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GAS EMBOLISM: A REVIEW, INSIGHTS INTO THE ETIOPATHOLOGY, AND FORENSIC IMPLICATIONS

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Abstract: Gas embolism represent a challenging problem in clinical and forensic medicine due to physical properties of air or another gases, which can forcefully, though inconspicuously, enter the vascular structures. Here, the gas creates bubbles as geometric shapes, making mechanical obstacles to the blood flow or causing many adverse reactions such as vasogenic edema, endothelial dysfunction, or neuronal cell injury. The medical problem of gas embolism is hidden in the physical properties of the gas itself. A thrombotic mass as a solid mechanical obstacle in the blood vessel remains more or less firmly fixed even after the vessel has been opened, but the gas from the bubble quickly dissipates into the surroundings and a significant pathologic phenomenon or even forensic proof may be definitely lost. In this paper, based on the literature review and the personal experience, the authors tried to pick up and enlighten the phenomenon of gas embolism from the aspect of forensic pathology, disclose the less common causes of gas embolism, define the types of gas embolism, and point out the possibilities of post-mortem diagnosis.

Keywords: gas embolism, gas detection, etiology, autopsy, diving, decompression sickness.

INTRODUCTION

The presence of gas in blood vessels excites "quo ad causam" generations of morphologists. The ancient anatomists considered arteries to be air-conducting vessels because at autopsy they found them empty, without any blood (artery from Greek origin arteria - aer-air, aeirein-windpipe). Since the time of Morgagni (1682-1771), the presence of gas in the blood vessels has been considered as the pathology with possible fatal outcome. Contemporary forensic medicine, using the term gas embolism for the mentioned phenomenon, is more or less focused on the fundamental causes of gas emboli, lethal quantities of gas or suitable autopsy techniques. Hence, forensic medicine with findings of gas in blood vessels (except for putrefaction gas) must basically answer the question of its origin and its causal link with the death of the subject.

The invention of helmet diving dress by the Deane brothers in 1835 and the following era of sea sponge harvesting in the Mediterranean and Aegean Sea brought new aspects to the discussion on the presence of gas in blood vessels - arterial gas embolism and decompression sickness. These forms of 'gas-packed vessels' were even more enhanced in the era of recreational diving, which has become very popular worldwide nowadays. Thus, at present there have been some changes in the views on gas bubbles in the human circulation. The growth, distribution, and biologic behavior of gas bubbles *in vivo* have been extensively described, including the local endothelial damage up to systemic reactions of the organism to the presence of gas in circulation. The gas bubble in the blood vessel represents a foreign body, potent enough to initiate a cascade of pathophysiologic reactions with its specific morphologic features. The knowledge and correct interpretation of these particular morphologic changes is helpful in establishing a key diagnosis of the cause of death in such cases, which is sometimes not easy to interpret such as in cases of traumatic gas embolism,

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post-surgical gas embolism, and fatal diving accidents. In the daily practice of forensic pathologists, such cases are rather rare, but possible. The aim of this article is to provide a comprehensive view of the gas embolism, the causes and possibilities of their origin, gas bubble morphology, and to mention briefly the systemic reactions of the organism in relation to the presence of gas in the vasculature. Besides providing a better understanding of the causes of gas embolism, the article also offers contemporary diagnostic possibilities of gas embolism as a specific pathomorphologic phenomenon.

Origin of gas bubbles in the human body

In 1769, the Italian anatomist G.B. Morgagni described two autopsies of deceased humans, where in both cases he verified tiny gas bubbles in the arterial circulation of the brain. In both cases, he assumed cerebral arterial occlusion by gas bubbles as the cause of death. In the words of contemporary medicine, the cause of death was arterial gas embolism [1]. Thus, a gas embolism is a pathologic condition, when air or another gases enters the circulation (arterial or venous) and forms bubbles due to various biomechanical reasons, or the gas bubbles develop directly in the blood vessels according the principles of biophysical laws [2, 3].

