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Cardiac output and the pharmacology of general anesthetics: a narrative review

El gasto cardíaco y la farmacología de los anestésicos generales: una revisión narrativa

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Abstract

The relationship between cardiac output and anesthetic drugs is important to anesthesiologists, since cardiac output determines the speed with which a drug infused into the bloodstream reaches its target and the intensity of the drug's effect. But rather than focus on how anesthetic drugs affect cardiac output, this narrative review focuses on how changes in cardiac output affect the pharmacokinetics and pharmacodynamics of general anesthetics during the three phases of anesthesia.

At induction, an increase in cardiac output shortens both the onset time of propofol for hypnosis and the neuromuscular blocking effect of rapid-acting neuromuscular blockers, favoring the conditions for rapid sequence intubation.

During maintenance, changes in cardiac output are followed by opposite changes in the drug plasma concentration of anesthetic drugs. Thus, an increase in cardiac output followed by a decrease in the plasma concentration of the anesthetic could expose the patient to a real risk of intraoperative awakening, which can be avoided by increasing the dose of hypnotic drugs.

At emergence, an increase in cardiac output secondary to an increase in pCO_2 allows for a more rapid recovery from anesthesia. The pCO_2 can be increased by adding CO_2 to the respiratory circuit, lowering the ventilatory rate, or placing the patient on partial rebreathing. Finally, the reversal action of sugammadex for rocuronium-induced neuromuscular block can be shortened by increasing the cardiac output.

Key words: Anesthetics, general; Anesthetics, intravenous; Blood circulation; Cardiac output; Pharmacokinetics; Anesthesiology.

Resumen

La relación entre el gasto cardíaco y los fármacos anestésicos es importante para los anestesiólogos puesto que el gasto cardíaco determina la velocidad con la cual un medicamento que se infunde al torrente sanguíneo llega a su diana y la intensidad del efecto del agente. Pero en lugar de concentrarnos en cómo los fármacos anestésicos afectan el gasto cardíaco, esta revisión narrativa se enfoca en cómo los cambios en el gasto cardíaco afectan la farmacocinética y la farmacodinámica de los agentes anestésicos generales durante las tres fases de la anestesia.

En el momento de la inducción, un incremento en el gasto cardíaco acorta tanto el tiempo de inicio del efecto del propofol para la hipnosis como el efecto del bloqueo neuromuscular causado por los bloqueadores neuromusculares de acción rápida, favoreciendo las condiciones para la intubación de secuencia rápida.

Durante la fase de mantenimiento, los cambios en el gasto cardíaco vienen seguidos de cambios opuestos en la concentración plasmática del medicamento de los agentes anestésicos. Por lo tanto, un aumento del gasto cardíaco, seguido de una reducción en la concentración plasmática del anestésico, podría exponer al paciente a un riesgo real de despertar intraoperatorio, lo cual puede evitarse aumentando la dosis de los fármacos hipnóticos.

En la educción, un aumento en el gasto cardíaco secundario al incremento en el pCO2 permite una recuperación más rápida de la anestesia. El pCO2 puede aumentar agregando CO2 al circuito de la respiración, reduciendo la tasa ventilatoria, o colocando al paciente en re-inhalación parcial. Finalmente, la acción de reversión de sugammadex en caso de bloqueo neuromuscular inducido por rocuronio, puede acortarse aumentando el gasto cardíaco.

Palabras clave: Anestésicos generales; Anestésicos intravenosos; Circulación sanguínea; Gasto cardíaco; Farmacocinética; Anestesiología.

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INTRODUCTION

The relationship between hemodynamic status and general anesthetic drugs has traditionally been addressed from the point of view of how anesthetic drugs impact the hemodynamic status, including cardiac output (CO). (1) However, this review examines the opposite approach, that is, how the effect of the general anesthetics is modified by changes in CO.

Following intravenous or inhaled administration, general anesthetic drugs enter the bloodstream, which serves as a vehicle for the drugs to reach their pharmacological targets so that they can exert their clinical effects. The time course of plasma drug concentration is related to the temporal pattern of clinical effect; therefore, the clinical effect could be influenced by any factor that alters the time course of the plasma concentrations. The hemodynamic status of the patient is a key factor, specifically cardiac output (2). Knowledge of this relationship allows for a better understanding of the interindividual differences observed in terms of the dose requirement of anesthetic drugs at induction and for maintenance of anesthesia, and in the variability existing both in the time of onset at induction, and the time to recovery at emergence.

Pharmacological models: compartmental versus recirculatory

The temporal pattern of plasma concentrations followed by any drug can be depicted by taking blood samples to monitor drug concentrations. From the concentrations, different mathematical models of varying complexity can be built.

Of these, compartmental models are the most well-known. In this model, the human body is considered to be made up of different compartments. Simply put, the fundamental premise is that drugs are infused into a static volume of blood. The main pharmacokinetic parameters are the apparent volume of distribution and the apparent plasma clearance. Both parameters can be easily calculated by dividing the dose of the drug administered by two non-actual concentrations; i.e.: the concentration at time zero, and at steady state. these concentrations can be calculated from the concentration-versus-time curve. The volume of distribution and plasma clearance are very useful in calculating the loading dose and the maintenance dose, respectively. However, the mathematical equations of the compartmental models have some limitations in the anesthetic setting (3), since changes in plasma concentrations and drug effects occur within minutes (4). For example, these equations do not allow for the calculation of the time elapsed between the drug administration and the onset of action; this is a key parameter when using hypnotics and neuromuscular blockers (NMB).

