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Sedation with Inhaled Anaesthetics in Intensive Care Units: Intravenous Route is not the Only Way

Toledo-Medina C, Rodriguez-Capitán M, Guerrero-Orriach Jose L*, Ramirez-Fernandez A, Malo-Manso A, Escalona-Belmonte J, Rubio Navarro M and Cruz Mañas J

Department of Anaesthesia, Hospital Virgen de la Victoria, Málaga, Spain

Abstract

The action and side effects of intravenous anesthetics are difficult to control in critical patients. The inhaled anaesthetic agents are, at the moment, an alternative to intravenous drugs for sedation in these patients. The Anesthetic Conserving Device (AnaConDa®) facilitates the use of volatile anesthetics in critical care units as part of prolonged sedation. This device (AnaConDa®) is a vaporizer that is integrated into the respiratory circuit, between the -piece and the patient. It consists of a heat-moisture exchanger filter. The volatile anaesthetic gas is applied continuously in liquid form using a syringe pump. During inspiration, the volatile substance is released via the evaporator and transported in such a way to the patient. During the expiration phase, the anaesthetic is exhaled by the patient and is stored in the carbon layer, followed by a rerelease into the gas mixture during the next inspiratory cycle. More than 90% of the anaesthetic gas is recirculated in such a way. 10% of the anaesthetic agent passes through the filter and is released outside through the fan expiratory outlet. The use of volatile anesthetics in critical patients could adopt a permanent position in various intensive care analog sedation concepts in future.

Keywords: Sedation; Anaesthetics; Benzodiazepines

Sedation with Inhaled Anaesthetics in Intensive Care Units

Sedation is an essential element in the treatment of Critical Care Units. Patients receive sedation for hours or days, mainly because of its dependence on mechanical ventilation [1-3]. The sedative drugs most commonly used in these Units are intravenous hypnotic drugs generally used and recommended in the Clinical guides [4,5]. However, its use in these patients poses a number of problems. On one side, the sedation level is hard to assess, intravenous sedation cannot be controlled by its plasmatic concentration, but by its effects [6]. On the other side, there seems to be some disadvantages and serious side effects. Therefore, propofol is limited for use up to 4 mg/kg/h and up to 7 days because of the risk of the propofol infusion syndrome. Furthermore, negative hemodynamic effects are observed especially in cardiac insufficient and hypovolemic patients. For benzodiazepines, an increased tolerance, possible accumulation after long-term use, and an increased risk of an acute withdrawal syndrome are described [7]. All this render the intravenous hypnotic drugs far from the ideal drugs.

The inhaled anaesthetic agents are nowadays an alternative to intravenous drugs for sedation. Among their main upsides, the gas concentration at the end of the expiration, (FEt), can be controlled, which represents a good indication of the drug concentration in the organ in question. On the other side, the minimum levels of metabolism and release, independently of the renal or hepatic function, together with the low levels of accumulation of the inhaled agents, provide great precision in the sedation control, with a faster action beginning and shorter and more previsible awakening times than after sedation with intravenous agents [6].

Another advantage lies in its pharmacodynamic effects. The halogenated agents have strong bronchodilator properties. Furthermore, administered at normal sedation doses, they provide a higher hemodynamic stability than intravenous drugs do.

Volatile anaesthetic drugs act mainly on the cerebral cortex and, even at low concentration levels, they are able to reach a total conscience depression level, and leave many autonomous functions unaltered. Respiration and intestinal motility are not depressed, facilitating modern therapeutic concepts such as early enteral feeding and augmentation of spontaneous breathing [6,7]. Protection from de consequences of ischemia in the heart, brain, kidney and other organs, may obviously constitute a major advantage for our patients and particularly for severely ill ICU patients with haemodynamic instability or circulatory failure [7].

Experience has shown that administration of the inhalational anaesthetic gases isoflurane and sevoflurane in intensive care units has been considerably simplified by the AnaConDa® device.