Trauma-induced gas embolism

While analyzing the traumatic causes of gas embolism, a few notes concerning the human circulation are mandatory. The circulatory system is a dense network of mutually interconnected vessels of various volume (arteries, veins, capillaries, the heart), closely sealed against the external environment. The venous circulation represents the 'low-pressure' part of the system, whereas the arterial circulation represents the 'high-pressure' part. Hence, in the heart and major arteries, the blood pressure is relatively high (compared with atmospheric pressure), whereas in the venous system, the blood pressure is significantly lower. Physiologically, the central venous pressure (CVP) averages 4.6 mm Hg and fluctuates with cardiorespiratory activity (it differs from 0 to 6 mm Hg), in the peripheral veins varies usually between 8-10 mm Hg. In the upright body position, the venous pressure above the heart level is decreased by the force of gravity by 0.77 mm Hg for each centimeter (e.g. in the superior sagittal sinus is -10 mm Hg). The arterial pressure is also influenced by gravity, albeit at a lesser extent [4]. The dural venous sinuses with rigid bone walls cannot collapse, so in the standing or sitting position, the pressure in these vessels, being a part of a venous system, is even subatmospheric. If a dural venous sinus is forcefully opened (e.g. cranial injury, neurosurgical intervention), surrounding atmospheric air can even be sucked into such particular veins [2,5]. Thus, the main physical condition for the entry of air from the outside into the bloodstream is the blood pressure gradient favoring the passage of gas into the damaged vessel. The risk of gas entering a vein increases proportional to the diameter of the opened vessel: it is almost negligible for small peripheral veins, whereas the air entering the dural venous sinuses, diploic veins, and the large venous stems within or close to the thorax can be life-threatening [6].

According to Madea *et al.* [5], trauma-induced air embolism is very probably overlooked and thus underdiagnosed in daily autopsy practice. Hence, every forensic pathologist performing an autopsy of an individual who died of traumatic causes should keep the possibility of traumatic air embolism in mind. Also the autopsy procedures should be organized according such suspicion. Air in the circulation has been obviously described as a complication of penetrating injury (e.g. gunshot wound, stabbing wound) and blunt trauma of the chest (e.g. sudden chest compression leading to disruption of airways and/or lung parenchyma), abdominal trauma, head injuries with rupture of the sinus or suicidal cut-throat injury (opening of jugular veins) [7, 8]. The penetrating chest injuries in close proximity to the pulmonary hilar region due to the location of pulmonary vein and airway branches are also at the highest risk of air embolism [9]. Massive venous air embolism was also described in the context of suicidal behavior [10]. Air embolism associated with blast injury (momentarily forceful compression of the chest) should be also taken into account in the aspect of air embolism. At the autopsy of a suspect blast injury case (e.g. explosion), a well-proven aid should be an external examination of the tympanic membranes of the ears. If the tympanic membrane is injured (rupture and bleeding into the eardrum membrane and middle ear cavity) by a blast wave, injury of lung parenchyma is also likely [11]. Traumatic air embolism in pregnancy and delivery is rather rare; however, cases of fatal air embolism due to vaginal insufflation or even vaginal insufflation of cocaine during orogenital sexual intercourse in pregnancy have been described [6, 12].

Rather specific is the situation in divers, where the gas entering the circulation comes from two independent sources, totally different in the physical aspect:

- Gas (breathed by the diver) enters the circulation due to overexpansion of the lungs and

mechanical disruption of alveolar walls (overpressure lung injury, barotrauma of ascent in divers). In such a situation, the process of gas-blood interference is purely traumatic.

- Gas (inert gas in the gas mixture breathed by the diver) creates bubbles directly in the blood within the process of inert gas off-gassing, if supersaturation occurs to a certain degree. This peculiar biophysical process leading to decompression sickness is mentioned later.

The gas mixtures breathed by the diver underwater are compressed air, Nitrox (oxygen enriched air), Trimix (helium-oxygen-nitrogen in deep diving), Heliox (helium-oxygen in commercial diving) and even Hydreliox (hydrogen-oxygen in experimental deep dives) [13]. In most cases, a forensic pathologist confronted with a diving fatality is not clearly informed about the composition of gas the deceased diver breathed. Thus, the general term gas embolism has a much better descriptive validity in such cases, until the contents of the gas mixture breathed by the deceased is exactly known after technical analysis of the breathing apparatus. In diving, the principal biophysical condition of mechanical flushing of breathing gas into the vasculature is based on overpressure lung injury (pulmonary barotrauma of the diver's ascent). It belongs to forensic mythology that only massive damage of pulmonary parenchyma, as well as a diver's ascent from greater depths, is necessary for the development of fatal gas embolism. In fact, as little as 10% of the lung parenchyma damaged by overpressure after a breath-hold ascent of a diver with breathing apparatus from depths as little as 1-2 meters of water is enough for the development of massive gas embolism with fatal outcome. An exceptional mechanism may cause pulmonary barotrauma that may result in gas embolism in breath-hold diving, if a diver performs s. c. buccal pumping prior his dive. In buccal pumping, which is also known as glossopharyngeal insufflation, diver tries to pump some more air to his lung after a deep inspiration. The volume of air and intrapulmonary pressure may reach to a level to rupture the alveoli. Physically, gas embolism due to lung overpressure injury is primarily of arterial type. In every autopsy involving diver fatality, gas embolism, and especially lung injury, even local, should be excluded first [2, 14].

