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Perioperative and anesthetic deaths: toxicological and medico legal aspects

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Abstract

Background: Anesthesia has become safer during decades, though there is still a preventable mortality; the complexity of medical and surgical interventions, increasingly older and sicker patients, has created a host of new hazards in anesthesiology. In this paper, some of these perioperative (PO) fatal adverse events are investigated in terms of health responsibility. Selective literature research in several data bases, concerning perioperative and anesthetic deaths and medical responsibility, was performed.

Main text: A generally accepted definition of the anesthesia and perioperatory-related death still remains one of the major concerns in forensic pathology, and the terms "operative deaths" and "anesthetic deaths" are usually applied inaccurately within the medico-legal literature. Such events involve comprehensively PO fatalities and allow for subtle separation of natural and unnatural death, at least from the prospective of forensic pathology. Iatrogenic deaths in this field can be separated into some major categories, as attributable to previous patient's unfavorable conditions or depending from surgical procedure per se (such as PO cardiac and cerebrovascular events). In this review, the authors carried out syntheses of specific research areas regarding epidemiology, complications of general and spinal anesthetic, failure in airway management and patient's circulatory homeostasis, and adverse drugs reactions; analysis considering the challenge of anesthetic-related mortality, epidemiology and classifications, by indicating causal chain of death, in respect of both contributing and associated anesthetic and surgery facts.

Conclusions: Perioperative quality control programs and its relevance for medico-legal evaluation are emphasized as, although mortality rates have decreased worldwide over the last decades, however, preventable drug-related deaths still happen. Such fatal events have to be considered within the field of forensic pathology experts, with regard of malpractice claims, to implement a strategy for preventing potentially fatal complications.

Keywords: Anesthesia, Causal chain, Drugs, Epidemiology, Errors, Fatalities, Medico-legal, Responsibility, Surgery

Background

It is believed that the first case of death related to anesthesia happened in 1847, as a consequence of pulmonary unrecognized pulmonary disease caused by the administration ("ab ingestiis") of brandy administered to counter the effects of inhaled chloroform (Vassalo 1997). From the beginning of anesthetic practice, concerns were expressed that inhaled gasses might cause brain hypoxia, despite medical usefulness. From evidence, anesthesia has become safer over the decades (Gaba 2000), and anesthetic and PO mortality rates have decreased worldwide over the last decades. However, as the developments of the surgery allow to treat patients with multiple diseases in the extreme ages of life (Gaba 2000), the surgical and anesthetic risks increase (Lagasse 2002). There have been significant efforts to analyze errors and investigate critical incidents, and these are recently discussed in the Helsinki declaration on patient safety in anesthesiology (Mellin-Olsen et al. 2010). The decreasing mortality rate depends on adopted safety measures, for example improved monitoring actions and the systematic use of risk prevention guidelines (Cooper et al. 1984). However, preventable drug-related deaths remain (Bainbridge et al. 2012); though, the goal of "zero anesthesia-related deaths" (Macintosh 1948) is still far from being achieved as the epidemiology of PO deaths shows (Abeysekera et al. 2005). Currently, mortality from

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anesthetic procedures is at least 1 to 10,000 over decades (Lienhart et al. 2006). PO mortality rates vary from country to country (Harrison 1978; Hovi-Viander 1980, Tiret et al. 1986; Pitt-Miller 1989; Tikkanen and Hovi-Viander 1995; Newland et al. 2002; Kawashima et al. 2003) and are fewer than 20 deaths per 10,000 anesthetics in developed countries. However, Brazilian studies showed higher PO mortality rates, from 19 to 51 deaths per 10,000 anesthetics (Bainbridge et al. 2012). Perioperative deaths (PODs) affect neonates, children under 1 year, and elderly male patients with comorbidity. Emergency surgeries and general anesthesia and cardiac, thoracic, vascular, gastroenterologic, pediatric, and orthopedic surgeries are considered at risk. Perioperative mortality rates, are higher in developing countries, while anesthesia-related mortality rates are similar, and these data may be useful for deaths prevention. More recently, meta-analysis using standardized reporting forms created by the American Society of Anesthesiologists (ASA) for identifying studies for inclusion and extracted informations (year, country of origin, and method of data collection) taken into account, with the object to identify anesthetic sole mortality (anesthetic-associated mortality (AAM)) and anesthesia-contributory mortality (Table 1). Total PO mortality (commonly considered as "death from any cause and cardiac arrest (CA)) has also interest in this field. Globally, there is strong evidence of reduction in anesthetic-related and perioperative mortality over the past 50 years, despite the increasing patients ASA risks (Table 2) and decreasing of CA in the perioperative setting (Braghiroli et al. 2017). Developing countries are affected two or three times more by anesthetic-related and perioperative mortality, if compared with developed countries (Avidan and Kheterpal 2012). Early and late mortality are also considered (Stefani et al. 2018). These data lead to a prior effort to reducing total perioperative and anesthetic-related mortality by preventive measures in those countries.

