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Review Article

Minimum alveolar concentration: ongoing relevance and clinical utility

A. Aranake,[1] G.A. Mashour[2] and M.S. Avidan[3]

1 Medical Student, 3 Professor of Anaesthesiology, Washington University School of Medicine, St. Louis, Missouri, USA
2 Assistant Professor of Anaesthesiology, University of Michigan Medical School, Ann Arbor, Michigan, USA

Summary

Since its introduction in 1965, minimum alveolar concentration (MAC) has served as the standard measure of potency for volatile anaesthetic agents. It is defined as the minimum alveolar concentration of inhaled anaesthetic at which 50% of people do not move in response to a noxious stimulus. Within the last 20 years, it has been discovered that volatile anaesthetics inhibit mobility largely through action on the spinal cord, whereas the amnesic and hypnotic effects are mediated by the brain. Studies suggest that the concentration of volatile anaesthetic needed to prevent explicit memory from developing, and to produce unconsciousness, is usually substantially lower than the concentration required to prevent movement in response to surgery. This review highlights the contributions and limitations of MAC and its derivatives as metrics of anaesthetic potency with respect to particular behavioural outcomes. Recent evidence is presented suggesting that a protocol that alerts anaesthetists whenever MAC falls to < 0.5 or 0.7 has the potential to decrease intra-operative awareness with explicit recall, possibly to a similar extent as does a protocol based on processed electroencephalography-driven alerting.

Correspondence to: M. S. Avidan
Email: avidanm@anest.wustl.edu
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For more than 165 years, inhaled volatile anaesthetics have played a central role in anaesthetic practice [1]. They are relatively inexpensive, convenient to use, and have predictable therapeutic and side-effects. Today, measurement of end-tidal anaesthetic concentrations provides real-time feedback, and facilitates target-controlled titration of volatile anaesthetic agent administration.

Between the 1840s and the 1960s, the introduction of new agents underscored the need for methods to measure and compare anaesthetic potencies and to determine adequacy of dosing [1]. Early methods proposed to assess depth of anaesthesia were based on clinical observations. Guedel defined stages of anaesthesia based on alterations in breathing, muscle tone, pupil diameter, lacrimation and eyelid reflex [2]. In Woodbridge's concept of 'nothria' (a term intended to encompass mental and motor inactivity coupled with insensibility) depth of anaesthesia was assessed clinically according to changes in sensation, movement, reflexes and mentation [3]. However, these qualitative assessments varied with different anaesthetics, limiting their clinical utility. In 1965, Eger et al. introduced the concept of minimum alveolar concentration

(MAC), relating concentration or partial pressure of inhaled anaesthetics to a single clinically relevant endpoint of general anaesthesia: immobility in response to a surgical stimulus [4].

The utility and reliability of MAC as an anaesthetic metric assumes that the end-tidal anaesthetic partial pressure is an accurate reflection of alveolar partial pressure, which in turn reflects partial pressure at the effect site. Pharmacokinetic studies report that partial pressures do indeed equilibrate in the alveoli, arteries, brain and other tissues at varying rates, depending on the physical properties of the particular volatile anaesthetic agent [5, 6]. By determining the relationship of measured anaesthetic partial pressures to a given anaesthetic effect, specifically the suppression of movement in response to a surgical stimulus, Eger et al. created a measure of potency. Unlike the earlier qualitative methods proposed by Guedel and Woodbridge to assess anaesthetic potency, MAC is quantitative and can be applied to all inhaled anaesthetics [4, 7]. Early studies demonstrated that MAC was a useful and reproducible metric in both animals and humans, and that MAC did not increase with stimulus intensity beyond a certain point (supramaximal stimulation) [4]. Given these important characteristics and the ease of measurement of end-tidal anaesthetic agents, MAC remains the standard index for comparison of volatile anaesthetic potency.

Although volatile anaesthetics bind to protein targets [8], the Meyer-Overton relationship, that volatile anaesthetic potency varies directly with lipid solubility [9, 10], holds true for commonly used inhaled anaesthetic agents [11, 12]. Therefore, MAC can be estimated from the following equation [13]:

$$\text{MAC} \times \lambda \approx 1.82 \text{ atmospheres}$$

where λ = olive oil/gas partition coefficient. Expressed more simply, the product of MAC and lipid solubility is a constant; as lipid solubility decreases, MAC increases (Fig. 1). Thus, if a new volatile anaesthetic was introduced with a MAC of 9%, we could conclude that it was less potent (given its higher MAC) and less soluble than desflurane (which has a MAC of 6%).