Iatrogenic causes of gas embolism

The risk of gas embolism accompanies the diagnostic and therapeutic interventions in almost all clinical specialties. Some general circumstances (e.g. patient position, hypovolemia) lead to a venous pressure drop under the level of atmospheric pressure and accomplish conditions for intravenous gas sucking. These could be:

- Surgery performed in Fowler's position (e.g. neurosurgery) for veins located above the superior vena cava, or in the Tredelenburg position for veins located under the inferior vena cava;
- Surgery of the large venous stems above the diaphragm (jugular, subclavian, superior cava, azygos veins) or under the diaphragm (inferior cava, hepatic, renal, uterine veins);
- ENT surgical interventions;
- Surgery of the thyroid gland;
- Surgery of the heart;
- Pulmonary or hepatic surgery;
- Abortions, surgical procedures on the uterus [6, 15, 16].

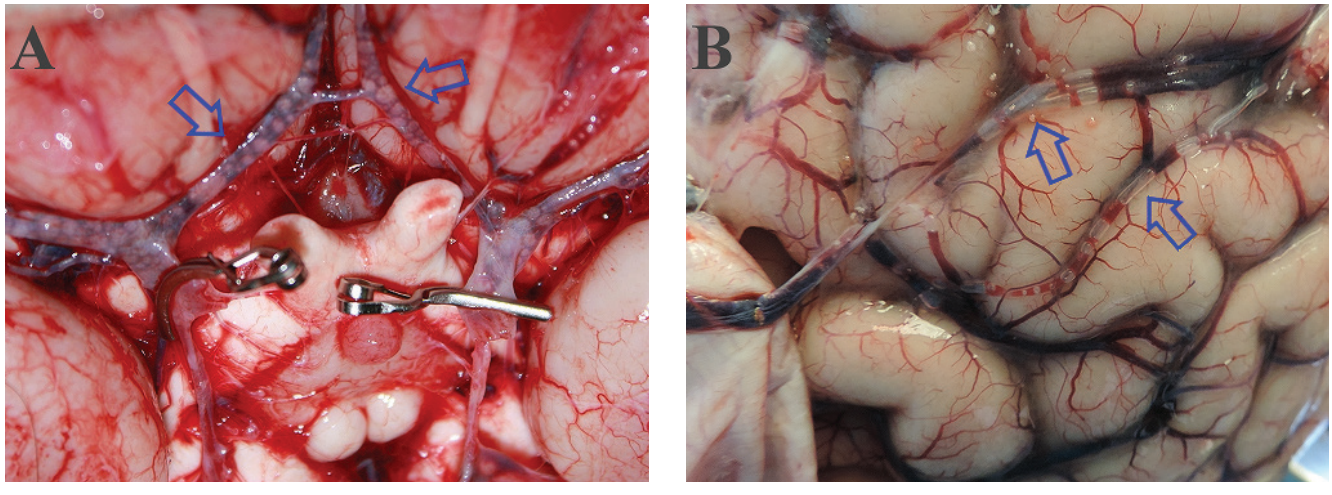

Figure 1. A. cerebral arterial gas embolism in diving fatality. A huge mass of spherical air bubbles in the circulus arteriosus cerebri (blue arrows). Both internal carotid arteries are occluded by clamps; **B.** artificial cerebral arterial air embolism due to forceful cardiopulmonary resuscitation with overpressure lung damage. Cylindrical gas bubbles with semispherical end caps are seen in the dural vessels (blue arrows)

Air embolism could be a serious complication associated even with minor medical interventions e.g. puncture of the central venous stems (subclavian, jugular veins), intravenous infusions or transfusions. Air can influx to the venous system also via medical catheters. The risk of catheter-related air embolism is increased with:

- General insertion/removal of catheter;
- Fracture or detachment of catheter connections;
- Dysfunction of self-sealing valves in plastic introducer sheaths;
- Deep inspiration during insertion/removal of catheter (increases the magnitude of intrathoracic pressure);
- Hypovolemia (reduces CVP);
- Upright positioning of the patient (reduces CVP) [6, 17].