Main text

Definitions of anesthetic perioperative-related mortality and classifications

A generally accepted definition of the anesthesia-related death still remains one of the major concerns in forensic pathology (Deshpande 2011). As observed, the terms "operative deaths," "intra-operative," and "anesthetic deaths" are usually still applied inaccurately within the medico-legal literature (Saukko and Knight 2016; Di Maio and Di Maio 2001) (Table 1). Iatrogenesis, defined as illness resulting from errors (culpable or not) committed by physicians or other health care professionals, may include any

Table 1 Classification of perioperative deaths and possible medico-legal conclusions about health care professionals' responsibility

DEFINITIONS	EXPLANATION	CAUSE(s)	COMPLICATIONS/ CONSEQUENCES	ROOT CAUSES ANALYSIS
ACD ⇩ **Peri-operative deaths**	Mortality due to disease or injury , during surgery -anesthetic activities	Primary Or Contributing	Worsening of cardiovascular/ respiratory/nervous balance or collapse Unexpected death of inward patient	Conclusive Exclusion of culpable role of Human factors (Natural deaths) Possible culpable role of Human factors and/or preventable Equipment / System failure
AAD ⇩ **Anesthetic deaths**	Mortality directly caused by anesthetic activities	Primary	• Hypersensitivity (anaphylactic and anaphyloctoid reactions) - • Adverse drug reaction • Toxicity due to overdosing	Novus actus interveniens excluding causal role whether not preventable Possible culpable role of Human factors and/or preventable Equipment / System failure

Table 2 Perioperative mortality rate according to time after surgical interval, age, and patients' ASA status

Age	Mortality rate per 100,000 anesthetic procedures	Mortality rate by ASA physical status		Early mortality rate (< 24 h)**	Late mortality rate (≤ 30 days)**
0–7 years	0.60 (0.12–3.2)	I	0.40 (0.12–0.81)	76	243
8–15 years	1.20 (0.30–3.2)	II	5.0 (1.6–9.1)		
16–39 years	0.52 (0.24–0.93)	III	27.0 (12.0–44.0)		
40–74 years	5.20 (2.7–8.1)	IV	55.0 (1.1–130.0)		
≥ 75 years	21.00 (8.3–34.0)				

Adapted from Lienhart et al. (2006)
**Incidence of death analyzed in the perioperative period of 11.562 procedures

negative consequences of invasive procedures (Lau 2005). Such events involve comprehensively perioperative and non-perioperative fatalities. The use of such a broad definition allows for subtle separation of natural and unnatural death, at least from the prospective forensic pathology (Madea and Argo 2014). Critical areas of anesthesia-related mortality are airway management difficulties and cardiocirculatory disorders, some related to anesthetic drugs, while others occur as a consequence of aging synergistically and preexisting pathologically, which requires a carefully investigation and evaluation for professional health care responsibility (McCarthy 1999). Selective literature research in PubMed data bases, concerning perioperative and anesthetic deaths and medical responsibility, was performed. As a result, a total of 239 papers was included and considered, as related to selected topic (perioperative, anesthetic, and medico-legal). Following analyzed literature, iatrogenic deaths involve the following categories.

Inevitable mortality caused by an illness or lesion(s) for which surgical/anesthetic was performed

From the medico-legal point of view, both injury and/or disease(s) have to be considered as principal and proximate cause of death, or predominantly procedural in nature. The original condition is certified by some medico-legal systems as the cause of death by omitting the surgical intervention. Many of these fatalities can be regarded as *mors in tabula*, regarding patients in extreme physical condition, with unfavorable surgical outcome. In this regard, the well-known classification of the American Society of Anesthesiologists (ASA), which is used worldwide, specifies different risk levels attributable to increasing seriousness of patient's physical condition. Under the ASA classification, mortality risk can also be stratified by age.

Caused by a disease or abnormality not done regarding procedure, nor resulting from wrong technical surgery, or related, as inevitable complications (perioperative cardiac and cerebrovascular events)

Determined by the conditions or illness requiring invasive/surgical procedure, even rare and/or undiagnosed illness or conditions to death (Abate et al. 2014; Maresi et al. 2013; Maresi et al. 2006; Rancati et al. 2018), especially preventable conditions and complex clinical interactions, account for overall 90% of PODs. Myocardial infarction (MI) in the perioperative period, even in patients without medical history or ischemic heart disease, takes import role. In addition to the usual pathologic findings, cardiovascular factors or metabolic, hyperlipidemia, and/or wrong lifestyle are usual revealed (Serretta et al. 2018). It is not a simple matter to resolve, though this question involves the field of forensic investigation, the causative role of that illness and pathologies distress, in terms of causation or not influencing role. Within incidence rates, risk of early PODs in patients undergoing non-cardiac surgery is less than 1%, while in patients with coronary risk factors for heart disease, it accounts for 17% (Ashton et al. 1993).

PO myocarditis is less common and often presents as an unexplained viral infection or an adverse drug reaction (ADR), rarely reported as fatal giant cell myocarditis, as expression of foreign body reaction caused by cardiac valve surgery or coronary artery bypass (Rashid and Williams 1994). Is a matter of debate whether deaths after events such as stent embolism and re-stenosis after percutaneous transluminal coronary angioplasty, with resultant worsening of the underlying myocardial ischemia or extension of the original MI, should be considered to be iatrogenic in nature, at least from a forensic perspective. Similar considerations are to be applied to the occurrence of cerebral vascular stroke occurring after variable perioperative time intervals. Higher risk (about twice) of stroke is reported in patients undergoing coronary artery bypass grafting affected by unstable angina or non-Q-wave myocardial infarcts (Josefson 2001).