Minimum alveolar concentration for various inhaled anaesthetics and factors that influence MAC have been identified [14]. Equipotent administration of different agents (i.e. expressed as MAC equivalents) has enabled comparison of pharmacological effects on physiological variables to be described, such as respiratory rate and blood pressure. In this review, we summarise the current literature regarding MAC, examine factors that modulate MAC, discuss advantages and disadvantages of its use as a metric, and highlight key clinical studies that attest to its utility.

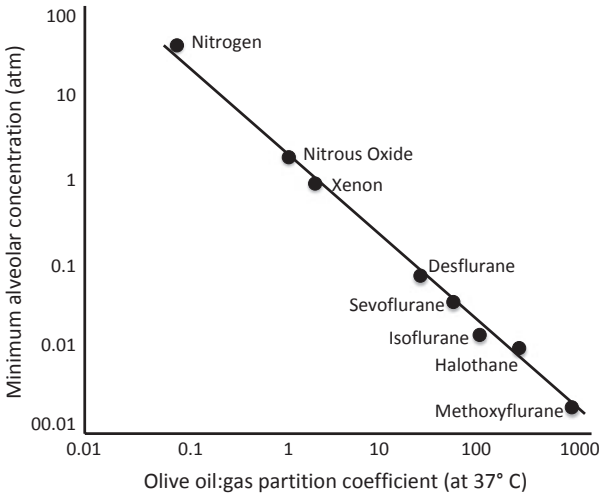

Figure 1 Relationship between MAC (log scale) and olive oil to gas partition coefficient (λ; log scale) [91]. The figure illustrates that for commonly used inhaled anaesthetic agents, the product of MAC and λ is a constant. In general, decreased solubility is associated with decreased potency, increased MAC and faster onset of action.

Definition of MAC

Minimum alveolar concentration is defined as the minimum alveolar concentration at sea level of inhaled anaesthetic required to prevent apparently purposeful movement in 50% of patients in response to surgical incision [4, 14]. Synonyms for MAC include 'EC_{50} for immobility', 'MAC-movement', 'minimum alveolar partial pressure (for 50% immobility)' and 'median alveolar concentration (for immobility)'. In typical human studies to determine MAC, anaesthesia is induced (in a volunteer) with the inhaled agent of interest and maintained at a preselected end-tidal anaesthetic concentration (ETAC) for 15 min to allow equilibration of alveolar and arterial partial pressures. A standard noxious stimulus is then applied and the volunteer is observed for an apparently purposeful

response, such as head or limb movement [4, 15]. These steady-state concentrations may be increased or decreased based on the observed response. Plotting the proportion/percentage of patients not moving (dependent variable) against anaesthetic concentrations (independent variable) creates a dose-response curve [4, 15]. MAC is a single point on this curve, corresponding to the concentration of anaesthetic at which 50% of patients do not move in response to the stimulus (Fig. 2). The standard deviation (SD) of MAC is generally ~10%, indicating that 1.2 MAC (i.e. MAC + 2 SD) should produce immobility to stimulation in ~95% of patients [16]. The steepness of this curve reflects that there is relatively little variability in the concentration of inhaled anaesthetic agent required to prevent movement to a noxious stimulus between subjects. This relatively narrow range of volatile anaesthetic concentrations highlights the clinical utility of these drugs. Compared with potent volatile anaesthetic agents, there is wider interpatient percentage variability in the concentration of propofol required to prevent movement in response to a noxious stimulus [17]. Therefore, notwithstanding other information, practitioners can better predict the concentration at which the majority of patients are very unlikely to move in response to noxious stimulus during volatile-based anaesthesia compared with propofol-based intravenous anaesthesia [16]. However, the steepness of the slope for volatile agents also means that a large proportion of patients could start moving in response to noxious stimulation with relatively small decrements in anaesthetic concentration just below MAC (Fig. 2). This can occur rapidly and cause adverse consequences with more insoluble volatile anaesthetics such as desflurane if, for example, the vaporiser is turned off and the practitioner forgets to restart anaesthetic delivery, or if the vaporiser becomes empty unnoticed or if the practitioner intentionally turns off the vaporiser before reversing neuromuscular blockade.