Anaesthetic Conserving Device: AnaConDa®

Today we have a device designed to administer inhaled volatile anaesthetic gases, isoflurane or sevoflurane, through a standard Intensive Care Unit ventilator, called AnaConDa® (ACD, sedana Medical AB, Uppsala, Sweden) (Figure 1).

This device is a vaporizer that is integrated into the respiratory circuit, between the Y-piece and the patient. It consists of a heat-moisture exchanger filter with additionally interwoven lipophilic active carbon fibers that absorb, store and rerelease the used volatile anaesthetic.

The volatile anaesthetic gas is applied continuously in liquid form using a syringe pump. It has a capacity of 50 ml of liquid anaesthetic. The anaesthetic agent bottle is connected to the syringe through a special adapter, thus avoiding leakage and environmental pollution.

***Corresponding author:** Guerrero-Orriach Jose L, Department of Anaesthesia, Hospital Virgen de la Victoria, Campus Universitario Teatinos C.P. 29010, Malaga, Spain, Tel: 0034951032217; E-mail: guerreroorriach@terra.com

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1. Port to monitoring expired anesthetic gas;
2. Connect to endotracheal tube;
3. Connect to the Y-piece of the circle system;
4. Anesthetic gas supply line;
5. Evaporator rod and vaporization chamber;
6. Antibacterial and hydrophobic filter;
7. Activated carbon filter.

Figure 1: Anaesthetic Conserving Device. AnaConDa ®

During inspiration, the volatile substance is released via the evaporator and transported in such a way to the patient. During the expiration phase, the anaesthetic is exhaled by the patient and is stored in the carbon layer, followed by a rerelease into the gas mixture during the next inspiratory cycle. More than 90% of the anaesthetic gas is recirculated in such a way [8].

10% of the anaesthetic agent passes through the filter and is released outside through the fan expiratory outlet.

This device reduces anaesthetic consumption at a level equivalent to that produced by an anesthesia machine with a circular system, using a fresh gas flow of 1.5 liters/minute [9].

Attention must be paid to adjustment of the temperature of the applied anaesthetic to the current ambient temperature; due to its high vapour pressure, if exposed to high temperatures, the volatile anaesthetic agent might evaporate and form undesired gas bubbles in the system. If the volatile anaesthetics accumulate in these bubbles, they may expand and thus render the dosage [10]. We only use syringes provided by the manufacturer, since these anaesthetic can dissolve the materials used in the standard syringes. We need to use a gas analyzer to measure the anaesthetic concentration inhaled by the end of the expiration phase. Is a single use device. Change is recommended after 24 hours, and then you must follow the usual antibacterial filter change protocol. Technical specifications are described in Table 1.

Gas Scavenging System

Benchmarks for workplace exposure are determined by a regulation of the National Institute of Occupational Safety and Health [11]. In 2005, the term "maximum allowable concentration" was replaced in Europe by "occupational exposure limit". This term measure in parts per million [ppm] is determined on a basis of an exposure of 8 hours per day for 5 days per week. The tolerated exposure limits are not uniform around the world. It is recommended by National Institute of Occupational Safety and Health that in case of isoflurane nobody should be exposed to more than 2 ppm of any halogenated agent [12]. A specific occupational exposure limit has not yet been determined for sevoflurane.

Because the AnaConDa™-system is an anesthetic gas recirculation system, 90% of the gas remains within the respiratory machine. The residual portion of 10% reaches the expiration outlet of the respirator, either via the gas monitor or directly via the respiratory apparatus. Hence there is a need to scavenge the anesthetic gas. To minimize occupational exposure, the expiratory port must be connected to an extraction fan of inhaled anaesthetic agent, which in turn is connected to the central vacuum system of the hospital; the aspiration is done with small negative pressures allowing high flows, if necessary [13]. Not all critic patient care units have this anaesthetic gases scavenging system; absorbent drums constitute an alternative for it. There are three types: Aldasorber, Novasorb and a contraflurano, all of them based on activated carbon filters. These systems are connected through a flexible pipe to the exhaled gas release valve of the respirator. You can only use a single inhaled agent per container, and these containers have to be replaced once they exceed the maximum allowed [12].