Although recirculatory models lack the former limitation, the mathematical equations are much more complex than those of the compartmental model. However, the advantages of recirculatory models are that not only can the key parameters for anesthetic management be calculated, such as the above-mentioned time to onset of effect, but also the time to reach the maximum plasma concentration and even the value of such concentration (5). The recirculatory models are based on the fundamental premise that drugs are infused into a dynamic blood flow (2,3,6-8); therefore, the time course of the plasma concentration is highly influenced by the hemodynamic status of the patient. Obviously, CO plays a fundamental role in this model. (2,5-12)

Cardiac output

Cardiac output is the volume of blood pumped by the heart in one minute; it is determined by the stroke volume (stroke volume depends on the preload, afterload, and contractility) and the heart rate. Prior to surgery, the patient's CO may vary due to various clinical conditions (preoperative anxiety, fever, pregnancy, heart failure, use of beta-blockers, etc.). During the maintenance and emergence phases of anesthesia, the CO could vary due to several factors, both pharmacological (atropine, ephedrine, beta-blockers, prostigmine, etc.) and nonpharmacological (bleeding, mechanical ventilation, laparoscopic surgery, pain, etc.). These variations could partially explain the interindividual variability observed in the dose-response relationship of anesthetic drugs. For instance, they may explain why anxious patients usually require higher doses of anesthetics for the induction of anesthesia than patients who received beta-blockers. (8,13,14)

This relationship also works in reverse. Anesthesiologists can intentionally vary the CO in order to adapt the dosage of the drug to the different anesthetic phases. Specifically, both the time required to obtain optimal conditions for orotracheal intubation in the induction phase (12,15) and the time required for emergence (16) can be shortened. In addition, the doses required for the induction and maintenance of anesthesia can also be reduced. (17)

The objective of this narrative review is to make anesthesiologists aware of how CO influences the effects of general anesthetic drugs in routine clinical practice. It is intended to provide a general view of this relationship, instead of delving into any specific aspect of this topic. To conduct this review, a search was conducted in Pubmed from inception to 2021 with no language restriction using the following key words, both alone and in combination: "cardiac output," "pharmacokinetics" "anesthetics, general" "anesthetics, intravenous" and " blood circulation". Then, secondary manual searching from the reference lists of papers considered most relevant for the topic was also implemented.

Both preclinical experiences in animals and clinical experiences in healthy volunteers and adult patients are discussed. Pediatric patients are beyond the scope of this work. Furthermore, this narrative

review does not address the influence of regional blood flow variations on the effect of general anesthetics nor the influence of CO on the duration of the effect of local anesthetics.

Influence of cardiac output on general anesthetics

The review is organized following the natural chronological order of the three anesthetic phases: induction, maintenance, and emergence.

Influence of cardiac output during the induction phase

Induction is the anesthetic phase in which the relationship between CO, plasma drug concentrations, and the time required until the effect of the drug occurs; this is the phase most widely studied. (7) This is logical, considering the historical anesthetic interest in achieving rapid sequence induction. (18)

Hypnosis

Propofol is by far the most widely used intravenous hypnotic. Thus, this section will focus on reviewing the relationship between CO and the pharmacokinetics and pharmacodynamics of propofol. The actual relationship is more complicated as propofol depresses CO: however, as already mentioned, how anesthetic drugs affect CO is a well-known topic beyond the scope of this review.

Relationship between cardiac output and the latency of hypnosis

Once in the bloodstream, the drugs will reach their targets faster the higher the CO concentration and the faster the blood flow rate; in theory, the time to onset of effect should be directly proportional to CO, and therefore, latency should be inversely proportional to CO. However, contrary to expectations, in a study in which propofol was administered to patients through short continuous infusions, the time to hypnosis was longer at higher CO. (15) To understand this apparently contradictory result, it must be taken into account that CO influences not only the speed at which a drug is transported through the blood but also the plasma concentrations achieved. In the context of continuous infusion, the higher the CO, the lower the plasma concentration; this is explained by the diluting effect of circulating blood on drug concentration (see the next section for further elaboration on this topic). Therefore, an increase in the CO will shorten the drug onset time only when the dose administered is large enough to overcome this dilutional effect (12).

Relationship between cardiac output and the dose needed to achieve hypnosis

Due to the dilutional effect, an inverse relationship is expected between CO and the peak arterial concentration reached after the infusion of a dose of propofol. While this inverse relationship has been demonstrated with theoretical mathematical models (19,20), it has also been observed in vivo in both animal models (21) and patients. (15) On a practical level, the obvious consequence is that the dose of propofol required to achieve hypnosis must be increased or decreased depending on whether the patient's CO is higher or lower, respectively. This proportional relationship between dose and CO has been experimentally confirmed in the anesthetic setting, since the doses of propofol required to achieve hypnosis were lower in patients pre-treated with esmolol (13) and higher in patients pre-treated with atropine (22) (Table 1).