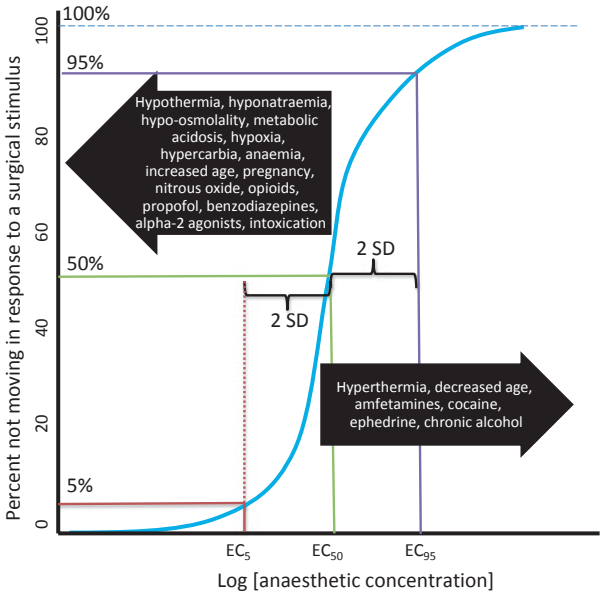

Figure 2 Relationship between anaesthetic concentration and the percent of people not moving in response to a surgical stimulus [4]. This figure illustrates the relatively narrow interperson variability in the anaesthetic concentration required to suppress movement. Factors that shift the curve to the left (i.e. decrease MAC) and to the right (i.e. increase MAC) are shown in the arrows [14]. Population effective concentrations are shown for 5% (EC_5), 50% (EC_{50}) and 95% (EC_{95}) of the population [16]. The EC_{50} is synonymous with MAC. SD, standard deviation.

MAC derivatives

A similar approach to the one described to ascertain MAC has been used to determine the potency of inhaled anaesthetics for other desirable clinical endpoints of general anaesthesia, such as unconsciousness (usually inferred from the surrogate of unresponsiveness) or amnesia.

In an effort to develop a standard expression for the anaesthetic concentration at which consciousness might be regained, Stoelting et al. introduced the concept of 'MAC-awake'. An appropriate voluntary response (e.g. eye-opening) to verbal command was considered a positive response that indicated the presence of consciousness; MAC-awake was then defined as the anaesthetic concentration needed to suppress a voluntary response to verbal command in 50% of patients [18]. It was determined by averaging anaesthetic concentrations in research participants that just permitted and that just prevented a positive response during recovery from general anaesthesia. While the ratio of MAC-awake to MAC varies considerably across different volatile agents, it is comparable for the commonly used volatile anaesthetics isoflurane, sevoflurane and desflurane (Table 1). Clinically, the ratio describes emergence from anaesthesia; a ratio closer to

Table 1 Minimum alveolar concentration (MAC) and MAC-awake values for commonly used inhaled anaesthetic agents for 40-year-old humans.

Agents	MAC*	MAC-awake*	MAC-awake/ MAC
Halothane	0.76	0.41	0.55
Isoflurane	1.15	0.49	0.38
Sevoflurane	2	0.62	0.34
Desflurane	6	2.5	0.34
Nitrous oxide	105	68	0.64

*values expressed as percentage at 1 atmosphere.

1 signifies patients will recover responsiveness sooner, i.e. at relatively higher anaesthetic concentrations or MAC equivalents (e.g. ~ 0.5 MAC for halothane vs ~ 0.3 MAC for desflurane). Yet, despite its use as a surrogate, 'unresponsiveness' does not always indicate 'unconsciousness'. Furthermore, MAC-awake studies have been conducted with volunteers who were not exposed to noxious stimuli. Therefore, anaesthetic concentrations at MAC-awake during surgical stimulation do not necessarily imply that 50% of patients are unconscious; they may only be unresponsive in the absence of noxious stimulation.