Complications of general and spinal anesthetic

Deaths due to anesthetic errors seem to be less frequent than those caused by surgical or invasive procedure but usually with worsening consequences. Contributing effect of anesthesia to death generally varies to 1:1700–1:10,000 operations (Lau 2005). Lau reported in his coronial autopsy practice only six deaths attributable to adverse anesthetic events out of a total of 572 PO autopsies (Lau 2000). When deaths occur within 24 h after administering

anesthesia, medico-legal questions are almost always an issue. With regard to relevant causes and mechanisms, most authors emphasize two fundamental pathways responsible for most deaths: missing control of respiratory airways/exchange and management of circulatory homeostasis (Moar 1996; Lagasse 2006). Further, each can be subdivided as errors in airway control and ventilation and defects in blood volume management and arrhythmic trouble control. Causal chain of the anesthesia-related deaths can be explained by a "tree" representation, which appears of useful application in medico-legal context regarding general anesthesia (Fig. 1).

Failure in airway management

Anesthesia management determines morbidity and mortality, as investigated in survey studies (Arbous et al. 2005). Data from many sources can be analyzed: patient claims and related requests for reimbursement and questionnaires returned by anesthetists often, as well as national surveys committed by the Health Minister all can provide valuable information (Van der Walt et al. 1993; Clergue et al. 1999; Morray et al. 2000; Jimenez et al. 2007; Bhananker et al. 2007).

Within that data, the lack of airway management is the most common general cause of ACD, and two-thirds of these result from complications of endotracheal intubation (Hofmann et al. 2002; Auroy et al. 2009), accidental esophageal intubation is a common mistake in inexperienced anesthetists (Frova and Tuzzo 1999) or delay in intubation (Bono et al. 2008). The most common of the endotracheal mishaps is unsuccessful intubation after muscle relaxant administration (Auroy et al. 2009). Inadequate pre-anesthetic examination does not prevent unexpected anatomical or pathological abnormality (El-Ganzouri et al. 1996; Paix et al. 2005, Lee et al. 2006); disconnection and dislodgement of the endotracheal tube, endotracheal tube mishap determined by endotracheal tube obstruction, tube kinking or cuff herniation, tension pneumothorax, and errors of oxygen cylinder causing the patient to breathe an anoxic gas mixture lead to anoxia; more commonly, anoxia may be determined by pus, blood, or secretions obstacle in breath (Tourtier et al. 2004) vomiting, regurgitation, and aspiration (Neelakanta