There are everyday situations, such as preoperative anxiety, that favor a hyperdynamic state. Under such hyperdynamic conditions the propofol dose required for loss of consciousness should be higher than usual. (14) This is a logical assumption, since anxiety increases heart rate, which correlates well with CO in healthy subjects. Considering that a higher degree of preoperative anxiety predicts the need for an increase in the propofol dose required for anesthetic induction, it has even been suggested that the degree of

Table 1. Influence of drugs with the potential to change cardiac output on the hypnotic dose of propofol.

Reference	Subjects	Anaesthetic	Modifying Intervention	Comments
Wilson, et al. (13)	Patients (n = 60)	Propofol iv until loss of response to stimuli, using a TCI pump with target Cp = 10 µg/mL at 5 min	Esmolol 1 mg/kg bolus followed by 250 µg/kg/min iv (n = 20)	Compared with placebo, HR was reduced by 7.6 bpm in the esmolol group ($p < 0.02$). Propofol induction dose was significantly reduced by 25% with esmolol and 45% with midazolam compared with placebo.
			Midazolam 0.04 mg/kg bolus (n = 20)	
			Placebo (Saline) (n = 20)	
Takizawa, et al. (22)	Patients (n = 40)	Propofol TCI for Cp = 6 µg/mL, until loss of response to stimuli	Atropine 0.01 mg/kg (n = 20)	Compared with placebo, atropine significantly increased the required propofol dose by 9%.
			Placebo (Saline) (n = 20)	

CO: cardiac output; **Cp:** plasma concentration; **HR:** heart rate; **iv:** intravenous; **TCI:** target-controlled infusion. **Source:** Authors.

preoperative anxiety should be considered when adjusting the propofol dose (23).

Conversely, the propofol dose should be lowered in patients who have a hypodynamic state, such as those who are on long-term treatment with beta-blockers. In line with this, esmolol premedication has been found to reduce the propofol dose required for anesthetic induction by up to 25%. (13) Since esmolol can be used prior to induction to reduce cardiovascular stress from direct laryngoscopy, its use should be considered to adjust the induction dose of propofol.

NEUROMUSCULAR BLOCKING

Relationship between cardiac output and the latency of neuromuscular blockers

The onset of effect of NMBs is a key factor in rapid sequence intubation. For decades, succinylcholine has been the benchmark for a fast-acting NMB, but at the same time, there has been considerable interest in shortening the action time of nondepolarizing NMBs (NDNMB). Various strategies have been studied, such as increasing the doses, combining drugs, or administering priming doses. These techniques are generally safe, although they are not devoid of potential risks, such as the attenuation or even loss of the airway's protective reflexes (24).

The influence of cardiovascular status on the onset of action of NMBs has been extensively studied. The latency of NMBs is inversely proportional to CO and muscle blood flow. Therefore, the idea of intentionally increasing CO to make rapid-sequence intubation even faster is very appealing.

As for succinylcholine, it has long been known that the onset of its depolarizing action shows a linear relationship with blood flow velocity. (25) On this basis, the time to onset of effect can be reduced by administering ephedrine prior to induction (26,27) (Table 2).

Concerning NDNMBs, it is known that a pharmacologically driven increase (or decrease) in CO allows for a shortening (or lengthening) of the intubation time. This effect is mediated by an increase (or decrease) in blood flow velocity which, in turn, allows for an earlier (or delayed) arrival of the NDNMB at the neuromuscular junction. Furthermore, the cardiovascular drugs most frequently used to explore these relationships have been the indirect sympathomimetic agonist ephedrine (9,12,24,28-36) and the beta-blocker esmolol. (9,12) Ezri et al. (12) conducted a thorough investigation of these drugs in humans. The authors used a partial CO2 rebreathing technique to measure changes in CO after the administration of ephedrine (70 µg/kg) or esmolol (0.5 mg/kg) 30 s before the administration of rocuronium (0.6 mg/kg). They found that the time to onset of action of rocuronium was markedly shortened (by 35 s) in patients pre-treated with ephedrine, while it was markedly delayed (by 27 s) in those pre-treated with esmolol.

Regarding the effect on rocuronium in particular, numerous investigations have shown that the administration of ephedrine prior to induction reduces the latency of the onset of action of this NDNMB by up to 20-30% (9,12,24,28-30) (Table 2). More recently, two meta-analyses concluded that administration of ephedrine at doses of approximately 70-100 µg/kg one minute prior to the induction of anesthesia with propofol improved overall intubation conditions without causing adverse effects (37), and that pre-treatment with ephedrine would reduce the time required to achieve optimal intubation conditions with rocuronium by 22 s. (38)

Vecuronium, atracurium, and cisatracurium have been less investigated in this context because they are less suitable for rapid sequence induction; furthermore, the results are more controversial than the results for rocuronium. Regarding vecuronium, prior administration of ephedrine did not shorten the time to onset of effect in one report (31), but it did in two others (32,33). Of these latter two reports, ephedrine improved intubation conditions in one (32) and did not in the other (33) (Table 2). With cisatracurium, ephedrine shortened the time to onset of effect (34,36) and improved the intubation conditions (34,36). In contrast, the administration of ephedrine did not shorten the time to onset of effect of atracurium (30) (Table 2).

