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Advances in precision anaesthesia may be found by testing our resistance to change

Sarah L. Eagleman* and M. Bruce MacIver

Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Palo Alto, CA, USA

*Corresponding author. E-mail: saraheagleman@stanford.edu

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Anaesthetic depth changes spontaneously over the course of an anaesthetic for pharmacological and physiological reasons. Traditional methods for determining the efficacy of anaesthetic agents in individuals rely on population statistics, which limits progress towards precision anaesthesia for each individual. The laboratories of Proekt and Kelz have begun to quantify this variability in anaesthesia in mice, both at the level of the individual mouse[1,2], and also regarding differences between specific anaesthetic agents.[2] In a study from their groups published by Wasilczuk and colleagues[2] in this issue of *British Journal of Anaesthesia*, three volatile anaesthetics (isoflurane, sevoflurane, and halothane) were quantitatively assessed with regard to stability over time of the loss of righting reflex, a surrogate measure of loss of consciousness in rodents.[3] Steady-state concentrations at the minimum alveolar concentration dose for each agent were administered, and the ability to right was determined at 3-min intervals in each mouse over 2 h. Although the responses of the population of mice resulted in a calculable half maximal effective concentration (EC_{50}) for each anaesthetic, the response dynamics of each individual mouse were highly variable. Over the 2-h measurement period, some mice exhibited the righting reflex on a majority of trials, while other mice failed to right on a majority of trials. The majority of the mice, however, exhibited seemingly random fluctuations between responsiveness and unresponsiveness during anaesthetic administration. The authors quantified this as a *resistance to state transitions* (R_{st}) using models of stochastic processes (Fig. 1).

Interestingly, different volatile agents exhibited differing degrees of R_{st}. Halothane produced the most stable behavioural responses during anaesthesia (highest R_{st}), whereas sevoflurane, and more so isoflurane, produced lower resistances (i.e. higher fluctuations between response and no-response trials). Wasilczuk and colleagues[2] argue that pharmacokinetic factors could not have played a role since animals were held at fixed inhaled concentrations for more than 2 h before behavioural measures commenced. Thirty minutes

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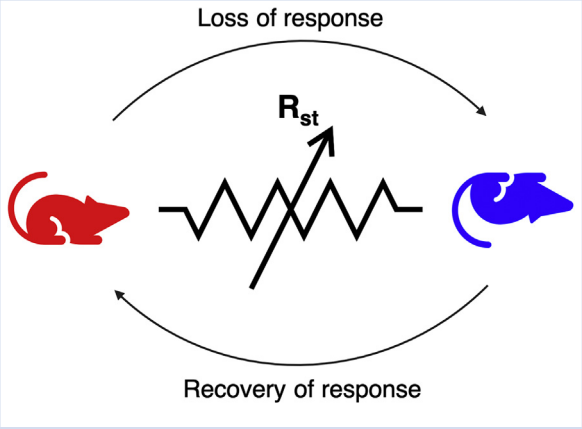

Fig 1. Quantifying a variable resistance in anaesthesia. Variable resistors (shown here using the resistor symbol with the arrow through it) are used to vary the amount of current flow in electrical circuits (e.g. an amplifier volume control). For individual subjects and different anaesthetic agents, there appear to be varying degrees of resistance to switch between awake (red) and anaesthetised (blue) states. Wasilczuk and colleagues[2] have quantified this resistance to state transitions (R_{st}) for different individuals and for different volatile anaesthetic agents. Some mice have a low R_{st} and rapidly switch between responsive and unresponsive states at a fixed agent concentration, while others have high R_{st} and switch less frequently. Different agents exhibit different R_{st} patterns as well, with a high R_{st} anaesthetic producing a more 'stable' anaesthetic state.

would be more than sufficient time for complete concentration equilibration at anaesthetic effect sites. Resistance to state transition provides a new measure of anaesthetic effect stability and provides a further example of agent-selective effects produced by different volatile anaesthetics.[4–7]

Results from this study do not provide an explanation for the mechanism underlying the observed individual *biological* variability in anaesthetic effect between mice, nor do they probe the mechanisms accounting for observed differences in R_{st} between agents. However, they do show that the variability can be individually measured, providing a way forward for more detailed studies of these phenomena. Future research should include incorporating these measures into experimental paradigms where the resistance to state transitions metrics are quantified for mice of different genotypes. Wasilczuk and colleagues[2] hypothesise that differences in brain structure and function must exist between mice, and that these differences must lead to differentially distributed anaesthetic target sites of action that each anaesthetic can act upon. It remains to be seen what these target sites might be, or even how many sites might be involved in producing the differential actions for each anaesthetic.[4]

Growing evidence suggests that multiple sites of action contribute to anaesthesia, including some types of sodium,[8] calcium,[9] and potassium[10] channels, many ligand-gated channels,[11] including channels gated by acetylcholine,[12] catecholamines, glutamate,[13,14] and GABA,[6,15–18] and presynaptic neurotransmitter release proteins.[19–21] Many additional protein targets remain to be explored, and thus there are potentially hundreds of anaesthetic sites of action contributing to the observed biological variability.[22] Making the connections from these molecular dynamics to the emergent behavioural dynamics remains a challenge for understanding the neurophysiology of general anaesthesia.

Clinically, it is well known that anaesthetic depth changes over the course of administration, and anaesthesiologists must titrate doses of various agents to adjust for this. Often stimuli such as the pain of surgery or simply saying a patient's name can prompt changes in anaesthetic depth. This new study indicates that even when stimuli are held relatively constant, fluctuations in depth of anaesthesia occur, independent of arousing stimuli. In layman's terms, the *depth* of anaesthesia changes spontaneously through time. Thus, targeting anaesthetic concentrations to obtain an ideal state remains a moving target.

Authors' contributions

Wrote the manuscript, designed the figure, and are solely responsible for the content: both authors.

Declarations of interest

The authors declare that they have no conflicts of interest.

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