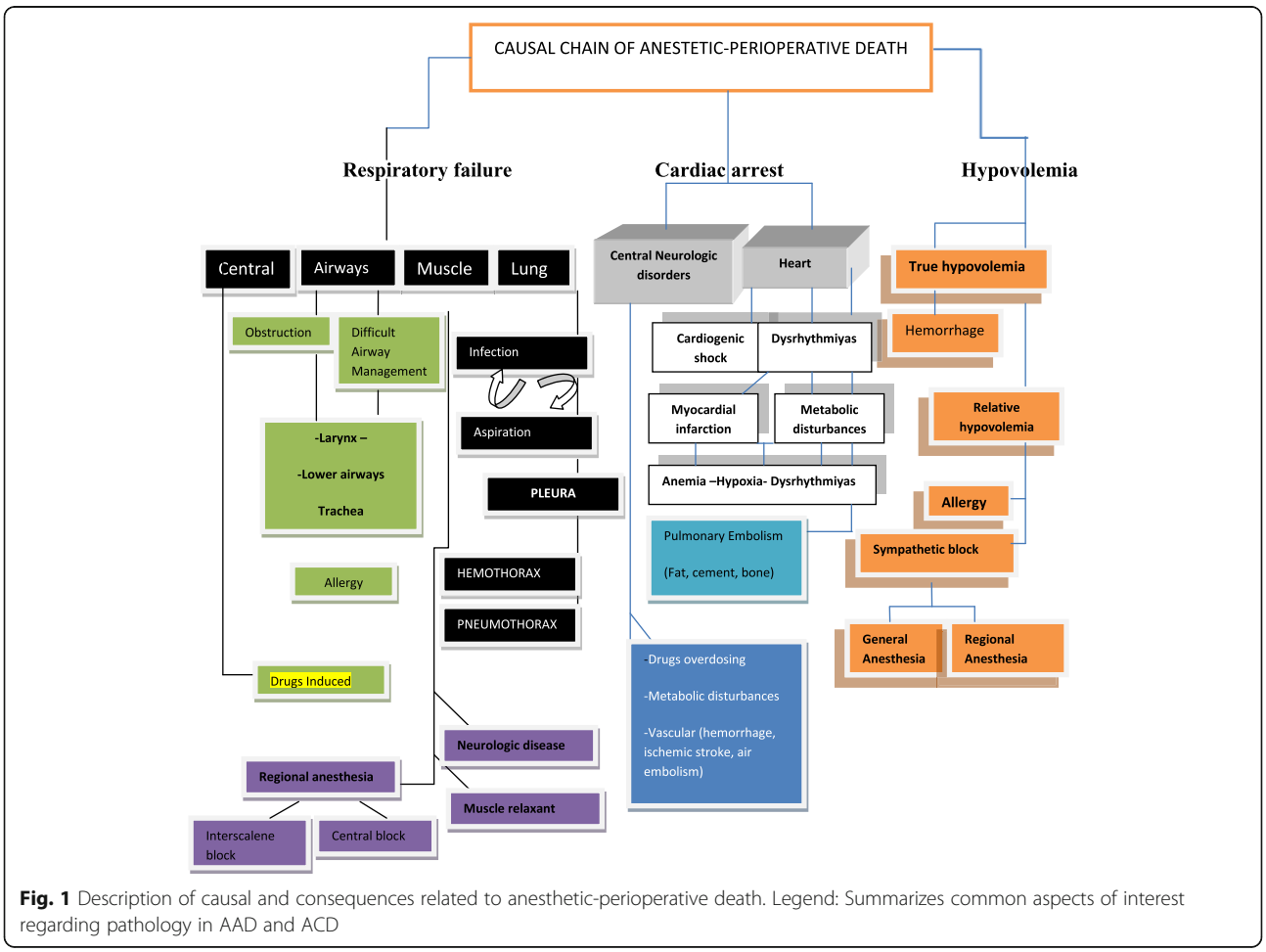

Fig. 1 Description of causal and consequences related to anesthetic-perioperative death. Legend: Summarizes common aspects of interest regarding pathology in AAD and ACD

and Chikyarappa 2006). Secondly, inadequate pulmonary ventilation during anesthesia accounts for about 20% of anesthetic-related deaths. The delay in treating attempted reversal of neuromuscular blockade is a common mistake. To report the post-anesthetic respiratory depression after fentanyl administration, misdiagnosis of the post-operative restlessness of anoxia as being due to pain, with wrong administration of more narcotic (Preckel and Bolten 2005). In studies of Tiret et al. (1986), errors commonly involved were difficulty to maintain oropharyngeal airway during recovery to full consciousness of patients after anesthesia and fluid overload in the immediate post-anesthetic recovery phase, causing pulmonary edema. In accord with Harrison (1978), the occurrence of these tragic errors requires a careful recognition of medical instructions to health care professionals, missing adequate communication teamwork (Cook and MacDougall-Davis 2012).

Inadequate balance of the patient's circulatory system

Around 35% of ACD are due to failure in control circulatory homeostasis, and these can be further attributed to blood volume regulation (hypo- or hypervolaemia) and arrhythmia management; CA due to hypovolaemia is preceded by functional myocardial ischemia; inadequate cardiac venous return may cause intractable post-induction hypotension; and commonly excessive blood transfusion and/or electrolyte components, causing cardiac overload and pulmonary edema, may lead to CA. Anoxic or anoxic/ischemic encephalopathy may result from CA during application of cardiopulmonary resuscitation (CPR) and this imposes to supervise regaining consciousness of patients, as Lunn and Mushin (1982) first stated, the surveillance period should be extended to the sixth post-anesthetic day. In a Danish study (Hove et al. 2007), post-induction hypotension following administration of thiopentone, bupivicaine (epidural/spinal anesthesia) was a relevant anesthetic complication causing collapse. Bradycardia or CA was attributed to suxamethonium, succinylcholine, and neostigmine and ventricular fibrillation to halothane, intravenous digoxin, isoxsuprine, and droperidol. As reported by Pitkänen et al. (2013) the majority of patients suffering serious complications related to spinal and epidural blocks were the elderly having comorbidities.

Summary of the most common, potentially lethal, general anesthetic complications

Most publications on the subjects include the following potentially lethal anesthetic complications (Solazzi and Ward 1984):

- Hypoxic–ischemic encephalopathy and brain death due to oxygen deficiency by failed intubation (caused by inexperienced operator or technical difficulties due to anatomic abnormalities), misplacement of the endotracheal tube, wrong oxygen sources, now minimized by modern anesthesia machines; these complications are classified by inclusion criteria and by severity of harm using National Audit Project of the Royal College of Anesthetists and Difficult Airway Society (Cook and MacDougall-Davis 2012).
- Airway obstruction, resulting from bleeding or secretions or foreign bodies. Problems with the airway and/or ventilation are the most likely causes of anesthetic mishaps. They often begin as slight respiratory embarrassment that progress to hypoxia and hypercarbia, and then degenerate into cardiovascular crises. Unfortunately, the adequacy of ventilation is more difficult to assess than alterations in the cardiovascular system. The pulse oximeter and the capnograph have markedly improved respiratory monitoring compared to the rather crude assessments of the past which were based upon observation of the reservoir bag, chest excursions, patient color, and auscultation of breath sounds (Cook and MacDougall-Davis (2012). Mechanical obstruction of the airway by the tongue is very common and easily managed if recognized. Enlarged tonsils, edema, pharyngeal gauze partition, and foreign bodies are also risk factors for obstruction. Repositioning the head, insertion of an oral or nasopharyngeal airway, performing direct laryngoscopy, endotracheal intubation, or cricothyrotomy may be necessary to alleviate mechanical obstruction (Warner et al. 1993). Secretions, irrigation solution, blood, and surgical debris may initiate laryngospasm. It is important to remember that laryngospasm is a protective reflex that seals the entrance to the tracheobronchial tree to foreign matter. During partial or incomplete laryngospasm, high-pitched "crowing" sounds are produced on inspiration; no sounds are produced during a total or complete laryngospasm. Suctioning deeply into the posterior pharynx and the gentle application of positive pressure oxygen is the initial treatment. Anesthesia may also be deepened to decrease laryngeal irritability. If oxygen saturation drops significantly, a small intravenous dose of succinylcholine (5–10 mg) may be given to relax the laryngeal muscles and permit positive pressure ventilation. Early diagnosis and aggressive treatment of laryngospasm are imperative, as a succinylcholine administration in the face of hypoxia and hypercarbia is associated with profound bradycardia and asystole.
- Aspiration of gastric contents or contrast medium. Aspiration of foreign bodies, such as teeth and bone fragments, is a recognized danger during dental procedures performed under general anesthesia when endotracheal intubation is not used to protect the airway. A properly positioned pharyngeal gauze