Sackey et al. [13] were able to demonstrate that the occupational load from the volatile anesthetic, in the presence of a central anesthetic gas scavenging system at the bedside, is minimal and within the international standard (mean of 0.1 ppm), using isoflurance.

Sedation with Anaconda® Device

Drugs commonly used for sedation and their main pharmacokinetic and pharmacodynamic characteristics are described in Table 2.

The AnaConDa® device can use isoflurane or sevoflurane as inhaled anaesthetic agent, but cannot use desflurane. With the use of desflurane, molecules do not reflect in the activated carbon layer, and they condense on the surface, due to the higher vapour pressure [6,7]. Most studies on inhalational sedation were performed with isofluarane. Isoflurane has been used for almost two decades in some centres in Great Britain, Canada and the US. Common indication is status asthmaticus and status espilepticus [7]. However, the physical, chemical and pharmacocynetic properties of sevofluorane, and its low blood /

Anaesthetic agents	Room temperature isoflurane or sevoflurane
Syringe	Only use Anaconda syringe REF 26022
Stability of filled syringe	7 days at room temperature and dark environment
Tidal volume working range	Minimun 350 ml
Anaconda dead space	Approx. 100 ml
Resistance to gas flow at 60 1/min	2.5 cm H_2O (250 Pa)
Efficiency of carbon filter at patient concentrations <2% of volatile agent at tidal volume: Vt 500 ml Vt 750 ml	Recirculation of exhaled concentration: Approximately 90% Approximately 80%
Moisture loss at : 0.75×12 breaths/min 1.01×10 breaths/min	5 mg/l (corresponding to 30 mg H_2O/l moisture output) 7 mg/l (corresponding to 29 mg H_2O/l moisture output
Filter capacity: Bacterial filtration Viral filtration	 99.999% 99.98%
Weight	50 g
Agent line length	2.2 m
Connectors (according to ISO 5356)	15F/22M-15M
Gas sampling port	Female Luer lock

Table 1: Technical Specification Device Anaconda® Instructions for use. Sedana Medical, Uppsala, Sweden Authors permission.

Inhaled Anesthetics						
		Nitrous Oxide	Halothane	Isoflurane	Desflurane	Sevoflurane
Pharmacokietics	Partition coefficient blood/gas	0.47	2.4	1.4	0.42	0.65
	Partition coefficient brain/blood	1.1	2.9	2.6	1.3	1.7
	MAC %	105	0.75	1.2	6.0	2.0
	Metabolism	0.004%	15- 20%	0.2%	0.1%	2- 3%
Pharmacodynamics	Cardiovascular	↑ SNS BP, HR, SVR, CO unchanged	↓↓ BP ↓HR ↓CO	↓↓SVR ↓↓BP ↑HR CV	↓↓SVR ↓↓BP CO unchanged/↓ HR unchanged/↑	↓BP HR unchanged ↓SVR ↓CO
	Respiratory	↑ RF ↓ Vt ↑ Pa CO_2 ↑ PVR	↑↑ RF ↓↓ Vt ↑ Pa CO_2 BD	↑ RF ↓↓ Vt ↑ Pa CO_2 BD	↑ RF ↓ Vt ↑↑ Pa CO_2 airway irritant	↑ RF ↓ Vt ↑ Pa CO_2 BD
	Cerebral	↑ CBF ↑ IP ↑ VO_2	↑↑ CBF ↑↑ IP ↓ VO_2	↑ CBF ↑ IP ↓↓ VO_2	↑ CBF ↑ IP ↓ VO_2	↑ CBF ↑ IP ↓ VO_2
	Renal	↑RVR ↓↓RBF ↓↓GF	↓↓ RBF ↓↓ GF	↓↓ RBF ↓↓ GF	↓ RBF ↓ GF	↓ RBF ↓ GF

