide a better outcome than anesthesia titrated to set points that are currently used most commonly?" This question is appropriately answered by the study design chosen by Struys *et al.* One may argue that the improved outcomes they noted were caused by titration to a Bispectral Index rather than by the use of a closed-loop system. The study leaves this as an unanswered question that needs to be answered as the natural evolution of good science. Their study has necessitated that we now carefully consider the value of closed-loop anesthesia.

Closed-loop systems for anesthesia are more difficult to design and implement than those for aviation, but considerable progress has been made. It is only with the development of reliable and robust monitors of consciousness that we could even consider developing clinically viable closed-loop systems. The evolution of pharmacokinetic models, including the biophase and the implementation of such models into drug delivery systems, has made closed-loop delivery of anesthesia a viable possibility. The study by Struys *et al.* implies that the development of closed-loop delivery systems for anesthesia are no longer esoteric. Rather, the challenge is now to establish fully the safety, efficacy, reliability, and utility of closed-loop anesthesia for its adoption into the clinical setting.

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## New Mechanisms for Inhaled NO

### Release of an Endogenous NO Inhibitor?

THE endogenous signaling molecule, nitric oxide (NO), plays a significant role in many physiologic and pathophysiologic processes in the lung.<sup>1,2</sup> In addition to its role as an endothelial-dependent vasodilator, NO has been shown to regulate ciliary motility, to participate in angiogenesis and vasculogenesis, and to prevent leukocyte adhesion and platelet adhesion. Produced in excess, NO may contribute to the vascular remodeling of pulmonary hypertension, to inflammatory lung injury, and to reactive airway disease.

Exogenous inhaled NO has been widely investigated in the therapy of lung diseases associated with increased pulmonary vascular resistance.<sup>2</sup> In this regard, inhaled NO has been shown to be effective in reducing the use of extracorporeal membrane oxygenation in neonates with persistent pulmonary hypertension of the newborn. Inhaled NO has significant promise as effective therapy in several other diseases of the lung, particularly those in which the increased pulmonary vascular resistance is likely to reverse within a period of a few days.

The role of endogenous NO in pulmonary vasoconstriction is complex and is dependent on the specific physiologic circumstances. The disease-free, normoxic lung has very little NO synthase expressed in the small resistance vessels.<sup>3</sup> Consistent with this lack of expression, numerous studies using inhibitors of NO synthase failed to demonstrate an increase in normal lung vascular resistance, suggesting that NO does not play a significant role in the normally low pulmonary vascular resistance.<sup>1</sup>

Nitric oxide content is regulated by oxygen in a complex manner. NO content is dependent on its rate of production from NO synthase and its stability once produced. Low- and high-oxygen environments can each regulate NO production and stability.<sup>1,4-6</sup> NO requires two molecules of oxygen as substrate in addition to L-arginine. The Michaelis constant ( $K_m$ ) of the eNOS for oxygen,  $7.7 \mu\text{M}$ , suggests that NO production would be significantly reduced with a partial pressure of oxygen ( $P_{O_2}$ ) of less than 30 mmHg.<sup>4</sup> Because of the second

order kinetics of the chemical interaction between NO and oxygen, in an environment with high oxygen content, NO rapidly combines with oxygen to form nitric acid, making it unavailable for vascular action. NO also combines with superoxide radical to form peroxynitrite.<sup>5,6</sup> Thus, lowering oxygen tension prolongs the half-life of NO in counterbalance to its reduction of NO synthesis through limitation of oxygen substrate. High oxygen tension provides adequate oxygen substrate but accelerates NO metabolism to peroxynitrite and nitric acid. In addition, prolonged exposure to low oxygen tension up-regulates the endothelial and inducible isoforms of NO synthase in the lung.<sup>3</sup>

In multiple human and animal studies, when acute hypoxia reduces lung oxygen to a physiologically relevant degree, the net effect of all these interactions seems to be an increase in NO available for vascular action.<sup>1</sup> In this context, when inhibitors of NO synthase are administered to the hypoxic lung, the vasoconstriction normally seen with hypoxia is increased because of the inhibition of NO.<sup>1</sup> NO is thus an important modulator of hypoxic pulmonary vasoconstriction, but it plays a small role in regulating pulmonary blood flow during normoxia.

Hambraeus-Jonzon *et al.*<sup>7</sup> have made the interesting observation that in anesthetized humans, inhaled NO to a single hyperoxic lung increases the blood flow to this lung, but only if the other lung is hypoxic. This increase in regional blood flow caused by unilateral inhaled NO did not occur in the absence of regional hypoxia when both lungs were either normoxic or hyperoxic. This observation suggested a much more complex mechanism of action for inhaled NO, involving an interaction between the hyperoxic lung regions receiving inhaled NO and the hypoxic lung regions not directly reached by inhaled NO. In work published in the current issue of ANESTHESIOLOGY, Hambraeus-Jonzon *et al.*<sup>8</sup> investigated the mechanism of this response in a pig model. Their work provides strong evidence that inhaled NO to the hyperoxic lung releases a blood-borne mediator that inhibits NO synthase in the hypoxic lung that is not receiving inhaled NO. Inhaled NO is traditionally thought to improve oxygenation by dilating vessels in ventilated lung areas and thereby redistributing blood flow to these ventilated areas and away from the non-ventilated regions, with a resulting decrease in shunt fraction. The current findings suggest an entirely novel mechanism by which inhaled NO may improve shunt and oxygenation. In addition to dilating vessels in the ventilated lung regions, it seems that NO somehow re-

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sults in the release of a factor that constricts vessels in regions that do not receive inhaled NO.