partition and the constant availability of a high-volume evacuation system and Magill forceps are necessary to decrease this risk. Aspiration of at least 25 mL of gastric contents of a low pH (2.0) is required to produce serious morbidity. Management of aspiration includes vigorous suctioning of the pharynx and administration of 100% oxygen.

- Bronchospasm that must be included in any differential diagnosis whenever ventilatory difficulties are encountered. Whether the consequences of asthma, histamine release, anaphylaxis, airway manipulation and stimulation, or aspiration, it must be recognized early and vigorously treated. Unlike laryngospasm, bronchospasm is not protective. Increased airway pressures and significant wheezing during bronchospasm may be accompanied by severe hypoxemia and hypercarbia. Halothane produces bronchodilation but unfortunately sensitizes the myocardium to the arrhythmogenic effects of the beta-adrenergic bronchodilators. Glucocorticosteroids may also be effective for bronchospasm, but their prolonged onset times render them ineffective in managing the initial emergency (Rosenberg and Weaver (1991).
- Side effects of neuromuscular blockade depend on excessive, or duration; induction of anesthesia with thiopentone, pre-medication with trichloroethylene and atropine is believed to cause cardiorespiratory collapse.
- Malignant hyperthermia is a rare autosomal dominant condition that predisposes to sudden uncoupling of oxidative phosphorylation, with potentially lethal hyperthermia. Mutations in the genes coding for the skeletal muscle ryanodine receptor (RYR1) and alpha 1 subunit of the dihydropyridine receptor (CACNA1S) have been identified as causative for malignant hyperthermia (MH). It is most likely to occur when known triggering agents (use of volatile inhalation anesthetics like halothane and certain muscle relaxants (e.g., suxamethonium, succinylcholine) are used. Clinically, malignant hyperthermia is usually first manifested as an unexplained, progressive tachycardia and an elevation in end-tidal carbon dioxide. Masseter muscle spasm after the administration of succinylcholine may also signal the onset of malignant hyperthermia. Muscle rigidity, cyanosis, dysrhythmias, and elevated temperature are also noted. In addition to the contracture test, requiring muscle biopsy sample, the use of metabolic test may indicate susceptibility to malignant hyperthermia, as susceptible individuals will have a considerably higher intramuscular pCO2 than controls (Anetseder et al. 2001).
- Halothane hypersensitivity disorder has an estimated incidence of 1:6000 to 1:600,000 anesthetic procedures and may be associated to worst consequences of halothane-induced hepatitis, or massive hepatocellular necrosis, after repeated exposure to the agent (Gelven et al. 1996).

Halothane hypersensitivity is mediated by the immune sensitization of susceptible individuals. Halothane, enflurane, isoflurane, and desflurane are metabolized through the metabolic pathway involving cytochrome P-450 2E1 (CYP2E1) and produce trifluoroacetylated components, some of which may be immunogenic.

- Lethal effect of propofol (alkylphenols), a sedative-hypnotic agent that is the most commonly used intravenous agent for induction of anesthesia and for sedating mechanically ventilated patients in intensive care units, is now increasingly being used for conscious sedation during endoscopic procedures. Propofol is an extremely rapid-acting intravenous anesthetic, and its advantages include less residual post-operative sedation and less psychomotor impairment than the barbiturates, with low incidence of nausea and vomiting. Propofol produces dose-dependent cardiovascular and respiratory depression with a profile similar to methohexital (Procaccianti et al. 2017). It has been associated with fatal heart failure both in children and in adult patients with head injuries (Maas et al. 2018). The propofol infusion syndrome includes myocardial failure, metabolic acidosis, and rhabdomyolysis in children receiving propofol infusions for more than 48 h (Cremer et al. 2001).

Spinal anesthesia fatalities

Spinal anesthesia is one of the most used anesthetic techniques, believed to be very safe, though severe complications may occur (Ishiyama et al. 2012). The first cases of CA occurring after spinal block anesthesia were reported in the 1940s and since then, the ability of spinal anesthesia to cause cardiopulmonary arrest was considered (Arruda et al. 2011). With regard to the etiology of cardiopulmonary arrest, Caplan et al. (1988) analyzed 14 episodes of unexpected CA during spinal anesthesia in healthy patients (physical status I and II ASA classification). The highest level of sensorial blockade achieved in any of the cases was T4; 12 out of the 14 patients were sedated and not adequately monitored. Despite cardiopulmonary resuscitation, six deaths were observed, with severe consequences in eight survivors. Lovstad et al. (2000) reported CA preceded by bradycardia of a 17-year-old patient, ASA I, underwent knee arthroplasty under spinal anesthesia. Probably because death is such a rare occurrence, the