Intravenous Anesthetics						
		Propofol	Midazolam	Etomidate	Ketamine	Thiopental
Pharmacokinetics	Vdss (l/Kg)	2.8	1.1	2.5	3.1	2.3
	Clearing ml/Kg/min	59.4	7.5	17.9	19.1	3.4
	T ½ distribution min	2-4	7-15	2-4	11-17	2-4
	T ½ elimination min	0.9	2.7	2.9	3.1	12
	Protein union	97	94	77	45	83
	MEC	1.1	0.16	0.31	0.5-2	19.2
Pharmacodynamics	Cardiovascular	Vasodilator Negative inotropic (↓ BP, CO, SVR) ↓CF y VO_2 miocardial	Minimal effects (↓ PVR ↓ BP)	Minimal effects	↑BP, HR, CO, SVR PAP y VO_2	Negative inotropic Venodilator
	Respiratory	Apnea BD Laringuel reflexes depression	Respiratory depression ↓ Vm y Vt	Minimal effects on ventilation	No effects on ventilation Maintains laryngeal reflexes BD	Respiratory depression Maintains airway reflexes
	Cerebral	↓CBF, VO_2, IP, CPP	↓VO_2 y CBF Disinhibiion	↓CBF, VO_2, IP	↓CBF, VO_2 IP	↓CBP, VO_2, IP Protects against focal cerebral ischemia
	Other effects	Propofol infusión syndrome	Tolerante Pharmacological roof	Adrenocortical suppression	Psychic disorders	AIP, APV crisis

MAC: Minimum Alveolar Concentration; **SNS:** Sympathetic Nervous System; **BP:** Blood Pressure; **HR:** Heart Rate; **SVR:** Systemic Vascular Resistance; **CV:** Coronary Vasodilator; **CO:** Cardiac Output; **RF:** Respiratory Frequency; **BD:** Bronchodilator. **Vt:** Tidal Volume; **Pa CO_2**: CO_2 arterial pressure; **PVR:** Pulmonary Vascular Resistance; **CBF:** Cerebral Blood Flow; **IP:** Intracranial Pressure; **VO_2**:oxygen consumption; **RVR:** Renal Vascular Resistance; **RBF:** Renal Blood Flow; **GF**: Glomerular Filtration Rate; **Vss**: Volume of Distribution; **T½ distribution**: distribution half life; **T½ elimination:** elimination half-life; **PVR:** Peripheral Vascular Resistance; **MEC:** Minimum Effective Concentration; **CF:** Coronary Flow; **CPP:** Cerebral Perfusion Pressure; **Vm:** minute volume; **AIP:** Acute Intermittent Porphyria; **APV:** Acute Porphyria Variegate

Table 2: Inhaled and Intravenous Anaesthetics Used in Sedation.

gas partition rate and low solubility rate in fats provide induction speed, control and faster recovery than the isoflurane. Nevertheless, due to their hepatotoxicity and nephrotoxicity caused by fluorine, residual consequence of its metabolism, its use is limited to those procedures under 12 hours. For this reason, the use of sevofluorane still has some controversial aspects regarding long term procedures; isoflurane could be in this case the agent of choice.

The fractional exhaled (FEt) in cases of inhaled sedation must be slightly higher than the minimum alveolar concentration- awake (MAC-awake). It could be defined as 1/3 of the MAC which prevents movement in case of a supramaximal stimulus. The MAC-awake values are 0.4% for isoflurane and 0.6% for sevoflurane [6].

Currently, it's recommended a contributing treatment with low dose opiates, less than half of the dose used for intravenous sedation.