Amnesia is also a clinically important effect of general anaesthetics. Memory can be divided into explicit (conscious) and implicit (unconscious) recall, with explicit recall being further subdivided into episodic (memory of events) and semantic (memory of facts about the world). The primary goal of anaesthetists regarding memory is to suppress explicit episodic memory of surgical or procedural events, which is the form of peri-operative memory that has been associated with post-traumatic stress disorder [19]. Although less-well studied, the anaesthetic concentration required to suppress recollection of a noxious stimulus in 50% of patients (MAC-amnesia), is theoretically important both to the patients and the practitioners. Studies have demonstrated that the alveolar concentration of volatile anaesthetics at which amnesia is achieved is lower than MAC; however, there is probably more interpatient variability for MAC-amnesia [20, 21]. Human and animal studies suggest that the concentration required to prevent explicit recall varies substantially among volatile anaesthetic agents. A rodent study demonstrated that the amnesic potency differed significantly for five inhalational anaesthetics, ranging from 0.06 MAC to 0.3 MAC [21]. Amnesic potency followed the Meyer-Overton relationship; nitrous oxide was the most potent amnesic agent relative to its MAC and halothane was the least potent amnesic agent relative to its MAC [21]. Interestingly, this result was not replicated by a human study in which nitrous oxide was found to be far less potent at suppressing memory than isoflurane [22]. Anaesthetics are therapeutically useful because at sub-hypnotic doses, both volatile and intravenous agents often prevent consolidation of episodic memories [21, 23]. Even if patients are occasionally aware and have untoward experiences during surgery, it is possible that they will not remember these experiences at anaesthetic concentrations exceeding MAC-amnesia. Whether or not it is ethically acceptable for patients to experience intra-operative distress, without explicitly remembering the experience postoperatively, is a subject of heated debate [24–26]. Importantly, the concentration required to prevent recall of painful stimulation may be considerably higher than that required for the verbal stimulus often used in studies investigating amnesic potency [22, 27].

Another derivative of MAC is the minimum alveolar concentration of volatile anaesthetic that blocks autonomic responses to surgical incision in 50% of patients (MAC-BAR) [28]. The autonomic responses commonly used to define MAC-BAR are changes in pupil dilation, heart rate and blood pressure. Autonomic blockade can be accomplished to varying extents; MAC-BAR is therefore an estimate at best. Various other MAC measures, such as MAC for tracheal stimulation or reflex pupillary dilatation, have also been explored [29, 30], but have the same limitations as MAC-BAR in relation to precision of the outcome measure.

We return to the discussion of MAC-awake to illustrate an important point regarding the neurobiology of anaesthetic induction and emergence. It is often assumed that the measure of MAC-awake reflects the MAC at which one both loses and regains consciousness. However, this assumption is not necessarily valid. MAC-awake is the alveolar concentration of volatile anaesthetic at which 50% of patients remain unresponsive to verbal commands when anaesthetic concentration the *decreased* (the emergence pathway). MAC-unawake would then be the alveolar concentration of volatile anaesthetic at which 50% of patients

remain responsive to verbal commands when anaesthetic concentration is *increased* (the induction pathway). Anecdotal experience with patients, theoretical models and compelling murine and fruitfly data suggest that these processes might not be mirror images; there is an observed hysteresis between the induction and emergence pathways [31] (Fig. 3). The concentration of anaesthetic required to achieve unresponsiveness or immobility at induction is often much higher (e.g. two to three times) than the concentration of anaesthetic at which the mice or fruitflies start to respond or move at emergence [31]. The path-dependent dose-response curves also illustrate greater variability in responsiveness to anaesthetic concentration for emergence than for induction. Thus, anaesthetic concentration predicts loss of responsiveness much more reliably than recovery of responsiveness.

Although conceived independently, the concept of 'neural inertia' bears relevance to the interpretation of