available data is contradictory, and the incidence rate is not really known. Investigators have reported rates ranging from 1.3 to 18 cases in 10,000 spinal anesthesias. Auroy et al. (2009) described an incidence of spinal anesthesia-related CA of 6.4 ± 1.2 in 10,000, significantly higher than combined rates reported for epidural anesthesia and peripheral blockades together (1.0 ± 0.4 in 10,000 procedures), similarly reported by Pollard et al. (2001) during spinal anesthesia (0.03%) and epidural anesthesia (0.01%). Whatever the true rate, it is clear that CA is more common during general anesthesia, applied more commonly in complex, high-risk surgeries performed on. Respiratory depression or hypoxemia induced by sedative drugs are not reviled by Lovstad et al. (2000) in cases of primary asystole; other authors have shown that the majority of patients who experienced CA had not received sedative drugs (Liguori and Sharrock 1997). Mechanisms of bradycardia or asystole induced by spinal anesthesia are still controversial, but absolute or relative increase in activity of the parasympathetic nervous system lead patients with increased vagal tone at an elevated risk of developing those complications (Kumari et al. 2014).

Reduction of blood pressure and central venous pressure are effects of spinal block anesthesia related to the sympathetic nervous system blockade. Sensorial blockade in T4 can determine a blockade of all cardio-accelerator fibers (T1–T4), with progressive reduction in heart rate. Sympathetic blockade at the T1 level or above results in increased vagal tonus, which causes negative inotropic, chronotropic, and dromotropic changes without opposition from the sympathetic nervous system. A second reflex is attributed to mechanoreceptors, in the right atrium and ventricle, and baroreceptors, in the right atrium and vena cava. The third reflex is caused by mechanoreceptors in the infero-posterior wall of the left ventricle, whose stimulation increases activity in the parsympathetic nervous system and inhibits the activity of the sympathetic nervous system, producing bradycardia, systemic vasodilation, and hypotension. All these reflexes involve an increase in autonomic-vagal response (Gratadour et al. 1997), ranging from flow imbalance to CA. It is remarkable that the level of sensorial blockade in elderly patients is usually higher than that of young adults given the same dose of local anesthetic. Overdose of local anesthetic by subarachnoid route is a known cause of CA in elderly patients (Auroy and Benhamou 2001). Potent sympathomimetic agent is the first treatment option to increase coronary perfusion pressure, which increases peripheral vascular resistance, diastolic pressure, and coronary perfusion pressure, improving cerebral blood flow, and the use of mixed agents (α- and β-adrenergic) is effective in increasing blood pressure, with less significant increase in systemic vascular resistance. Obviously, from a medico-legal perspective, prevention and treatment of potentially avoidable consequences have to be the main consideration (Sheppard and Anandampillai 2019).

Whatever the true number, the mortality differential between spinal and general is almost certainly declining as a result of increased knowledge of the physiology of spinal anesthesia, together with the use of less toxic local anesthetics and improved monitoring during spinal anesthesia (Patil et al. 2019; Finsterwald et al. 2018).

Adverse drug reactions (ADRs) and anesthesia

An adverse drug reaction (ADR) is an unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use and is suspected to be related to the drug and is responsible for the deaths of some 0.1 and 0.01% of medical and surgical inward patients, respectively; Lau (Lau 2000) during a 5-year period (1999–2003) reported fatal ADRs range between 0.3 and 0.5% of coronial autopsies. In medico-legal context suspicious cases of fatal ADR have to be assigned to type A reactions as being pharmacological, or type B (idiosyncratic). The type A (about 80% of ADRs) are dose-dependent with reversible effects of drug intake; the B type is usually largely unpredictable and unpreventable. Type A reactions relay to the innate toxicity of a therapeutic drug, or from drug interactions used in combination. Extreme age of life and comorbidity determine a considerable risk of ADR. Type B reaction, less common, accounting for ADR-related deaths, is associated with various complex immunologic (e.g., anaphylaxis), metabolic (e.g., CYP2D6 deficiency), cell receptor (e.g., malignant hyperthermia), and multifactorial pathogenic mechanisms (e.g., halothane-induced hepatitis).

The majority of fatal ADRs (intended as perioperative anaphylaxis) that come to forensic attention are usually idiosyncratic reactions occurring around the time of surgery/anesthesia, with the incidence of 1/10,000 of patients suffering surgery, often using neuromuscular blockers.

Pathological effects are massive hepatocellular necrosis, skin or mucocutaneous drug reactions (e.g., Stevens-Johnson Syndrome), toxic epidermal necrolysis complicated by sepsis, coagulopathy, and eventual multiorgan failure.

This subset of anesthetic-related deaths also includes overdose of drugs administered during general or local anaesthesia. Some cases of sudden death after injection of lidocaine to perform local anesthesia are occasionally reported in forensic literature (Hasegawa et al. 2008). They are related to iatrogenic effects, with different implications for physician liability, mostly depending on the demonstration that a true overdose was administered.

Anaphylactic deaths (ana- = beyond; gr. fülaxis = defense)

Despite the increasing frequency of perioperative allergic reactions, probably caused by the increase in surgical procedures performed under anesthesia and the growing

complexity of drugs used, there is still a lack of accurate epidemiological data. ADRs are not uncommon: most of the data on perioperative prophylaxis come from the registry of Australia, France, New Zealand, Spain, and UK. Although anaphylaxis is a rare event (1:10–20,000 general anesthesia, 1: 6500 in the case of anesthesia with use of Neuromuscular blocking agents (NMBA), it is often associated with a high mortality rate (3–9%) and major sequelae, especially if not properly treated (Calapai et al. 2016).