This new work by Hambraeus-Jonzon *et al.*<sup>8</sup> used both a single pig model and a cross-circulation model to suggest strongly the existence of a blood-borne mediator. In the single pig study, delivery of inhaled NO to only the normal right lung resulted in a reduction of blood flow and a decrease in exhaled NO from the isolated hypoxic left lower lobe. Thus, the delivery of NO to one area of the lung resulted in an effect on an area to which NO was not delivered. This response in the single piglet model could potentially be explained by changes in shear stress. It is established that NO production from the endothelium is stimulated by shear stress. Decreasing shear would reduce NO production. Administration of inhaled NO to the normal lung could vasodilate that lung, shunt blood away from the left lower lobe, decrease left lower lobe blood flow, decrease shear stress, and therefore decrease NO synthase activity and exhaled NO. An alternate explanation would be a blood-borne mediator that potentially inhibits NO synthase or acts *via* another contractile mechanism. To address this question, the investigators used a cross-circulation model that administered inhaled NO to a normal pig and cross-circulated that animal's blood to another pig with an open chest and an isolated, hypoxic left lower lobe. As in the single-pig model, an increase in pulmonary vascular resistance to the left lower lobe and a decrease in exhaled NO occurred. In addition, a modest decrease in NO synthase activity was demonstrated through biochemical studies. These data are clearly consistent with the authors' conclusion that inhaled NO releases a blood-borne mediator that down-regulates endogenous NO production in lung regions that do not receive inhaled NO, and more so in hypoxic than hyperoxic regions.

These studies are remarkable for two reasons. First, they suggest that our previous simplistic understanding of inhaled NO acting simply through vasodilation is much more complex. They also suggest a novel regulatory pathway for NO signaling through NO-stimulated production of an endogenous NOS inhibitor. At this time, the authors have not further characterized this response or attempted to isolate the factor involved. It would be interesting to know whether blood from animals with inhaled NO shows vasoconstriction in an isolated vascular ring. Would blood from the lung receiving inhaled NO alter an NO synthase activity assay? Is there response with serum, or is whole blood required? What is the role of hemoglobin *versus* other serum proteins? What is the biochemical nature of the factor?

Endogenous inhibition of NO synthase has been reported, and a few of these inhibitors have been identified and characterized.<sup>9-17</sup> However, none have been shown to be released by NO. L-arginine analogs that have been chemically modified at the terminal guanidino nitrogen group, such as L-NMMA, have been used as syn-

thesized products to inhibit NO synthase. L-NMMA and other methylated L-arginine analogs have also been shown to be synthesized endogenously.<sup>9-13</sup> Among these, asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) have been shown to be most abundant. ADMA is an inhibitor of NO synthase, whereas SDMA is inactive. ADMA is produced by a family of *N*-methyl transferases that methylate L-arginine residues within specific proteins. ADMA is subsequently released after proteolytic cleavage of these proteins. ADMA also undergoes specific enzymatic metabolism by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). Endothelial dysfunction has been observed when DDAH activity has been inhibited and increased ADMA concentrations are present. Several studies have now implicated ADMA as a factor in atherosclerosis, hypercholesterolemia, end-stage renal failure, hypertension, and heart failure.<sup>9-13</sup> Recently, ADMA has been shown to increase endothelial oxidative stress and potentiate monocyte adhesion to the endothelium.<sup>9</sup> Whether exogenous NO can enhance the production of ADMA is unknown but can be readily investigated.

Another endogenous inhibitor of NO synthase, first described in regard to the neuronal NOS, is the protein PIN-1.<sup>16,17</sup> PIN-1 is homologous to dynein and was first shown to inhibit the neuronal NO synthase. Subsequently, PIN has been shown to inhibit all three isoforms of NO synthase.<sup>17</sup> However, there is currently no evidence that PIN-1 plays a significant role in vascular responses of NO.

The current study results could also be explained by feedback inhibition of NO synthase by NO. Our laboratory and others have shown that NO itself is an inhibitor of NO synthase.<sup>14</sup> This is because of the high affinity of NO for the iron and other sites (*e.g.*, cysteine 93) in protoporphyrin heme groups and the binding of NO to the protoporphyrin heme present in NO synthase isoforms. In the current studies, inhaled NO was only given to the normoxic lung and was not given to the hypoxic lung, where the inhibition of NO production and vasoconstriction was observed. It is possible that the NO is actively transported to hypoxic regions where it is released and able to inhibit NO synthase. Interesting recent work by Gow and Stamler<sup>18</sup> and by Gow *et al.*<sup>19</sup> has suggested that NO bound to hemoglobin plays a physiologic role in oxygen delivery and that NO bound to hemoglobin facilitates oxygen transport. This work suggests that NO binds to hemoglobin (in the R state; fully ligand bound) in the high-oxygen pulmonary circulation, enhancing oxygen binding. Then, in low-oxygen tissues, NO is released from hemoglobin (T state; partially nitrosylated) and simultaneously enhances the release of oxygen to the tissues (negative cooperativity).<sup>17-19</sup> This released NO has been shown to exchange between hemes and cysteines of other proteins.<sup>18-22</sup> Transfer to the heme of NO synthase would inhibit NO production.

This would be consistent with the current study, in which the endogenous inhibitor response was observed primarily in the hypoxic lung lobe.

The models used by Hambraeus-Jonzon *et al.*<sup>8</sup> are complex and unsuited to isolation, identification, or biochemical characterization of a novel mediator. Initially, these complex physiologic studies need to be confirmed and complemented by bioassay for the blood-borne factor of question. If a blood-borne factor is confirmed, then the next and exciting steps will be to isolate, identify, and characterize that factor and to understand how NO enhances its production. Studies can address the three potential inhibitory pathways discussed but must also consider the possibility of novel factors that may be involved in this fascinating physiologic observation.

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