Priming of the anaesthetic agent line should be performed before the AnaConDa® device is connected to the patient. This is done by operating the syringe pump at 25 ml/h; it takes 1.2 ml of fluid to flush

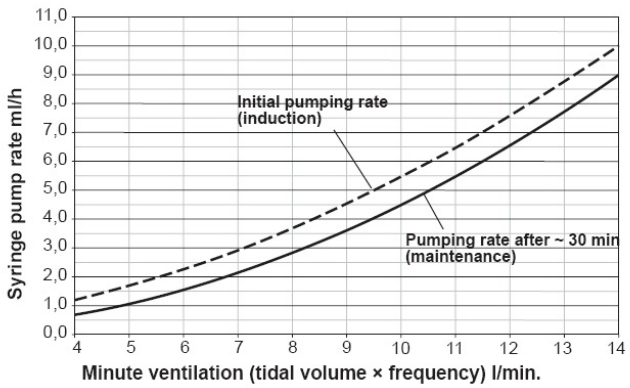

Figure 2: Required Syringe Pump Rate to Reach 0.5% Gas Concentration at Different Minute Volumes.

the line, that is, 2.5 minutes at 25 ml/h [6,7].

In order to administer inhaled anaesthetic agents with the AnaConDa® device, the manufacturer recommends in the instructions manual an infusing table summarized in Figure 2. According to this table, an initial infusion rate is used to reach the desired anaesthetic fractional exhaled (FEt) and, afterwards, the infusion rate is reduced to keep that concentration level. Therefore:

Induction: apply the upper curve in Figure 1 for setting the correct pump speed. Use this setting until correct concentration is reached.

Maintenance: upon reaching the desired concentration, adjust the maintenance value of the pump according to the lower curve in Figure 1.

Concentration modification

The relationship between the concentration and the pump rate is practically linear. If speed is doubled, concentration is doubled too. The following formula can be used to calculate the new pump rate: (current syringe flow rate/current concentration)×desired new concentration=New syringe flow rate.

After changing the flow, wait 10-15 minutes before performing new modifications. If you need to change the concentration quickly, disconnect the AnaConDa® device from the patient.

However, this guide provided by the manufacturer is only a guide, not based on any pharmacocynetic model including any absortion and distribution characteristics for inhaled anaesthetic agents.

In this respect, Belda et al. recommend a dosing table for sevoflurane, if this is the selected agent, built following a pharmacokinetic model based on the classic Lowe model. In order to get the total infusion volume per hour, the model includes two components: the anaesthetic agent given to the patient, estimated according to a nine-compartment model, and the anaesthetic agent loss through the AnaConDa ® device. The calculation of the losses occurred through the AnaConDa® filter includes two determining factors: the ventilation per minute of the patient and the anaesthetic agent FEt. Once the model had been developed, a clinical study was carried out in fifty sevoflurane-sedated patients for six hours in the Intensive Care Unit, in order to determine the predictability. It showed a global precision level of 3.8%, with a negative variation of 2.4%, and it was much more precise than any other infusion algorithm controlled and used for intravenous drugs. Generally, in the case of sevoflurane, with an infusion rate of 2-8 ml/h gets an anaesthetic concentration of 0.5% at the end-tidal (FET); for isoflurane, an infusion rate of 1-3 ml/h will get a concentration of 0.3-0.5%. These values are sufficient to achieve adequate sedation. After 10-20 minutes of infusion, values of anaesthetic concentration at the end of the expiration phase become stable, and after 60 minutes, in order to maintain the adjusted FEt, the infusion rate should be slightly decreased during the next 2-4 hours. From that moment on, the infusion rate rarely needs to be modified [6].

During maintenance, if required, bolus of anaesthetic agent can be applied. These should be of 0.1-0.2 ml maximum, and it is possible to repeat the application after 5 minutes, if necessary. If you want to quickly reduce the concentration administered, you should stop the infusion pump. For faster removal, you can remove the Anaconda ® device and have it replaced by a bacterial filter / standard humidifier [7,12]. Finally, you need to stop the pump, disconnect the device from the patient, beginning with the Y-piece, disconnect the gas monitor, shut off the gas monitor with the lid pointing to the gas inlet probe, close the device connectors with red tops, disconnect the agent supply line of the AnaConDa ® syringe and close the syringe with the cap provided.