The incidence of perioperative anaphylaxis can vary depending on the degree of exposure of the environment population to hazardous substances (Ewan et al. 2009). In Norway, the frequency of this condition is due to the fact that NMBA decreased since it is a cough syrup based on pholcodine (an analogue of morphine) able to sensitize the population was retired from the market in 2007. Medications containing pholcodine were withdrawn from the Swedish market in 1989, in accord with new published guidelines for the treatment of cough. The comparison of epidemiological data between Norway and Sweden showed that anaphylactic reactions to NMBA were over six times more common in the Norwegian population than Swedish (Kroigaard et al. 2007). Incidence of anaphylaxis to latex dramatically increased everywhere in Europe over the last decades and more recently appears to have reduced by primary prevention measures (interventions in latex-free environment). The incidence of anaphylaxis from chlorhexidine seems currently on the rise, while anaphylactic reactions to colloids remain relatively stable (around 4%). Immune reactions to local anesthetics are still rather rare, representing less than 1% of the possible reactions adverse to these drugs; the majority of such reactions are caused by accidental intravascular injection, leading to side effects, especially on the cardiovascular and central nervous. Systemic allergic reactions to opioids are uncommon, though it should be noted that morphine causes mast cells to release histamine, while synthetic narcotic do not exert this effect. The prevalence of allergic reactions to corticosteroids varies from 0.5% to 5% and has so far been reported in the literature anaphylaxis anesthetics inhalers (Venturini et al. 2006). There is little information about the epidemiology of anaphylactic reactions in the PO of children surgery. A study conducted at a pediatric hospital department reported 68 cases of children who presented anaphylaxis during anesthesia (Karila et al. 2005). It was recognized as an IgE-mediated mechanism in 51 patients; 31 cases (60.8%) were caused by NMBA, 14 cases from latex (27%), 7 cases by colloids (14%), 5 cases by opiate (9%), and 6 cases by hypnotics (12%), with prevalence of vecuronium within the neuromuscular blocking agent reactions. Twenty-three of the 31 children demonstrated cross-reactivity between NMBA, particularly between vecuronium, atracurium, and pancuronium. Allergic reactions during anesthesia generally have variable frequencies in different countries and in different series between. The reactions rate ranges between 1/10,000 and 1/13,000, and 3–9% of these cases ultimately proved fatal (Chen et al. 2016). Adults between 30 and 50 years, mostly female (female/male ratio = 3–4:1) seem most vulnerable. The frequency with which the different drugs used in general anesthesia cause allergic reactions varies in different series. Muscle relaxants are responsible for more than half of anaphylactoid reactions (up to 70%) followed by hypnotics, colloidal plasma substitutes, benzodiazepines, and opiates (Barke and Hough 1993). A very important role in determinism of these reactions is that latex is implicated in over 10% of cases. Allergic reactions to non-depolarizing muscle relaxants, including d-tubocurarine, metocurine, pancuronium, gallamine, atracurium, and vecuronium, are the most serious, affecting mainly females. These reactions seem to be due to the nonspecific release of mediators and hypersensitivity induced by quaternary ammonium ions antigenic determinants shared by all members of this class of drugs. The frequency and severity of anaphylaxis to non-depolarizing muscle relaxants finds its explanation in the structural features of the molecule and in the ease of contact with the quaternary ammonium ions in the environment (acquired latent sensitization). Substances containing quaternary ammonium ions are present in eye drops, antiseptics, laundry detergents, food preservatives, and cosmetics. The universality of these agents within the environment raises the possibility of a reaction even at the first anesthesia. It has been found that 80% of subjects sensitized to muscle relaxants have specific IgE to these drugs even 14 years after a shock. Among the factors favoring the anaphylactoid reactions in general anesthesia, common food should also be mention. Within foods, potatoes, tomatoes, and aubergines may contain naturally occurring solanaceous glycoalkaloids (which are naturally occurring insecticides that remain in the body for several days after ingestion). The inhibition of butyrylcholinesterase and acetylcholinesterase by solanaceous glycoalkaloids may cause persistence of anesthetic agents and muscle relaxants in the body and a prolonged clearance time (last as long of 5–10 h (Tanne 1998).

A cascade of signs (hypotention, pruritis, urticaria, tightness in the chest, wheezing) and symptoms (faintness, shortness of breath, collapse) are seen during anaphylactic attack. Anaphylactic deaths develop usually immediately or within 20 min. After exposure to a particular antigen, death usually occurs within 1–2 h. A fatal anaphylactic reaction results in acute respiratory distress or circulatory collapse (Baido and Pham 2013). Obstruction of the upper airway can be caused by pharyngeal or laryngeal edema of the lower airway, by bronchospasm with contraction of the smooth muscle of