Overpressure pulmonary barotrauma with subsequent air embolism can occur as a complication of positive-pressure ventilation of the lungs. At risk are mostly adults with acute respiratory distress syndrome (ARDS) or premature neonates with hyaline membrane disease, because positive-pressure pulmonary ventilation is used as their standard treatment method. If death can be linked to the medical interventions listed above, autopsies should be performed in such a way as to allow gas to be detected both inside and outside the vascular system [2]. Several cases of serious gas embolism associated with laparoscopy have also been reported. These were mostly curiosities without clinical impact, although some led to severe cardiovascular collapse [6]. Case of 16-month-old girl with erroneously connected catheter to the oxygen supply was published [18]. Paradoxically, hyperbaric oxygen therapy can cause air embolism in patients with preexisting pulmonary diseases [19].

Supersaturation causes of gas embolism

The crucial conditions of the gas bubble development de novo, either in tissues or in circulation, are diving with a breathing equipment, being under pressure during compressed air work, and through a sudden drop of environment pressure as in aviators. According to the worldwide diving safety organization DAN (Divers Alert Network), there are over 4 million active divers worldwide, which means a voluminous group of people at risk of supersaturation problems. The primary condition for bubble formation by supersaturation in the diver's body is previous saturation (on-gassing) of blood and tissues by breathing inert gas (nitrogen, helium). In the process of decompression (diver's ascent to the surface), inert gas bubbles can form directly in the blood vessels (intravascular, heterochthonous bubbles) or in tissues (extravascular, autochthonous bubbles), which remain in the place of their origin [20]. Heterochthonous bubbles, also referred to as 'wondering' bubbles, are passively carried by the bloodstream as true gas emboli. Autochthonous gas bubbles, which slowly expand their volume in the desaturation process, might cause catastrophic scenarios in sensitive organs (e.g. spinal cord). Nano-sized gaseous microbubbles of autochthonous origin can also enter the blood capillaries and further into the bloodstream through endothelial gaps, per diapedesim. The classification of supersaturation-induced gas bubbles as intravascular and extravascular is not entirely accurate because it only describes the location where the bubbles were observed, not their origin. Most supersaturation-induced gas bubbles, both in tissues and capillaries, can be recognized only by microscopy [14, 21].

Classification of gas embolism

Two basic types of gas embolism are generally recognized: arterial gas embolism (AGE) and venous gas embolism (VGE). The arterial type is less common, being most often associated with overpressure lung damage (barotrauma of ascent in diving, blast syndrome in explosions). The use of extracorporeal circulation (ECC) in heart surgery is a main cause of AGE by iatrogenic origin [6]. Venous-type gas embolism is typical for traumatic or iatrogenic episodes where the surrounding air is sucked into the venous vasculature, as well as for decompression sickness in divers. The morphologic barrier between arterial and venous systems represents the pulmonary parenchyma – an effective filter for gas microbubbles. However, such a natural self-defense barrier against abundant gas bubbles in the circulation can be overcome by:

- small-dimension gas bubbles: gas microbubbles with diameters smaller than that of pulmonary capillaries (less than 6 μm) can freely pass through the pulmonary capillary network into the arterial part of pulmonary capillary bed without being entrapped in the pulmonary circulation;
- large numbers of gas bubbles: more voluminous gas microbubbles can cause mechanical deformation and even direct damage of pulmonary capillaries, thus forcefully entering the arterial part of circulation [22,23].

Venous gas bubbles can penetrate the arterial

circulation also paradoxically via patent foramen ovale (PFO) or pulmonary right-to-left shunts. Such a paradoxical penetration of bubbles presupposes the fulfillment of the following conditions:

- patent foramen ovale (PFO) (in approximately one-third of the adult population);
- intrapulmonary arterio-venous shunting and/or sudden increase of pulmonary arterial pressure (physical load, Valsalva maneuver);
- presence of the gas bubbles in the arterial circulation, in the vicinity of the heart or lungs [24].

The gas bubble dilemma: volume or quantity?