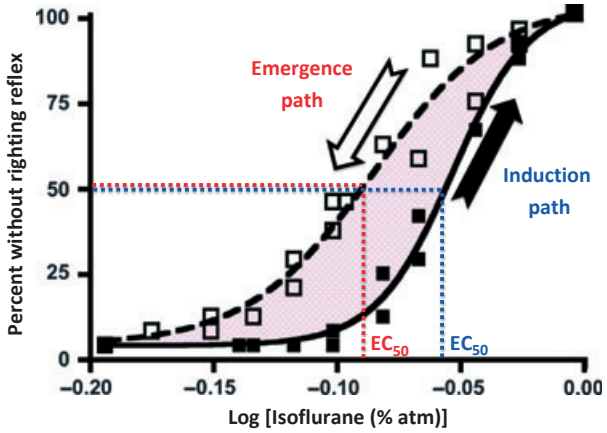

Figure 3 Relationship between isoflurane concentration and absence of righting reflex during induction of and emergence from anaesthesia in wild-type mice. This figure, which was modified from a figure by Friedman et al. [31], shows that there is a hysteresis between the induction and emergence pathways in wild-type mice. During induction of anaesthesia, a higher isoflurane concentration is required to achieve loss of the righting reflex than the isoflurane concentration at which the righting reflex returns during emergence from anaesthesia. Effective concentration 50 (EC_{50}) on the induction path corresponds to the concentration at which 50% of mice lose the righting reflex. Effective concentration 50 (EC_{50}) on the emergence path corresponds to the concentration at which 50% of mice regain the righting reflex.

MAC. Neural inertia has been defined as an intrinsic resistance to state transitions such as the induction of or emergence from general anaesthesia. It is now clear that the neurobiological substrates of these two processes are distinct and, as mentioned previously, that the hysteresis between 'going under' and 'coming out of' anaesthesia is not simply a matter of pharmacokinetics. Thus, the anaesthetic concentration at which consciousness is lost in humans (MAC-unawake) is likely to be higher than the anaesthetic concentration at which they will regain consciousness (MAC-awake).

From a practical standpoint, a gap between MAC-unawake and MAC-awake in anaesthetised patients could provide a safety cushion. When anaesthetic concentration falls slightly below the concentration at which induction occurred, the majority of patients might remain unaware and unresponsive. On the other hand, patients who had collapse of the hysteresis referred to previously (i.e. MAC-awake and MAC-unawake converge) or those who are resistant to the amnesic actions of anaesthetic agents could be at increased risk for intra-operative awareness with post-operative explicit recall. It is also possible that intense noxious stimulation could shift the MAC-awake and MAC-amnesia curves such that wakefulness and memory consolidation could occur at higher than expected concentrations of volatile anaesthetic agents. This emphasises the theoretical importance of trying to minimise noxious stimuli during general anaesthesia with appropriate supplementary analgesic strategies (e.g. regional anaesthetic techniques, multimodal analgesics).

Neurobiology of MAC

Motivated by the concept of MAC, investigators probing inhaled anaesthetic mechanisms sought to determine how these agents might produce immobility [32]. The lack of an obvious association between cortical electrical activity (e.g. measured by electroencephalography-based monitoring) and immobility to noxious stimuli suggested that inhaled anaesthetics might suppress movement by action at sites other than the cortex alone [33]. Studies suggested that immobility, as measured by MAC, is mediated by the action of inhaled anaesthetics on the spinal cord [34–37]. Several in-vivo studies in goats demonstrated that, when

preferentially delivered to the brain, the partial pressure of anaesthetic agent required to suppress movement was greater than when delivered to the whole body. Separating perfusion of the spinal cord and brain, and delivering anaesthetic agent preferentially to the brain, increased MAC for isoflurane from 1.2% to 2.9% [34]. An analogous study demonstrated a similar increase in MAC for halothane from 0.9% to 3.4% [35]. This increase in MAC with preferential delivery of volatile anaesthetic agent to the brain suggested an alternative primary site of action for volatile anaesthetic-induced immobility. Complementary studies in rats introduced lesions in the central nervous system (CNS) to sever connections between the spinal cord and the brain, such as precollicular decerebration and spinal cord transection at the thoracic level; neither of these lesions altered MAC [36, 37]. The lack of movement in these rats was produced by inhaled anaesthetic concentrations similar to controls, suggesting that the primary site of action is the spinal cord [36, 37]. Evidence suggests that anaesthetics suppress both sensory processing of noxious stimuli and motor-neuron reflex responses to prevent movement [38, 39]. Both animal and human studies have found that volatile anaesthetics depress spinal motor-neuron excitability, which is a possible mechanism by which they suppress movement in the setting of noxious stimuli [40, 41].