the lungs, vasodilation, and increased capillary permeability. CA may be caused by respiratory arrest; chemical mediators of anaphylaxis may directly cause shock caused by a combination of intravascular fluid loss from edema and vasodilatation. Anaphylactic shock due to an acute immediate allergic reaction may be suspected when unusually resistant hypotension is encountered. It may be accompanied by bronchospasm, rash, edema, and hives. Epinephrine in intravenous increments plus 100% oxygen are the immediate treatment, doses of 1 mg of epinephrine may be necessary. The sooner anaphylaxis is diagnosed and treatment instituted, the better the outcome and the less chance of total cardiovascular collapse and complete airway obstruction (Rosenberg and Weaver 1991). Unfortunately, pathological investigations both macroscopically and microscopically and ancillary laboratory investigations are often of poor relevance (Edston and van Hage-Hamsten 1998). In fact, autopsy findings are often nonspecific, like upper airway edema, but rarely complete obstruction of the airway and in suddenly occurring deaths, and the only finding might be visceral congestion. In the study of Roberts and Pumphrey (2001) of 56 anaphylactic deaths with autopsy investigation, 16 deaths were caused by food allergy and 13 caused by respiratory arrest. In 8 of 19 cases caused by insect venom and 12 of 21 caused by drugs reactions, shock without breathing symptoms occurred. The authors reported laryngeal or pharyngeal edema in 8% and 49%, respectively, of individuals who died immediately. Emphysema caused by the bronchoconstriction might be present. Visceral and pulmonary congestion, edema, and pulmonary hemorrhage are present but are nonspecific. Twenty-three of 56 anaphylactic deaths had no macroscopic findings at autopsy. Microscopic examination may show edema in the respiratory mucosa, with infiltrate of eosinophils and epithelial desquamation. In anaphylactic deaths, the quantity of degranulated mast cells from tissues is with difficulty evaluated and, furthermore, mast cells are further difficult to identify in postmortem tissues. More recently, immunological methods to detect and quantify mast cell proteases (tryptase), made possible to diagnose or confirm anaphylaxis postmortem (Edston and van Hage-Hamsten 1998; Payne and Kam 2004).

Moreover, tryptase was found to be elevated in a few cases where anaphylaxis was not diagnosticated (Randall et al. 1995). In addition, it is important to consider that an increase of tryptase may be caused by postmortem diffusion from tissues into the blood. Patient's medical history comprehensive of therapeutic agent administration and circumstances of death plays an essential role when investigating suspected anaphylaxis (Edston and van Hage-Hamsten 2005; Byard 2017). As diagnostic tools, tryptase measurements, and analysis of allergen-specific immunoglobulin E antibodies, a panel of common allergens, therapeutic agents like penicillin or iodine-containing contrast, may be considered (Fineschi et al. 1999).

Need for further perioperative quality control programs and its relevance for medico-legal evaluation

Increasing subspecialization and advanced medical technology, by treating greater numbers of older and ill patients, explains the elevated risk of invasive procedure; fields of medico-legal interest concerns now include relevant and new problems regarding unexplained PODs. Epidemiological data indicated that the "classical" complication (e.g., failure or mishap in airway management) have become more infrequent, and the anesthetic-associated death is usually multifactorial; also in the view of poor gross findings at autopsy of that occurrences, this cooperation is necessary to lead evidence and conclusions about death (O'Grady 2003). Considering these aspects, cases of *res ipsa loquitur* remain individual, and a broad spectrum of post mortem molecular investigative possibilities must be considered facing with perioperative deaths, by pathologists, anesthesiologists, and surgeons in synergy. Database retrospective analysis and evaluation of root cause analysis related to PODs, as implemented in different health systems (Norway, French, New Zeland, UK), showed useful strategies to reduce preventable avoidable deaths, f.i. in the field of PO medication errors (Nanji et al. 2016): worthy of mentioning adopted simple measures (as prefilled syringes) and facilitating system to report drug administration error by health care professionals.

In medico-legal field of interest, by contributing to explore why PO accident happens lead to simplify an audit process and manage distinct clinical responses and whether that can modify the adverse responses. In this view, a systematic interdisciplinary investigation which includes medico-legal evidence from autopsies, e.g., gross findings, ancillary laboratory investigations, and recent molecular autopsy indicating gene preventable diseases (Madea et al. 2010) may contribute to adopt strategies for patient safety in anesthetic-surgical practice. In the view of defense of the anesthesiologist (Lee et al. 2011), decisions about medical negligence are based on standard-of-care issues that imply also an indication about guidelines application or not, again within medico-legal approach (Rini et al. 2018).

Conclusions

The preventable perioperative complications are evaluated to improve the safety of health care, including also the medical-law point of view; the adaptation of monitoring techniques and the adoption of guidelines have already contributed significantly to this goal (Abeysekera et al. 2005) reducing mortality, and the detailed

investigation of actual or suspected iatrogenic deaths is a crucial piece for the continuous improvement of health care. Evidence gathered from postmortem investigation of PO deaths and audit program (centered on incidence, causes and consequences, included into a critical incident datasets) systematically adopted by health care systems may indicate an interdisciplinary, useful strategy of clinical risk management and support the decision about medical negligence.

Abbreviations

AAM: Anesthetic-associated mortality; ACDs: Anesthetic contributory deaths; ADRs: Adverse drug reactions; ARDs: Anesthetic-related deaths; ASA: American Society of Anesthesiologists; CA: Cardiac arrest; CPR: Cardiopulmonary resuscitation; MI: Myocardial infarction; NMBA: Neuromuscular-blocking agents; PO: Perioperative; PODs: Perioperative deaths

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AA conceived of this study and performed the draft; RB revised for drugs toxicological aspects; SBK partecipated in the design of the study, helped to drafting and editing language; and SZ, AL, and RR contributed to literature search and evaluation. All authors read and approved the final manuscript.

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