Overall, the disparity in the results found in the above-mentioned studies may be attributed to the fact that the time to onset of effect differs between all of these NMBs. Supporting this theory, the fast-onset NMBs succinylcholine and rocuronium showed homogeneous results, while conflicting results were found for the slow-onset NDNMBs vecuronium, atracurium, and cisatracurium.

Ephedrine was the most commonly used drug to improve the intubation conditions by modifying CO, and thus deserves additional elaboration. The dose most frequently used in the literature was approximately 70 µg/kg. (9,12,24,26-29,32-36) This dose has been shown to be high enough to increase CO without significantly increasing the heart rate or blood pressure. It has been suggested that, due to the weak sympathomimetic effect of ephedrine, venous constriction occurs to a greater degree than arterial constriction; this results in a redistribution of central blood with an improvement in venous return and, consequently, an increase in CO. (11) Doses as high as 210 µg/kg also improved intubation conditions (28,31,32,36), but these improved conditions came at the expense of clinically relevant increases in heart rate (30) and blood pressure. (32,36) The choice of ephedrine dose is especially relevant when dealing with patients with ischemic heart disease, in whom the risk of causing adverse cardiovascular effects should be carefully weighed against the benefit of improving intubation conditions. (28,29,32,36)

In addition to the dose, it is also important to establish the exact moment to administer ephedrine versus the other drugs for anesthetic induction and, in particular, with regards to the NMB. In most of the studies reviewed, ephedrine

Table 2. Influence of drugs with the potential to change cardiac output on the onset time and induction dose of depolarizing and non-depolarizing neuromuscular blockers.

Reference	Subjects	Anaesthetic	Modifying intervention	Comments
Ganidagli, et al. (26)	Patients (n = 50)	Succinylcholine 1 m/kg	Ephedrine 70 µg/kg (n = 25)	Compared with placebo, ephedrine caused a significant increase in HR and MAP 1 min after administration; shortened the onset time of succinylcholine by 38%, and shortened the time to OTI by 28%, although the OTI conditions were similar.
			Placebo (Saline) (n = 25)	
Belyamani, et al. (27)	Patients (n = 80)	Succinylcholine 1 m/kg	Ephedrine 70 µg/kg (n = 20)	There were no significant differences between groups in HR or MAP. Compared with placebo, ephedrine reduced the median time to OTI for succinylcholine by 43% and rocuronium by 29% and significantly improved the intubation conditions for both drugs.
			Placebo (Saline) (n = 20)	
		Rocuronium 0.6 mg/kg	Ephedrine 70 µg/kg (n = 20)	
			Placebo (Saline) (n = 20)	
Muñoz, et al. (24)	Patients (n = 60)	Rocuronium 0.6 mg/kg	Ephedrine 70 µg/kg (n = 30)	Compared with placebo, ephedrine shortened the onset time of rocuronium by 26%, without affecting the hemodynamic profile. The authors attributed such differences to variations in CO, yet it was not measured.
			Placebo (Saline) (n = 30)	
Szmuk, et al. (9)	Patients (n = 60)	Rocuronium 0.6 mg/kg	Ephedrine 70 µg/kg (n = 20)	Compared with placebo, the onset time of rocuronium was significantly reduced with ephedrine by 31% and prolonged with esmolol by 27%. The authors attributed such differences to variations in CO, yet it was not measured.
			Esmolol 0.5 mg/kg (n = 20)	
			Placebo (Saline) (n = 20)	
Ezri, et al. (12)	Patients (n = 33)	Rocuronium 0.6 mg/kg	Ephedrine 70 µg/kg (n = 11)	CO was measured by the partial CO_2 rebreathing technique. Compared with baseline, CO at 6 min showed minimal change in the placebo group, was significantly increased in the ephedrine group by 29%, and significantly reduced in the esmolol group by 30%. Compared with placebo, the onset time of rocuronium was significantly shorter in the ephedrine group by 40% and longer in the esmolol group by 31%.
			Esmolol 0.5 mg/kg (n = 11)	
			Placebo (Saline) (n = 11)	
Gopalakrishna, et al. (28)	Patients (n = 100)	Rocuronium 0.6 mg/kg	Ephedrine 75 µg/kg (n = 25)	The ephedrine groups showed significant elevations in HR and MAP for most of the study period, but the four groups were comparable in their 20% variations from baseline readings. Compared with placebo, OTI conditions were better with all doses of ephedrine, but statistical significance was only achieved at doses of 75 µg/kg and 100 µg/kg.
			Ephedrine 100 µg/kg (n = 25)	
			Ephedrine 150 µg/kg (n = 25)	
			Placebo (Saline) (n = 25)	