Clinical Experience with Inhaled Agents-New Lines of Research

Clinical experience with the AnaConDa® device is limited. Most clinical studies concern themselves with the use of isoflurane.

Korth and Opitz [14] evaluated 20 ventilated patients following sedation with isoflurane (2-27 days) and, apart from a clearly improved sedation quality and reduction in bronchial spasticity, could not detect any clinically relevant changes in the serum fluoride concentrations.

Kong et al. [15] investigated 60 ventilated patients. The patients of the isoflurane group could be extubated significantly earlier (60 minutes; 30-135 minutes range) than with the midazolam sedation (195 minutes; 50-1080 minutes range). The desired level of sedation could be achieved in 86% of the patients under isoflurane and only 64% of those under midazolam.

Spencer and Williams [16] found similar findings; surgical and medical patients were sedated for a mean period of 30 hours with isoflurane (0.1-0.4 vol%) or midazolam (1.5-7.3 mg/h). They also ascertained that the patients sedated with isoflurane recovered much more rapidly (10 vs. 90 minutes) and could be weaned off the respirator sooner than the patients sedated with midazolam (0.9 vs. 15 hours). There were no differences between the 2 groups at any time in terms of sedation quality.

Tempia et al. [9] evaluated 81 patients during surgery under general anesthesia. Sevoflurane consumption and fresh gas flow when using the AnaConDa® is comparable with low-flow anesthesia.

Soukup et al. [17] evaluated 23 patients sedated with sevoflurane. Duration of sedation was of 94.9 ± 55.9 hours, and the results were an easy to control, good sedation quality and awakening time of 13.3 ± 6.4 minutes.

New lines of research are being developed nowadays. There are studies pointing to the possibility of a pharmacological organ protection effect at the myocardial level, through the preconditioning and post conditioning phenomena, which would open new possibilities to therapies using anaesthetic agents in patients undergoing cardiac surgery.

Ischemic heart disease is a main cause of mortality and morbidity in the world. There are new strategies to maintain a balance between oxygen supply and myocardial demand in order to prevent perioperative ischemia. Volatile anaesthetics act as cardioprotective agents by reducing oxygen consumption at cardiac level.

The ischemic preconditioning is the phenomenon whereby a short duration sublethal stimulus causes myocardial protection, through an endogenous adaptation to low magnitude ischemic episodes, which produces a protection against an ischemic episode that normally might become letal [18]. The preconditioned tissues exhibit lower energy requirements, changes in energy metabolism and better electrolyte homeostasis. Besides, these tissues induce tolerance to reperfusion with lower release of reactive oxygen mediators and activated neutrophils, a reduced apoptosis and improved microcirculatory perfusion [19].

Cardioprotection in ischemic preconditioning is time-limited and is usually divided into two phases. The first phase, the faster one, is very powerful and is time-limited to 1 or 2 hours. The second phase occurs approximately 24 hours after the initial stimulus and offers lower protection but is maintained for 72 hours.

There is a possibility of pharmacologically inducing a myocardial protection effect offering a potentially beneficial alternative and without the risk of causing ischemia. There are multiple studies that have identified several substances with cardioprotective properties as agonists of the adenosine receptors, activators of protein kinase, opiates, volatile anaesthetics, ethyl alcohol, as well as natural substances such as acetylcholine, bradykinin, angiotensin II, norepinephrine, and platelet activating factor [20]. However, most of these substances are not used in practice because of the serious side effects they can cause or of their lack of clinical efficacy. Instead, halogenated agents have shown they can easily be used to induce preconditioning, offering a state similar to ischemic preconditioning and creating protection with an intensity comparable to that of ischemic preconditioning, decreasing also the cardiac dysfunction [21-23].

