Movement of the patient and the concept of minimum alveolar concentration (MAC)

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Introduction

I am certain that you have been there. There is a hush as the surgery proceeds; the quiet interrupted only occasionally by the words “artery forceps” and “diathermy, please”. You’re resting, perched on your stool and listening to the reassuring sound of bleeps from the ECG monitor. Then suddenly the patient moves and the bellow of “the patient is awake” resounds from beyond the green drapes.

But does movement mean that the patient is awake? Why does a patient lie still under anaesthesia? And, if the patient does move, will he or she remember it?

For more than 200 years, volatile anaesthetic agents have produced immobility during surgery. Despite their widespread usage and effectiveness, it has been difficult to determine exactly how these magical molecules work and it has been the subject of much speculation.

The three goals in anaesthesia have been suggested to be unconsciousness, analgesia and immobility. The depth of anaesthesia can be measured using, for instance, BIS or Entropy. Analgesia, on the other hand, is almost impossible to define or measure. Movement, however, is easy to define and it is a parameter that, dare I say it, even a surgeon can recognise. Immobility is a very important clinical end-point. And it is this simple end-point that has been used to assess adequacy of anaesthesia for over forty years and has been the basis of the familiar parameter MAC.

Minimum alveolar concentration (MAC) is the alveolar concentration of an anaesthetic (at one atmosphere) that prevents movement in 50% of the subjects in response to a surgical skin incision.1 But have you ever considered this? How is this movement prevented? This is an important question and one that we will examine.

How do inhaled anaesthetic agents produce immobility?

Presumed cerebral origin of MAC

The Meyer-Overton correlation, demonstrated over 100 years ago, shows the relationship between MAC and fat solubility.2 Simply, the more fat soluble the drug is, the less drug is needed to produce immobility during anaesthesia. As we know, general anaesthesia is associated with unconsciousness and impairment of memory; therefore, clearly, the brain is affected by anaesthetic agents. We know that neural tissue and myelin have a high fat content and lipid solubility is a powerful predictor of anaesthetic potency. Thus it is easy to make the connection and see why it was assumed that general anaesthetics produce all their effects, including immobility, through their action on the brain. Over the last decade or two, it has emerged that the most likely “anaesthetic targets” are probably ion channels rather than the membranes themselves. Nonetheless, the assumption that anaesthetic-induced immobility is due to cerebral effects has persisted.

If we say that anaesthetic-induced immobility is due to the anaesthetic’s suppressive effect on the brain, we imply that movement is a function of how deeply anaesthetised the patient is. However, if very high isoflurane concentrations, around 6–10%, are selectively delivered to the brain, spontaneous movement occurs.3,4 This is surprising, since one would expect the animal exposed to these concentrations of isoflurane, which are super-anaesthetising, to be the equivalent of clinically brain dead. We do not expect a super-anaesthetised animal to move. The fact that they can implies that immobility must be separate from depth of anaesthesia. Thus, there appears to be a tension in the relationship between depth of anaesthesia, as related to how deeply unconscious the patient is, and MAC, the descriptor of immobility.
**Demonstrated spinal cord origin of MAC**

If MAC is not due to depth of anaesthesia, where do inhaled anaesthetics act to cause immobility? There is significant evidence that anaesthetic induced-immobility is due to effects of inhaled anaesthetic agents on the spinal cord.

In the mid-90s, in one of the first experiments of its kind done, Rampil et al surgically removed the forebrain in some unfortunate rats and they found that the isoflurane requirements to prevent movement were unchanged.\(^6\) They concluded that the spinal cord is an important site for anaesthetic action.

Similarly, Antognini developed a model that utilised the unique vascular anatomy of goats. Using this model, he was able to selectively perfuse the brain of the goat and the body with differing concentrations of volatile anaesthetic agents, while the goat remained physically intact. Antognini came up with interesting results that support the concept that movement under anaesthesia is a spinal level based.\(^8\) He showed that the MAC of isoflurane in goats with intact native circulation was 1.2%. But the brain isoflurane concentration required to suppress movements was approximately 3%, more than double. These results support the concept that inhalational anaesthetics act primarily on spinal cord to promote immobility.