In the arterial circulation, a small volume of gas bubbles already leads to a serious clinical manifestation, whereas the same amount of bubbles in the venous circulation may be asymptomatic. In such cases, the subsequent diffusion of gas into the alveoli and exhalation from the body usually follows [6,22]. The estimated lethal amount of gas (10 mL to 480 mL) varies depending on its location. Large amounts of gas are usually fatal, regardless of the affected circulation type. One of the most important factors contributing to mortality, even more significant than volume, is the gas accumulation rate. Gas can enter the circulation suddenly as a bolus or gradually. Unlike blood, gas is a compressible substance that is not adapted to the movement of the heart, acting as a muscle pump of a non-compressible fluid. A bolus dose of gas obstructs right ventricular outflow and absorbs the mechanical energy of ventricular contractions with rapid progression to severe cardiovascular collapse. The gradual entry of gas results in gas mixing with blood in the right ventricle, forming a foamy mixture. This 'aerated' blood will be loaded into the pulmonary circulation with its partial or complete obstruction [2, 5]. Excessive gas volume in lung vessels leads to pulmonary hypertension and right heart failure or promotes the development of pulmonary edema, 'the chokes,' due to microvascular obstruction with vasoconstriction, endothelial damage, inflammation, and increased permeability of pulmonary capillary bed. Gas solubility, body position, cardiopulmonary reserve, and hemodynamic conditions (hypotension, hypovolemia) of the subject are other factors that influence the clinical symptomatology of such events [6, 14].

"Silent" gas bubbles

The clinical manifestation of gas embolism depends on the extent and location of any vascular obstruction. The onset of symptoms is usually rapid, but may be delayed from a few minutes to hours [6]. The presence of gas in the intact circulation does not necessarily lead to clinical manifestations. Current studies using ultrasound Doppler and precordial echocardiography in divers shortly after surfacing have shown that even conventional dives with shallow depths and short bottom time have led to the formation of gas microbubbles in their circulation, sometimes to a high degree as 'bubble showers.' Doppler bubble studies, after analyzing thousands of dives, suggests that although in most dives microbubbles of inert gas form in the venous circulation, in the majority of cases the clinical outcome is asymptomatic, without any symptoms of decompression sickness. Thus, the term 'silent bubbles' was established for such cases [25]. It is probably the number of gas bubbles, their volume, and localization in particular tissues, being responsible for presumable clinical symptomatology [14]. In clinical medicine, the problem of 'silent' bubbles should also be reasonably presumed in iatrogenic gas embolism in particular; however, the condition is not yet fully understood.

Gas bubble morphology

The traditional idea of gas bubbles assuming a spherical shape has been verified by studies of computed tomography (CT) images or autopsies in the cerebral vasculature. This is valid for small bubbles, which must keep the bubble surface to volume ratio in order to remain stable in the bloodstream. Another possibility is an elongated, cylindrical, sausage shape of mostly arterial gas bubbles, which form easily according to the diameter and length of the vessel. The vessel wall responds to the insult of gas bubbles as pathologic stimuli by various mechanisms, which can also be determined by the bubble shape. A spherical bubble with small contact surface area will cause vasodilation with minimal friction resistance against further movement of the bubble. On the contrary, movement of sausage shaped bubbles will be reduced due to shape-induced vasoconstriction over the whole length of the bubble. In these cylindrical bubbles, the endothelial damage and ischemic effect to the periphery is also more pronounced. Intravascular movement of gas bubbles is also limited by the stickiness of the protein-coated bubbles with the endothelial surface. The behavior of gas bubbles in the intravascular bed can follow several scenarios:

- bubbles can remain stationary stuck where they create occlusion of the vessel;

- bubbles can fragment to smaller bubbles;
- bubbles can merge to cylindrical sausage-like shape;
- bubbles may disrupt to separate parts on the edge of vessel bifurcation [22, 23].

In fatal diving accidents (cerebral AGE), large numbers of small bubbles in the form of 'strings of pearls' were described in the transparent cerebral vessels. Even the vascular network of abdominal fatty tissue was found infiltrated by many tiny gas bubbles, visible to the naked eye [21].

Non-hypoxic gas bubble-conditioned lesions

The primary and relevant pathophysiologic consequence of the presence of gas bubbles in the bloodstream is tissue ischemia. However, the consideration of gas bubbles being only mechanical obstacles, partially or completely clogging the lumen of blood vessels, is obsolete. Although the origins of gas bubbles may vary, the consequences of their longer presence in the vasculature largely remain the same. Bubbles formed *in vivo* or introduced into the body are biologically active and act as a trigger for complex pathophysiologic mechanisms. In addition to ischemic occlusion of vessels and mechanical damage (tissue compression, disruption of delicate structures of blood vessels walls), gas bubbles also have a biochemical effect [20, 24]. When a gas microemboli becomes stuck in a small arteriole (diameter 100 to 1000 μm) or capillary, the interaction of the bubble with the vascular endothelium and cellular blood elements activates the inflammatory cascade (complement, bradykinin, coagulation). An increase in vascular wall permeability occurs by the formation of gaps between the originally tightly attached endothelial cells, followed by plasma extravasation, interstitial edema, and hemoconcentration [14, 23]. These pathophysiologic changes also have their particular morphologic features that should be confirmed histologically in justified cases (e.g. diving fatality) [21, 26, 27].