During the period of ischemia, the primary objective remains to limit the consequences of ischemia-reperfusion and the injury progression. The cardioprotective strategies during the ischemic phase will address the different mechanisms responsible for the damage: free radicals formation, calcium and deterioration of the coronary vasculature. This includes myocardial preservation through the modulation of intracellular gradients, activation of inhibitors of the complement system, activation of neutrophils and antioxidants, among many others. Most of these measures have been tested in experimental situations with different drugs, but none has shown a clinically relevant protective effect. From the point of view of anesthesia, few agents have outstanding direct protective action when administered during isquemia. Observational studies on cardiac surgery patients suggest propofol as a mitigating factor of the free radicals oxidation. It suppresses the neutrophil activity and reduces intracellular calcium concentration mediated by lipid peroxidation and systemic inflammation. For that reason, propofol has benefits during reperfusion, though does not confer preconditioning or postconditioning effects [24].

Ischemic postconditioning [25] is defined as the protection conferred to ischemic myocardium by preceding brief periods of subletethal ischemia separated by periods of reperfusion [26]. The postconditioning reduces reperfusion induced damage, reducing oxidative damage and attenuating the local inflammatory response during revascularization, thus reducing infarct size, reducing the process of apoptosis, the activation of neutrophils and the endothelial dysfunction. This process can also be pharmacologically induced, and is known as pharmacological postconditioning. In this case, volatile anaesthetics show cardioprotection when administered after ischemia, during the period of reperfusion [27].

It appears that the preconditioning and postconditioning triggers may have common characteristics, their key biochemical elements being the protection of the mitochondria and the reduction of inflammatory mediators, both of which would be developed in various ways [28].

The role of mitochondria in preconditioning and postconditioning appears to be the determinant factor in its effect on cell viability, mainly through the elevated reactive oxygen species (ROS) and intracellular calcium. The main place through which the damage in the mitochondria occurs is through its mitochondrial permeability transition pore (MPTP). In normal conditions or mitochondrial homeostasis, this pore is closed. There is therefore a good coupling between its components when its ATP-dependent potassium channels are closed. During ischemia and reperfusion MPTP opens, the inner mitochondrial membrane becomes permeable and, as a consequence, several events occur [29]. Intramitochondrial proteins cannot pass through the pore, colloid osmotic pressure increases and there is a swelling of the mitochondrial matrix. Membrane lysis occurs on the outer mitochondrial membrane, releasing proteins such as cytochrome c and apoptosis inducing factor. Furthermore, the inner mitochondrial membrane that becomes permeable to protons decouples the respiratory chain and results in decreased production of ATP. The opened MPTP being more prolonged than normal is mediated by caspases 3, 6 and 9 and the myocardial cell apoptosis. The opening of these channels appears diminished with postconditioning and, therefore, this would be one of the greatest benefits, acting as the mediating pathways for this to happen the ones discussed above, although it should be noted that almost all studies are performed in an animal model.

Postconditioning reduces coronary vascular endothelial activation, cytokine production, production of reactive oxygen species (ROS) and neutrophil adhesion. Within the various postconditioning-related mediators, bradykinins, which are precursors of kininogens at cardiac and vascular endothelium, stand out. Myocardial B1 and B2 receptors of bradykinins are associated with increased influence in hypoxic condition. Its influence in the myocardial cell is related to the protection that occurs in the postconditioning. Its administration in animal models has shown a decrease of the ischemic area. The mechanisms behind the effects of bradykinins seem to be the nitric oxide and prostacyclin. There are two groups of kinases also related to the effect of postconditioning. The RISK (Reperfusion Injury Salvage Kinase) group, that consists mainly of proteins (PI3, Akt and ERK1/2), and whose influence appear to be related to the reduction of infarct size in animal models by around 40%-50%, in situations where myocardial postconditioning was performed. Another group of kinases are the SAFE group (Survivor Activating Factor Enhancement), in which STAT3 and the effect it has on the receptor of tumor necrosis factor stands out, stimulating the protective effect on mitochondria. The protein kinases C and G have also been associated with protection from ischemia by postconditioning. Although the beneficial effect of the activation of protein kinase C has been demonstrated in animal models, the same conclusions were not reached in the case of protein kinase G that has been related to beneficial effects in the preconditioning [30].