Reference	Subjects	Anaesthetic	Modifying Intervention	Comments
Han, et al. (29)	Patients (n = 75)	Rocuronium 0.6 mg/kg	Ephedrine 70 µg/kg 4 min and Saline 30 s before induction (n = 25)	Compared with the control group, the administration of ephedrine 30 s before induction shortened the onset time of rocuronium by a nonsignificant 10%, whereas there was a significant reduction of 20% when ephedrine was administered 4 min before induction.
			Saline 4 min and ephedrine 70 µg/kg 30 s before induction (n = 25)	
			Saline 4 min and Saline 30 s before induction (n = 25)	
Santiveri, et al. (30)	Patients (n = 80)	Rocuronium 0.6 mg/kg	Ephedrine 10 mg (n = 20)	HR increased significantly with ephedrine, and two patients had self-limiting sinus tachycardia (< 130 bpm). Regarding rocuronium: compared with placebo, ephedrine significantly shortened latency time by 17%, and onset time by 27%. Regarding atracurium: compared with placebo, ephedrine did not shorten either latency time or onset time.
			Placebo (Saline) (n = 20)	
		Atracurium 0.6 mg/kg	Ephedrine 10 mg (n = 20)	
			Placebo (Saline) (n = 20)	
Komatsu, et al. (31)	Patients (n = 53)	Vecuronium 0.1 mg/kg	Ephedrine 210 µg/kg (n = 27)	CI was measured using an impedance cardiography device. Baseline CI did not change after placebo but after ephedrine it significantly increased by 17%. Compared with placebo, ephedrine did not shorten the onset time of vecuronium., Ephedrine significantly increased HR and MAP, but without exceeding acceptable limits (100 bpm and 170 mmHg, respectively).
			Placebo (Saline) (n = 26)	
Kim, et al. (32)	Patients (n = 120)	Vecuronium 0.1 mg/kg	Placebo (Saline) (n = 30)	CI was measured by transthoracic echocardiography. Compared with placebo, all three doses of ephedrine significantly increased CI 1 min after OTI. Compared with placebo, all three doses of ephedrine shortened the latency of vecuronium, enhanced the neuromuscular blockade at the time of OTI, and improved the percentage of good or excellent OTI conditions, yet not all of these differences were significant. No cardiac arrhythmias were reported. The authors concluded that ephedrine 70 µg/kg had the best efficacy and safety profile for improving OTI conditions with vecuronium.
			Ephedrine 30 µg/kg (E30) (n=30)	
			Ephedrine 70 µg/kg (E70) (n=30)	
			Ephedrine 110 µg/kg (E110) (n=30)	
Anandan, et al. (33)	Patients (n = 60)	Vecuronium 0.09 mg/kg	Ephedrine 70 µg/kg (n=30)	Compared with the priming dose of vecuronium, ephedrine significantly reduced the latency of vecuronium by 27%. OTI conditions were similar in all groups. No arrhythmias or other adverse events were reported.
			Vecuronium priming dose 0.01 mg/kg (n=30)	

Reference	Subjects	Anaesthetic	Modifying Intervention	Comments
Albert, et al. (34)	Patients (n = 30)	Cisatracurium 0.15 mg/kg	Ephedrine 70 µg/kg (n = 15)	Compared with placebo, ephedrine significantly reduced the onset time of cisatracurium by 29%, and the percentage of patients with excellent OTI conditions was significantly higher by 86%. There were no hemodynamic alterations.
			Placebo (n = 15)	
Leykin, et al. (35)	Patients (n = 124)	Cisatracurium 0.145 mg/kg preceded 3 min before by a priming dose of 0.005 mg/kg	Ephedrine 70 µg/kg (n = 31)	60 s after cisatracurium, the percentage of OTI performed in less than 20 s was significantly higher in the ephedrine + priming group (100%) versus ephedrine alone (77%), priming only (74%), and neither ephedrine nor priming groups (64%). The percentage of patients who had good or excellent conditions for OTI was significantly higher in the ephedrine + priming group (100%) versus ephedrine alone (52%), priming alone (52%), and neither ephedrine nor priming groups (48%). The priming dose was well tolerated, and none of the patients experienced arrhythmias.
			Placebo (Saline) (n = 31)	
		Cisatracurio 0.150 mg/kg sin dosis de cebado	Ephedrine 70 µg/kg (n = 31)	
			Placebo (Saline) (n = 31)	
Cha, et al. (36)	Patients (n = 140)	Cisatracurium 0.15 mg/kg	Ephedrine 30 µg/kg (E30) (n = 35)	Compared with placebo, all ephedrine doses significantly shortened the onset time of cisatracurium by 31%, 32% and 33%, respectively. 90 s after cisatracurium, the percentage of good or excellent OTI conditions was higher with ephedrine, but the difference was only significant for groups E70 and E110. Five patients in the E110 group had very high blood pressure (>200/100 mmHg) after OTI.
			Ephedrine 70 µg/kg (E70) (n = 35)	
			Ephedrine 110 µg/kg (E110) (n = 35)	
			Placebo (Saline) (n = 35)	

CI: cardiac index; **CO:** cardiac output; **HR:** heart rate; **iv:** intravenous; **MAP:** mean arterial pressure; **NMB:** neuromuscular blocker; **ns:** not significant; **OTI:** orotracheal intubation; **TOF:** train-of-four.
Source: Authors.

was administered 30-60 s prior to the NMB. (9,12,24,27-29,32) However, it has been suggested that its effectiveness in accelerating the onset of action of NMBs could be further improved if ephedrine is administered a few minutes in advance since the maximum cardiovascular effect of ephedrine is reached after approximately 4 minutes. (29)

Influence of cardiac output during the maintenance phase

Similar to the induction phase, there is an inverse relationship between CO and propofol plasma concentrations during the maintenance phase. This relationship has been confirmed in animal models (10,11,39) and in clinical research of patients (17,40-43) (Table 3). Recently, Bienert et al. (44) conducted a clinical investigation of 22 patients undergoing abdominal aortic surgery under intravenous general anesthesia; their CO values were repeatedly measured using a pressure wave analysis system, and propofol and fentanyl concentrations were measured using chromatographic techniques. Despite the limitations inherent to the small sample size and because all the patients had some baseline deterioration in their hemodynamic status, these authors found a proportional relationship between CO values, anesthetic concentrations, and BIS values. Specifically, they found that the higher the CO, the lower the concentration of propofol and fentanyl and, consequently, the higher the BIS values. Inversely, this means that the lower the CO, the higher the concentrations of drugs and the lower the BIS values.