While the spinal cord largely mediates anaesthetic-mediated immobility, the actions of these agents in subcortical and cortical brain regions mediate amnesia and hypnosis. A study of healthy volunteers receiving sub-MAC concentrations of isoflurane found suppression of learning and memory at concentrations lower than those suppressing responsiveness and movement [23]. Studies of animals and humans have identified regions of the brain, such as the amygdala, hippocampus and cortex, that contribute to the formation of explicit episodic memory and may be targets for the amnesic effects of inhaled anaesthetics [42, 43]. Inhaled anaesthetics produce hypnosis by suppressing both arousal and subjective experience. Actions on subcortical structures, which modulate sleep-wake cycles, probably mediate effects on arousal. The actions of inhaled anaesthetics on thalamocortical and corticocortical networks are thought to inhibit subjective experience.

Factors that affect MAC

Many factors alter MAC, thereby increasing or decreasing the anaesthetic concentration required to prevent movement (Fig. 2). When a factor is present that increases MAC in an individual, volatile anaesthetics have decreased potency for that person. Thus, in the presence of these factors, patients will require a higher concentration of the volatile agent. Conversely, for factors that decrease MAC, the volatile anaesthetic agents have increased potency. In the presence of these factors, patients require a lower concentration of the volatile agent. It is important to qualify that factors that alter MAC might not similarly impact other MAC measures, such as MAC-awake, MAC-unawake, MAC-amnesia and MAC-BAR.

Physiological factors

Many physiological factors have been associated with alterations in MAC. For example, the concentration of anaesthetic agent required to suppress movement varies inversely with the age of an individual. Human studies have determined that MAC peaks at 6 months of age [44], after which it progressively decreases [45, 46]. A comprehensive meta-analysis determined the relationship between MAC and age could be described with reasonable accuracy by the following equation:

$$MAC_{age} = MAC_{40} \times 10^{-0.00269(age\ -\ 40)}$$

where MAC_{age} is the MAC at a given age and MAC_{40} is the MAC value at age 40 [46, 47]. Using this equation, charts outlining equipotent concentrations of volatile anaesthetics adjusted for age and concurrent nitrous oxide use have been developed to guide clinical practice (Fig. 4) [47]. Variations in body temperature have also been associated with differences in anaesthetic requirements. Studies in various animal models have demonstrated a positive linear relationship between temperature and anaesthetic requirement [48–50]. A murine model demonstrated that, for body temperatures of 32–37 °C, a decrease by 1 °C resulted in a 5% decrease in MAC for isoflurane [50]. The effect of temperature on MAC is hypothesised to be attributable to effects of temperature changes on cerebral oxygen consumption [51]. Elevations or reductions in serum sodium coinciding with changes in sodium concentration and osmolality in cerebrospinal fluid may alter anaesthetic

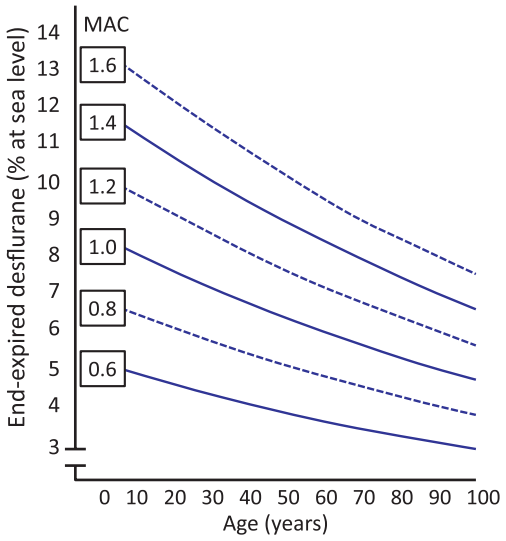

Figure 4 Age-adjusted iso-minimum alveolar concentration (iso-MAC) lines for desflurane. This is modified from a figure by Nickalls and Mapelson [47], which shows the effect of increasing age on the concentration (percentage at sea level) of desflurane required to achieve escalating MAC equivalents from 0.6 MAC to 1.6 MAC. Similar charts for all commonly used inhaled agents have been produced by Nickalls and Mapelson [47].

requirements. Hypernatraemia is associated with an increase in MAC, while hyponatraemia is associated with a decrease in MAC [52]. Several other physiological derangements, such as anaemia, hypercarbia and hypoxia, have also been shown to decrease MAC [53, 54]. The potency of inhaled anaesthetics is greater in women during pregnancy and in the early postpartum period, resulting in a decrease in MAC [55].