The first study to suggest that the use of halogenated anaesthetics may have important clinical benefits took place in 2002. In this study the use of sevoflurane was associated with better preservation of hemodynamics and left ventricular function, with a reduction in

Troponin I release, compared to postoperative patients anesthetized with intravenous sedative [31,32].

De Hert et al. [30,31] also demonstrated cardioprotective effects (less postoperative TnIc release and postoperative cardiac function preservation evaluated through peptide NT-pro BNP) of a sevoflurane anaesthetic regimen, being greater when the volatile anaesthetic is administered throughout the entire surgical procedure, in comparison with the administration before or just after ischemia [33]. These data support the idea that the cardioprotective effects of anaesthetic agents depends on an interaction of factors such as application protocols, the choice of a specific agent, and the variables used to assess myocardial function.

The literature has shown successful use of AnaConDa® as a mechanism for sedation in patients in intensive care units, demonstrating its safety profile, its reproducibility and the easy effect prediction to ensure the level of sedation. Some works have shown the direct benefit of these agents on the myocardium against ischemia and reperfusion improving treatment outcomes, not only in patients undergoing cardiac surgery but also in patients with heart disease undergoing other surgical procedures.

Röhm et al. [32] were the first to publish results from the only randomized clinical study that compares sevoflurane administered with the Anaconda® device vs. propofol sedation in 70 patients after elective aortocoronary bypass surgery. The use of sevoflurane for postoperative short-term sedation showed that significantly shorter respiration times could be achieved and also that the length of stay in the intensive care unit, and in hospitals, could be reduced.

Hellsstrom et al. [33] examined the sedation with sevoflurane in postoperative myocardial revascularization patients with cardiopulmonary bypass compared to those sedated with propofol. It showed no significant differences in enzyme levels, or variables of morbidity or mortality in ICU stay. In this study, patients were randomized to each group regardless of the intraoperative anaesthetic technique.

Steuert et al. [34] evaluated patients sedated with propofol and sevoflurane after elective cardiac surgery. They found significant differences in enzyme levels, in favor of sevoflurane, though the same anaesthetic technique was used in all patients.

Soro et al. [35] studied the differences in enzyme levels after cardiac surgery in 2 groups of patients. Propofol or sevoflurane was used from the start of the intervention to extubation; it showed no significant differences [19,32,34].

Guerrero et al. [36] evaluated the effect of intra-and postoperative administration of sevoflurane versus propofol, comparing hemodynamic values and biochemical markers of myocardial damage and cardiac dysfunction during the first 48 hours after surgery. The patients selected were those on which an off-pump myocardial revascularization was performed. Patients were divided into 2 groups (propofol and sevoflurane). At the end of surgery, patients were transferred to the intensive care unit, where they were kept sedated for 6 hours until extubation. Sedation with sevoflurane in postoperative off-pump cardiac surgery is safe and maintains the beneficial effect of preconditioning with halogenated agents. This is demonstrated by the decrease in biochemical markers of myocardial damage and dysfunction in the sevoflurane group

Conclusion

The correct sedation of patients in the Intensive Care Units represents a challenge for the healthcare professionals working in this area. Due to their pharmacokinetic and pharmacodynamic characteristics, in normal sedation dose, the inhaled anaesthetic agents could well be the ideal sedative drugs.

The Anaconda ® device facilitates sedation with isoflurane and sevoflurane as inhaled anaesthetic agents in the Intensive Care Units, and has showed safety regarding patients and healthcare professionals exposed to those agents, through the gas scavenging system.

Some of the studies carried out to this day show the superiority of inhaled anaesthetics compared with intravenous agents. In this sense, there is some recent clinical evidence that favour the protective cardiovascular effects that these agents can provide through conditioning. This would allow to open promising new lines of research on organic protection against ischemic damage, such as, for example, those of myocardic conditioning.

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