The question now begging to be asked is: how do inhaled anaesthetic agents cause immobility at a spinal level? Let us start by considering where in the spinal cord volatiles take effect. Is this a dorsal or spinal level? Let us start by considering where in the spinal cord volatiles take effect. Is this a dorsal or spinal level?

Anaesthetic-induced immobility is not a dorsal horn-mediated effect.\(^2,11\) Sensory-evoked potentials in humans can be recorded at concentrations well in excess of MAC. In addition, we all know that, at 1 MAC, incision produces an increase in arterial blood pressure and heart rate, and increases ventilation. Autonomic responses to noxious stimulation are surrogate measures of pain. MAC-BAR for sevoflurane, which is the dose needed to obliterate these responses, exceeds MAC by a factor of 2.2. Thus the lack of response to a stimulus is not because the patient does not feel the stimulus. And so it is unlikely that inhaled anaesthetic agents mediate immobility via action on the dorsal horn.

This is supported by evidence that anaesthetic action is not uniform in neurons residing in different anatomical areas of the spinal cord. Kim demonstrated that, while isoflurane suppressed the activity of ventral horn neurons, isoflurane appeared to have less effect on dorsal horn neurons.\(^12\) This was further elucidated by Barter, who showed that wide dynamic range neurons, which are most numerous in the dorsal horn, are not inhibited and may be stimulated by isoflurane.\(^13\) In contrast, nociceptive-specific neurons that populate the ventral horn are profoundly inhibited by volatile anaesthetic agents. These findings support the argument that anaesthetic-induced immobility is not due to the effects of inhaled anaesthetics on the dorsal horn.

Therefore, inhaled anaesthetics most likely affect the ventral horn, thereby affecting the motor response. Motor output is governed by a group of neurons called the central pattern generator (CPG). The CPG is a concept rather than a formal area and represents the spinal interneuronal network. This locus is, therefore, the local command post that coordinates movement. It is not surprising that depression of this area occurs at anaesthetic concentrations close to MAC.\(^14\) We asked earlier how anaesthetic agents inhibit movement at the level of the spinal cord, and this appears to be the answer: inhaled anaesthetic agents inhibit the central pattern generators and movement is disrupted. So it appears that MAC is a function of the depression of the CPG by inhaled anaesthetic agents.

**Effect of supraspinal structures on MAC**

We have seen that inhalational anaesthetics must primarily act on spinal cord to promote immobility and that just a minor component of immobility results from brain effects. What effects do supraspinal structures have on MAC? We know that forebrain and cerebellar structures do not play any role. But what about the brainstem?

There are areas in the brainstem that are involved in descending modulation of the central pattern generators in the spinal cord. It appears that there is an area in the brainstem, called the mesencephalic locomotor region (MLR), that is closely linked to the CPG. In fact, the MLR normally facilitates the CPG.\(^15\) Jinks elegantly demonstrated that transections of the brainstem immediately caudal to the MLR caused a 60% decrease in MAC. Similarly, local inactivation of the MLR with lignocaine caused a 32% decrease in MAC. Thus the removal or inhibition of the MLR action on the CPG decreases MAC.

Our patients don’t routinely have their brainstems transected, so how is this relevant to you and me? Jinks showed that isoflurane suppresses the MLR neurons. He demonstrated that the MLR neuron response to noxious stimuli is decreased by 87% at concentrations that bracket 1 MAC. Jinks went on to show that, as the concentration of isoflurane
increases, so the neuronal responses in the MLR are suppressed and the motor responses to painful stimuli are decreased to a similar degree. Thus, the effects of isoflurane on the activity of MLR neurons were predictive of MAC.

Thus there is a delicate interplay between the brainstem and the ventral horn in facilitating MAC. It appears that inhaled anaesthetic agents suppress motor responses at the spinal cord, more specifically at the CPG, as well as suppressing the MLR that usually facilitate the CPG. Therefore we can accept that there are important interactions between the brain and the spinal cord. And we have now seen that the brainstem modulates the precise immobilising requirements of anaesthetic agents.