Preliminary studies have provided evidence for other factors that may affect MAC, notably genetic background [56, 57]. Small studies in mice and humans have suggested that mutations in the melanocortin-1 receptor (MCR-1) gene are associated with increased requirements for volatile anaesthetic agents, or increased MAC [58, 59]. Obesity has also been explored as a modifier of MAC, but a recent animal study modelling human metabolic syndrome demonstrated no difference in MAC compared with non-obese controls [60]. Consistent with other investigations, this study also supported genetic background, but not biological sex, as an important determinant of MAC.

Pharmacological factors

Drugs administered in the peri-operative setting often increase the potency of inhalational anaesthetic agents. For example, sedative-hypnotic agents, such as benzodiazepines and barbiturates, decrease MAC [61–64]. Midazolam premedication results in dose-dependent reductions in MAC [65]. Similar to benzodiazepines, other commonly used intravenous drugs that potentiate or activate $GABA_A$, including propofol, also decrease MAC [66]. Evidence suggests that non-GABAergic drugs such as ketamine and α_2-adrenergic agonists decrease MAC [67, 68]. Numerous studies have demonstrated reductions in MAC with the use of opioid analgesics [69]. Again, it is important to emphasise that these drugs might all alter MAC, but not similarly affect other MAC derivatives. For example, through their nociceptive actions, potent opioid analgesics might help to prevent movement in response to surgical stimulation, but might not as profoundly decrease the concentration of volatile anaesthetic required to achieve amnesia.

In addition to peri-operative anaesthetic and analgesic agents, acute or chronic use of various medications and substances of abuse also alter inhalational anaesthetic requirements. For example, drugs that increase catecholamine release in the CNS, such as cocaine, increase MAC during acute intoxication [70]. Canine studies demonstrated a dose-dependent increase of MAC for halothane following acute cocaine administration [71]. In contrast, chronic cocaine exposure is associated with a decrease in MAC for isoflurane [72]. Similar results have been demonstrated with acute and chronic amfetamine exposure; MAC increased in a dose-dependent manner with acute use and decreased with chronic use [73, 74]. Conversely, the results of several studies suggest that chronic ethanol use increases MAC, while acute ethanol administration decreases MAC [75–77].

Pathological factors

In general, patients presenting with a depressed level of consciousness due to trauma or cerebrovascular insult have decreased anaesthetic requirements. Pathological changes associated with dementia or other neuro-degenerative changes may also affect anaesthetic

requirements. A murine model of Alzheimer's disease demonstrated that the neuropathology associated with Alzheimer's disease confers a resistance to the hypnotic actions of inhaled anaesthetics [78, 79].

Advantages and limitations of MAC and MAC derivatives

Several studies before the introduction of MAC suggested that alveolar partial pressures would mirror brain partial pressures after a sufficient period of time. By combining the pharmacokinetics of inhaled anaesthetics with an important categorical response – movement – Eger et al. created a novel index of anaesthetic potency. As a dosing metric of anaesthesia, MAC has several advantages. Early studies demonstrated a small inter-individual variance in MAC. That is, for a given stimulus, the anaesthetic concentration required to prevent movement is similar from person to person. End-tidal concentrations are easy to measure in clinical practice and administered anaesthetic concentration relative to MAC can be tracked in real time. The caveat is that there are equilibration delays for all volatile anaesthetics (especially the more soluble vapours like halothane and isoflurane) between end-tidal levels and effect-site concentration. In contrast to previously proposed metrics of anaesthetic depth, MAC applies similarly to all inhaled anaesthetics and thus allows for ready comparison of potency. The ability to quantify MAC for various volatile anaesthetics allowed practitioners to compare and contrast side-effects with specific anaesthetics at MAC equivalent multiples (e.g. ½ MAC, MAC and 2 MAC). Equipotent concentrations of each agent influence organ systems including cardiovascular, respiratory and neuromuscular to differing degrees. The quantitative comparisons of these side-effects (e.g. effects on airway reactivity, blood pressure and heart rate) help to inform the choice of inhaled anaesthetic in clinical practice. Furthermore, the concept of MAC has aided investigation of factors that alter anaesthetic requirements and helped guide investigation into the mechanisms of action of inhaled anaesthetics.