Awareness of such a relationship has important implications in routine practice, since it could allow for better management of the doses of anesthetics required to keep patients sedated or anesthetized. For example, patients treated with beta-

Table 3. Influence of cardiac output on hypnotic anaesthetic drugs during the anaesthetic maintenance.

Reference	Subjects	Anaesthetic	Modifying Intervention	Comments
Myburgh, et al. (10)	Animal model, sheep (n = 5)	Propofol 15 mg/min iv ci	After stabilization for 60 min, each animal randomly received the following infusions (separated by a 30-min washout period): Dopamine 10-20-40 µg/kg/min iv ci Epinephrine 10-20-40 µg/min iv ci Norepinephrine 10-20-40 µg/min iv ci	CO increased significantly with dopamine by 70%, with epinephrine by 70%, and with norepinephrine by 44%. Propofol baseline Cp were significantly reduced with dopamine by 53%, with epinephrine by 42%, and with norepinephrine by 63%.
Kurita, et al. (11)	Animal model, pigs (n = 13)	Propofol 6 mg/kg/h iv ci	Four 1-h phases: a) Initial baseline phase b) Hyperdynamic phase: Dobutamine 20 µg/kg/min iv ci c) Discontinuation of dobutamine and return to baseline d) Hypodynamic phase: Propranolol 2-4 mg iv bolus	Propofol Cp were measured by HPLC. CO was measured by thermodilution. Compared to baseline, dobutamine significantly increased CO by 33% and Cp decreased by 21%. After dobutamine discontinuation, CO decreased by 32% and Cp increased by 50%. Then, after propranolol CO further decreased by 34 % and Cp increased by 39%.
Kurita, et al. (39)	Animal model, pigs (n = 10)	Propofol 6 mg/kg/h iv ci (plus remifentanil 0.5 µg/kg/min iv ci)	Baseline: isoflurane 1.5% Phase 1: Stopping isoflurane 1.5% and starting dobutamine 20 µg/kg/min Phase 2: Stopping dobutamine and restarting isoflurane 1.5% Phase 3: Isoflurane dose doubled to 3%	Propofol and remifentanil Cp were measured by HPLC and LCMS, respectively. CO was measured by thermodilution. Propofol and remifentanil Cp rose or fell inversely proportional to the decrease or increase in CO in each of the three phases studied.
Takizawa, et al. (40)	Patients (n = 12)	Propofol TCI 2 µg/mL (plus nitrous oxide and sevoflurane)	Dopamine 5 µg/kg/min iv ci after infusing 10 mL of mepivacaine 1.5% by the epidural route (4 patients with SBP <80 mmHg received 4 mg of ephedrine).	Propofol Cp were measured by HPLC. CO was measured by indocyanine green injection. Compared with baseline, there was a significant increase in CO by 35% and a decrease in propofol Cp by 25%.
Ghosh, et al. (17)	Patients (n = 90)	Propofol iv ci for BIS 40-60 (plus nitrous oxide)	Metoprolol 100 mg (n = 30) Clonidine 200 µg (n = 30) Placebo (n = 30)	Compared with placebo, total propofol consumption to maintain the target BIS was significantly lowered after metoprolol by 25% and after clonidine by 35%.

Reference	Subjects	Anaesthetic	Modifying Intervention	Comments
O'Neill, et al. (41)	Patients (n = 7)	Propofol iv ci 25-150 µg/kg/min for BIS 50 ± 5 (plus remifentanil 25-100 ng/kg/min)	Isoproterenol 2-20 µg/min	From the start of isoproterenol, the BIS value increased by 11 points in a median time of 6.9 min. After infusion of a median isoproterenol dose of 25.2 µg, the median BIS value significantly increased from 46 to 64.
Ishiyama, et al. (42)	Patients (n = 43)	Sevoflurane 0.75% (plus ropivacaine 0.75% epidural, 5 mL bolus followed by 10 mL/h)	Ephedrine 0.1 mg/kg (n = 17) Phenylephrine 2 µg/kg (n = 17) Control; catecholamines were not administered if MAP did not fall > 30% from the pre-anaesthetic value (n = 9)	MAP was similar in the three groups, but ephedrine elicited a significant increase in HR. The ephedrine group showed higher BIS than the other two, and 7 patients with BIS > 60 needed an increase in the sevoflurane dose to avoid intraoperative awakening compared to none in the phenylephrine or control groups.
Moon, et al. (43)	Patients (n = 54)	Sevoflurane for BIS 50-60 (plus fentanyl)	Esmolol Bolus of 0.5 mg/kg followed by 30 µg/kg/min iv ci (n = 27) Placebo, same infusion (n = 27)	Compared to placebo, esmolol allowed a reduction in the mean dose of sevoflurane by 18%. Compared to placebo, the median total dose of fentanyl was significantly lower with esmolol by 50%.