Effect of anaesthetic-induced immobility on supraspinal structures

However, it is not all one way traffic. Normally, afferent input into the CNS from tonic sensory and muscle spindle activity modulates cerebral function, and thereby maintains a state of wakefulness. You, undoubtedly, have experienced this every time you have administered a spinal anaesthetic. I am sure that you have noticed that, after the subarachnoid block begins to take effect, the patient generally become sleepy. In other words, the loss of tonic afferent input into the CNS suppresses its activity. This phenomenon was demonstrated by Hermans when he showed that, after intrathecal injection of local anaesthetic, the patients exhibited a decrease in BIS and spectral edge frequency. \(^{16}\) When the spinal anaesthetic decreased the afferent input, cerebral activity was decreased.

Afferent input can also be decreased by neuromuscular blockade. We know that neuromuscular blockers act at the neuromuscular endplates to prevent movement. This loss of movement in turn results in less afferent input to the CNS. Less afferent input enhances hypnosis and immobility, and results in decreased anaesthetic requirements. This was demonstrated by Doufas et al, when they determined that succinylcholine and mivacurium reduced MAC for desflurane by 19% and 23%, respectively. \(^{17}\) In other words, these muscle relaxants reduced the anaesthetic demand for immobility. Doufas went on to demonstrate that, after receiving the muscle relaxants and at the lower end-tidal desflurane concentration, patients displayed similar BIS activation patterns in response to noxious stimulation compared with saline treatment. In other words, even though they received less desflurane, they were not anaesthetised any lighter, confirming that their anaesthetic requirements had indeed decreased.

In the same way that spinal anaesthesia and neuromuscular blockade decrease afferent input into the CNS, anaesthetic-induced immobility results in loss of afferent input into the CNS that may contribute to the loss of consciousness seen with general anaesthesia. While immobility is produced primarily at the spinal cord, the inhaled anaesthetic agent suppression of the MLR decreases MAC and resultant muscle relaxation decreases afferent input into the brain, thus decreasing the anaesthetic requirements.

Was the patient awake?

We started with a scenario where we illustrated how movement is interpreted that the patient is awake. Was this patient awake?

Animal studies have demonstrated that inhalational anaesthetic agents inhibit learning at doses around 0.3 MAC, so-called MAC aware, and MAC awake is 0.5–0.65. \(^{18}\) Therefore we expect the patient to move before experiencing recall, because lower anaesthetic concentrations are needed to prevent consciousness and awareness than to render immobility. Thus, many equate lack of movement with sufficient depth of anaesthesia to induce unconsciousness. It has been demonstrated that simultaneous high dose opioids dramatically decrease the amount of inhalational agent needed to suppress autonomic responses and movement. But it has less effect on the dose required to suppress awareness. Is this because the opioids also act at a spinal level, on spinal mu-receptors, to suppress movement and autonomic responses? Only further studies will clarify this, but high opioid-based anaesthesia creates a situation where it is entirely possible for a patient not to move and yet to be aware.

Conclusion

It is clear that movement and unconsciousness are not as closely linked as we may have previously assumed. And we have seen there is a physiological basis for considering these two properties of general anaesthetics as being somewhat distinct. MAC is a measure of the anaesthetic effect on primarily the spinal cord. Immobility as a depth of anaesthesia monitor, while useful, is not a direct indicator of the
anaesthetic effects on consciousness or the ability for recall, which are the main reason that an anaesthetic is given in the first place.

We have looked at some of the evidence that proves that anaesthetic-induced immobility is due to effects on the ventral horn, probably the CPG. We have seen that there is a delicate interplay between spinal cord and brain stem in modulating MAC.

Will this influence my practice? Well, probably not very significantly. But it will certainly foster a more informed interpretation of the signs and facilitate further research. And the next time the familiar phase: “the patient is awake” is flung your way, you can know that he or she isn’t, well, not yet!

References