Minimum alveolar concentration is a useful construct that has advanced clinical care and scientific investigation. However, it does have limitations. For example, MAC is not a reliable indicator of hypnosis or unconsciousness. The comparable metric for consciousness, MAC-awake, is also unreliable due to the behavioural component of the response. Anaesthetic concentrations that suppress goal-directed motor response to verbal stimuli do not necessarily produce unconsciousness, highlighting the distinction between responsiveness and consciousness. A recent review of studies using the isolated forearm technique (IFT), a method which spares one hand from the effects of neuromuscular blockers, reported that a median of 37% of patients demonstrated goal-directed responsiveness to verbal stimulation during general anaesthesia [26]. Of interest, spontaneous movement of the spared hand was rare (if not absent) in these patients, including those who reported pain. It is not known why a behavioural response was elicited by a verbal stimulus but not by the experience of noxious stimulus. These and other data that dissociate responsiveness and consciousness [26, 80] suggest that MAC – a measure of responsiveness – may not necessarily be informative regarding the state of consciousness. However, because loss of motor responsiveness occurs at a higher dose than loss of 'consciousness', MAC is a very good pragmatic end-point as it gives the anaesthetist reasonable confidence that the patient is likely to be unconscious.

One of the most notable limitations of MAC is that it is not directly applicable to the administration of total intravenous anaesthesia. Furthermore, modern peri-operative management incorporates various types of drugs, complicating the interpretation of MAC. The use of neuromuscular blockade to produce paralysis renders the concentration of inhaled anaesthetic required to suppress movement uninformative. While these drugs tend to decrease MAC they may not affect MAC-awake or MAC-amnesia in a parallel manner. Given that multimodal or balanced anaesthetic techniques (e.g. potent inhaled agent plus neuromuscular blocking drug plus opioid analgesic plus intravenous hypnotic agent) are commonly used, the utility of MAC as a 'pure' measure of anaesthetic effect is markedly curtailed.

MAC and clinical outcomes

Concentrations of inhaled anaesthetics, measured in MAC equivalents, have been used to study several clinical outcomes in surgical patients, such as intra-operative awareness with explicit recall (AWR) and

postoperative mortality. The former is a rare but feared complication of (inadequate) general anaesthesia associated with devastating psychological sequelae [81, 82]. Efforts to prevent AWR events have focused on attaining adequate depth of anaesthesia by adjustment of anaesthetic dosing in response to MAC or electroencephalographic measures. Several large randomised controlled trials compared protocols based on MAC and bispectral index (BIS) values in the prevention of AWR. In studies of patients at high risk for AWR, both protocols reduced the incidence of AWR from incidence rates previously reported in high-risk patients [83, 84]. The Michigan Awareness Control Study, a randomised comparative effectiveness trial conducted in more than 21 000 patients, was not able to detect a difference between MAC- and BIS-guided protocols [85]. Thus, across a wide spectrum of risk levels, MAC-based protocols may be useful in preventing AWR.

In a retrospective review of intra-operative data, the combination of concurrent low end-tidal levels (< 0.7 MAC) and low blood pressure (mean arterial pressure < 75 mmHg) and low bispectral index values (BIS < 40) was associated with an approximately four-fold increase in postoperative mortality [86]. It is not clear from this study whether the association with mortality of concurrent low end-tidal values, low BIS and low blood pressures (termed 'triple low' by the investigators) is causal or epiphenomenal [87]. Currently, there is no evidence to suggest that, within a clinically relevant range, volatile anaesthetic agents promote adverse outcomes [88]. Further studies are needed to clarify whether, based on concentration or patient vulnerability, volatile anaesthetics have the potential to increase serious morbidity or mortality unrelated to their cardiorespiratory side-effects. For example, there are studies that suggest that exposure to higher anaesthetic concentrations might increase the likelihood of postoperative delirium and cognitive decline [89, 90].

Conclusion

Despite its limitations, It remains the most commonly used measure of anaesthetic potency for inhaled drugs. It has withstood the test of time and prevails as the routine metric of anaesthetic depth almost 50 years since its description. Volatile-based general anaesthesia is the most common technique in both highly resourced and under-resourced care environments. Measurement of volatile anaesthetic concentration in real time is reliable, inexpensive and available around the world. Given its relatively narrow interpatient variability, MAC is a pragmatic surrogate for a meaningful anaesthetic end-point – absence of patient movement in response to surgical stimulation. Future candidate measures of anaesthetic depth will have to prove their superiority to MAC.

Competing interests

None of the authors has any relevant conflicts of interest or competing interests to declare.

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