BIS: bispectral index; **ci:** continuous infusion; **CO:** cardiac output; **Cp:** plasma concentration; **HPLC:** high-performance liquid chromatography; **iv:** intravenous; **LCMS:** liquid chromatography–mass spectrometry; **MAP:** mean arterial pressure; **SBP:** systolic blood pressure; **TCI:** target control infusion.
Source: Authors.

blockers would have lower anesthetic requirements for hypnotics such as propofol (13,17), inhaled anesthetics (43), and even opioids (39,42), which are important to avoid episodes of hypotension. Conversely, the administration of catecholamines to patients under continuous infusion of propofol caused an increase in BIS values, and patients presented with clinical signs suggestive of decreased depth of anesthesia. (40-42,45)

Remarkably, intraprocedural awakening from general anesthesia after exogenous administration of catecholamines was also reported. (46)

Theoretically, the above information should also be valid for newer drugs such as dexmedetomidine and remimazolam, though the effect of CO on their pharmacology has not been properly studied so far.

Influence of cardiac output on the emergence phase

In line with the arguments presented thus far, theoretically the emergence time from anesthesia could also be reduced by increasing CO, since it would accelerate both the clearance of anesthetics from the central nervous system and their redistribution to other tissues. (44) Historically, the most frequently used method to increase CO has been to simply modify the CO_2-end tidal pressure (EtCO2), since an increase in pCO_2 causes a further increase in CO. (47)

However, it is a common practice after inhalational anesthesia to increase the minute volume in order to hasten the elimination of halogenated anesthetics; and, consequently, pCO_2 tends to drop and results in the opposite effect. In addition, decreasing pCO_2 could have a negative impact on respiratory drive (48) and reduce the cerebral blood flow, thus lengthening the elimination time of anesthetics from the brain. (49) Theoretically, this limitation may be overcome by applying normocapnic hyperventilation, either by adding CO_2 to the system (49,50), or by using a rebreathing system to allow the patients to partially rebreathe expired air. (16,48) In a preclinical investigation in horses anesthetized with sevoflurane or isoflurane, the insufflation of a mixture of O_2 and CO_2 at concentrations of 95% + 5% or 90% + 10% was followed by a significantly shorter emergence time, especially in the case of isoflurane. (51) In patients undergoing inhaled anesthesia, avoiding postanesthetic hypocapnia and maintaining a situation of normocapnia or hypercapnia at the end of anesthetic maintenance was typically found to

significantly shorten the time to eye opening (16,48), the time to achieving normal BIS values (16,48,49), the time to tracheal extubation (16,48,49), and, ultimately, the time to emergence (16,48-50) (Table 4).

Intravenous anesthetics have been less studied in this context, even though it should technically be easier to achieve an increase in $EtCO_2$ as there is no need to balance the simultaneous removal of an inhalation agent. In patients who were anesthetized with propofol, a shorter emergence time was found in the subgroup of patients undergoing hypercapnic hyperventilation, which was obtained by adding CO_2 to the system, compared to patients undergoing normocapnic normoventilation. (49)

Pathophysiological knowledge suggests that normocapnia and hypercapnia should be associated with higher CO values than hypocapnia. This fact could explain the shortened emergence time found in the aforementioned investigations. (49) However, an important limitation of these preclinical and clinical studies is that CO values were not measured. Furthermore, in a recent report, Shinohara et al. (52) estimated CO values from heart rate and pulse pressure in patients under desflurane anesthesia. These patients were divided into two groups: normocapnia and hypercapnia, at the end of maintenance. Although CO was estimated and not actually measured, the hypercapnia group showed higher CO values both at desflurane discontinuation and at emergence from anesthesia. Additionally, the hypercapnia patients recovered spontaneous breathing before recovery of consciousness more frequently, and their emergence time was

Table 4. Influence of variations in the end-tidal carbon dioxide variations on the time to emergence.

Reference	Subjects	Anaesthetic	Modifying Intervention	Comments
Brosnan et al. (51)	Animal model, horses (n = 8)	Isoflurane (n = 8)	After discontinuing isoflurane, 100% O_2 was administered at 15 L/min	After anaesthesia with isoflurane, the time to standing was significantly shortened by 24% after adding both concentrations of CO_2. In terms of sevoflurane, time to standing was nearly the same with or without adding CO_2.
		Isoflurane (n = 8)	After discontinuing isoflurane, 95% O2 + 5% CO_2 was administered at 15 L/min	
		Isoflurane (n = 8)	After discontinuing isoflurane, 90% O2 + 10% CO_2 was administered at 15 L/min	
		Sevoflurane (n = 8)	After discontinuing sevoflurane, 100% O_2 was administered at 15 L/min	
		Sevoflurane (n = 8)	After discontinuing sevoflurane, 95% O_2 + 5% CO2 was administered at 15 L/min	
Vesely et al. (49)	Patients (n = 14)	Isoflurane (plus nitrous oxide)	Control: after discontinuing the anaesthetics, O_2 was administered at 10 L/min (n = 7)	pCO_2 remained at similar values in normocapnic hyperventilation and control groups despite the higher minute volume applied but time to extubation was significantly shortened by 70%. Normocapnic hyperventilation was well tolerated by the patients.
			Normocapnic hyperventilation: after discontinuing the anaesthetics, hyperventilation was started with a machine designed to maintain pCO_2 between 45 and 50 mmHg by adding CO_2, without rebreathing (n = 7)	