Post-mortem gas detection

In recent years, the development of post-mortem CT scans has significantly expanded the conventional autopsy approach in forensic medicine. Modern imaging technologies (CT, MRI) open up new possibilities for forensic pathologists to diagnose gas embolism, especially in cases of fatal diving accidents. In contrast with plain radiography, CT provides detailed information on the extent and distribution of gas in the body cavities, organs, blood vessels and tissues. MRI is more precise and allows detection of microbubbles in tissues (DCS-associated spinal cord changes). Although it has high sensitivity, it does not have specificity, but it is useful in pre-autopsy detection of any gas in the corpse [7, 28-30]. Hence, forensic pathologists are faced to strictly distinguish between true vital gas embolism as a vital phenomenon, post-mortem putrefactive gas artefacts, or even artificial gas, which can occur in blood vessels due to forceful resuscitation maneuvers (CPR). In diving fatalities, the intravascular tiny gas bubbles can appear as post-mortem decompression artefact (PMDA) due to physical off-gassing (post-mortem bubbling) of supersaturated tissues [26, 31]. Egger *et al.* [30] in their study using post-mortem multi-detector computed tomography (MDCT) presented a specific distribution pattern of postmortem gas. In the early stage of decomposition, gas was formed in deeper localized organs such as heart and liver. Putrefactive gas appeared very soon after death in the heart cavities, even before the liver parenchyma. Therefore, it can be very easily misinterpreted as gas embolism. Typical venous localization, small gas volume, and resuscitation anamnesis should suffice to exclude gas in the bloodstream as a contributor to death in non-traumatized patients [26, 29]. An autopsy should be performed shortly after death because the gas may dissolve in the tissues. In conventional autopsy, the diagnosis of gas embolism requires a special examination technique (e.g. as described by Mercier) [2]. An aspirometer can be used in order to measure gas volume and analyze gas composition. The collected gas mixture is subsequently processed through gas chromatography with separation of individual gases such as oxygen, nitrogen, carbon dioxide, methane, and hydrogen. Gas chromatography reliably distinguishes between vital gas embolism and post-mortem gas [32, 33]. The finding of air bubbles in the arachnoid cranial veins are always suspicious of an artefact that can be observed in many conventional autopsies without causality for gas embolism. Careless handling and forceful removal of the cranial vault always involves the suction of a certain amount of air into the arachnoid veins [2, 34]. Histologic examination should focus primarily on the contact sites of gas bubbles with the endothelium. In cases of fatal decompression accidents, the main sites of gas bubbles, in addition to the vasculature, are fatty and/or myelinated tissues such as brain and spinal cord. The zones of bleeding, accumulation of non-specific inflammatory cellular elements or microscopic tissue necrosis in the vicinity of gas bubbles can be found in bubble-disrupted tissues.

Such a microscopic image can serve to distinguish DCI from PMDA [26]. Highly perfused organs such as lungs and kidneys should be histologically examined for the presence of fibrin microthrombi, which may have arisen in direct response to the presence of microbubbles in blood vessels [21].

In conclusion, the presence of gas bubbles in human vasculature is a pathomorphologic entity, well known, and proven over the centuries; however, it is sometimes neglected, even today. In many cases, gas, as a volatile substance, may simply escape during autopsy or, if not in the forensic interest of a medical examiner, the gas may be overlooked. In autopsies of diving fatalities, the situation is favored by the fact that an informed forensic pathologist presumes the presence of gas bubbles anywhere in the corpse. Thus, the autopsy will be rationalized in spite of this fact. In other cases, the situation, both mental and tactical, is rather worse. The autopsy-performing specialist can simply exclude gas embolism from the scope of potential diagnoses, and when suddenly confronted with gas bubbles in vessels, it might be too late to conserve or document them.

Conflict of interest

The authors declare that they have no conflict of interest.

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