Reference	Subjects	Anaesthetic	Modifying Intervention	Comments
Sakata et al. (48)	Patients (n = 20)	Isoflurane	Hyperventilation to produce hypocapnia (pCO_2 = 28 mmHg) (n = 10)	Compared to hyperventilation with hypocapnia, partial rebreathing with hypercapnia significantly shortened time to eye opening, time to achieve normal BIS value, and time to extubation. Overall, recovery time was shortened.
			Partial rebreathing to produce hypercapnia (pCO_2 = 55 mmHg) (n = 10)	
Katznelson et al. (16)	Patients (n = 30)	Sevoflurano	Control: after discontinuing the anaesthetic, O2 was administered at 10 L/min (n = 15)	Compared to control normocapnic hyperventilation significantly shortened time to spontaneous breathing by 35%, time to eye opening by 58%, time to BIS > 70 by 55%, time to extubation by 50% time to leaving the operating room by 50%, and time to discharge from PACU by 26%.
			Normocapnic hyperventilation: after discontinuing the anaesthetic, hyperventilation was started with a machine designed to maintain pCO_2 between 45 and 50 mmHg by adding CO_2, without rebreathing (n = 15)	
Yaraghi et al. (50)	Patients (n = 80)	Isoflurane (n = 40)	Hypercapnic hyperventilation by adding CO_2 for an $EtCO_2$ of 45-50 mmHg (n = 20)	Isoflurane anaesthesia: compared to normocapnic normoventilation, hypercapnic hyperventilation significantly shortened time to recovery by 25% but not length of stay in PACU. Propofol anaesthesia: compared to normocapnic normoventilation, hypercapnic hyperventilation significantly shortened the time to recovery by 24% but not length of stay in PACU.
			Normocapnic normoventilation (n = 20)	
		Propofol (n = 40)	Hypercapnic hyperventilation adding CO2 for an $EtCO_2$ of 45-50 mmHg (n = 20)	
			Normocapnic normoventilation (n = 20)	
Shinohara et al. (52)	Patients (n = 46)	Desflurane	Normocapnia for an $EtCO_2$ of 30-35 mmHg (n = 23)	CO was estimated from HR and PP. Compared to normocapnia, hypercapnia showed a significant increase in CO at desflurane discontinuation by 50% and at emergence from anaesthesia by 36% whereas time to emergence was significantly shortened by 70%
			Hypercapnia for an $EtCO_2$ of 60 mmHg (n = 23)	

BIS: bispectral index; **EtCO2:** end-tidal carbon dioxide; **HR:** heart rate; **PACU:** post-anaesthesia care unit; **PP:** pulse pressure.
Source: Authors.

significantly shorter. The hemodynamic status was similar between both groups.

To the best of the author's knowledge, the influence of CO on neostigmine has not been studied. Concerning the new reversal agent sugammadex, two studies showed controversial results. In the first one, a high dose of sugammadex (8 mg/kg) was administered to patients receiving electroconvulsive therapy just after the elicited convulsion stopped; as expected, a significant inverse relationship between the onset time of rocuronium and CO was found, but the study failed to identify any relationship between recovery time from sugammadex and CO. (53) On the contrary, both the CO and the cardiac index were found to be inversely correlated with the speed of recovery from rocuronium-induced neuromuscular block after the administration of sugammadex (2 mg/kg) at the end of usual elective surgeries. (54) Maybe the different results could be explained on the basis of quite different doses and clinical conditions in which sugammadex was administered. In any case, what seems to be more relevant to the day-to-day practice of anesthesia is that the study conducted under usual anesthetic conditions did show a relationship between CO and sugammadex recovery time. (53) Based on that result, the onset time of sugammadex should be shortened by increasing the CO after increasing the pCO_2 with any of the above mentioned methods.

CONCLUSIONS

There is a close relationship between CO and the pharmacokinetics of general anesthetics; this is of great interest to clinical anesthesiologists for two main reasons. First, an in-depth knowledge of the variations in CO secondary to anesthesia and surgical processes could help to reduce the risk of anesthesia complications, such as a delay in the context of rapid sequence intubation or a decrease in the depth of anesthesia during the maintenance phase, representing a risk of intraprocedural awakening. Second, patients may benefit from intentional variations in CO to improve orotracheal intubation conditions and to hasten emergence from anesthesia. Overall, the role of CO in anesthesia deserves to be emphasized.

Author's contribution

MGP had the idea for the article, performed a first general literature search, wrote the first general draft, and critically revised the final work.

ESP conducted a deeper literature search focused on the induction phase and re-drafted the first version of this part, and critically revised the final work.

JVCR conducted a deeper literature search focused on the emergence phase and re-drafted the first version of this part, and critically revised the final work.

JÁMN performed a deeper literature search focused on the maintenance phase and re-drafted the first version of this part, and critically revised the final work.

All authors read and approved the final version of the manuscript.

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