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CASE REPORT

Calcified myocardial necrosis in pediatric patients after cardiopulmonary resuscitation

Claas T. Buschmann · Werner Stenzel · Hubert Martin · Frank L. Heppner · Saskia S. Guddat · Michael Tsokos

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Abstract We report three autopsy cases of wide-spread myocardial necrosis with calcification in pediatric patients after temporary generalized hypoxia and initially successful cardiopulmonary resuscitation, but subsequent in-hospital death. Autopsy and histological workup in all three cases showed multiple circumscribed calcified and necrotic areas in progressive stages of organization within the myocardium. We conclude that these macro- and microscopic autopsy features appear to be related to reperfusion injuries in children as a consequence of hypoxic-ischemic changes occurring in the peri- and postresuscitation period.

Keywords Pediatrics · Cardiopulmonary resuscitation · Hypoxia · Myocardial calcification · Autopsy

Introduction

An imbalance in oxygen supply and demand, e.g., during cardiac arrest, and generalized hypoxia before cardiopulmonary resuscitation (CPR) attempts, results in tissue hypoxia, microvascular dysfunction, and finally tissue necrosis with organ failure and cell death. Its extent depends on various factors, e.g., the affected cell/tissue type, the duration of ischemia, the patient's age and pre-existing diseases. After a prolonged period of ischemia, sufficient reperfusion may lead to an initial satisfactory performance of the impaired tissue or organ, but also might cause reperfusion injuries related to oxidative stress by peroxidation of the membrane phospholipids and resulting in changes in the permeability of the cell membrane and cell death [1]. Such hypoxic conditions with subsequent reperfusion-related tissue injury contribute to morbidity and mortality in a considerable range of pathologies. They are also a major challenge during cardiothoracic, vascular and general surgery and solid organ transplantation [2].

Generally, cardiac oxidative stress severely compromises the cardiac antioxidant cellular system, causes cardiac antioxidant cellular system injuries and may result in oxidative damage such as depletion of nonenzymatic antioxidants such as glutathione [3]. In particular myocardial reperfusion injuries after cardiac arrest and generalized hypoxia with subsequent successful CPR have been widely described and evaluated concerning occurrence, pathophysiology and therapeutic options, particularly in adult patients [2, 4–8]. When compared to adults, children present a different pattern of physiological response to myocardial ischemia with subsequent reperfusion, e.g., changes in protein expression, known from cardiac transplantation procedures in pediatric patients or surgical repair of congenitally malformed hearts in infants [9–11]. Perioperative myocardial injury due to ischemia can be the major determinant of postoperative dysfunction after cardiac surgery, and infants seem to be more vulnerable than adults during ischemia [1, 12]. Significant differences in antioxidant protein levels in newborns compared with adults have also been demonstrated, showing that newborn hearts have diminished scavenging capacity [13]. The immaturity of the infant's myocardial metabolic capacity which may affect its ability to respond

C. T. Buschmann (✉) · S. S. Guddat · M. Tsokos
Institute of Legal Medicine and Forensic Sciences, Charité, Universitätsmedizin Berlin, Turmstr. 21, Building N, 10559 Berlin, Germany
e-mail: claas.buschmann@charite.de
URL: http://remed.charite.de

W. Stenzel · H. Martin · F. L. Heppner
Department of Neuropathology, Charité, Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

to ischemia might serve as an explanation and promote unfavorable conditions [1].

We present three pediatric autopsy cases with uncommon cardiac findings in terms of hypoxic-ischemic necrosis with subsequent wide-spread dystrophic calcification of the myocardium after generalized hypoxia and initially successful CPR. The incidents which required CPR were survived for weeks and months. Except for temporary generalized hypoxia and subsequent primarily successful CPR with return of spontaneous circulation (ROSC), there were no other common clinical features in the presented cases that would potentially explain the significant calcifications. The myocardial calcifications with subsequent loss of functional myocardial tissue were possibly contributory, but did not cause death (alone) in these three cases.

Case 1

A woman gave birth to a female baby in a public restroom. The mother stated that she had not noticed that she was pregnant, and the baby was immature. Rescue personnel were called to the scene, where at first inspection the emergency physician refused to undertake CPR efforts on the lifeless and obviously immature baby. Only at the behest of immediate medical treatment by a rescue technician was CPR successfully initiated, and the baby was transported to a Pediatric Intensive Care Unit (PICU). Cardiocirculatory stability was achieved at admission, but despite extensive pediatric intensive care support including inotropics for maintaining blood pressure and loop diuretics, severe complications with multi organ failure developed. The extremely premature baby died 10 weeks after birth due to septic complications arising from peritonitis.

Autopsy

As the mother stated that she had not noticed that she was pregnant, the baby's probable age was assessed at autopsy by measurement of the body. The girl's body length was measured at 38 cm with a weight of 1,354 g, head circumference 22 cm and crown-rump length of 26.5 cm, indicating a birth in about the 5th month of pregnancy with extreme prematurity. Apart from prolonged surgical and invasive PICU therapy, external examination of the body yielded no evidence of external injuries or violence; there were no fresh or older resuscitation injuries. The heart (weight 7 g) was fixed before further examination. Consistent with age and immaturity, the brain showed a blurred corticomedullary boundary. Apart from pulmonary edema due to long-lasting artificial ventilation, the lungs (left 16 g, right 17 g) were without visible tissue changes. Yellowish, partially hardened focal and also confluent tissue changes were centrally located in the spleen (weight 2 g) and in the kidneys (left 16 g, right 16 g). Furthermore, adrenal hemorrhage and icteric inner vessel wall layers were also observed. Cause of death was macroscopically assessed as septic multiple organ failure with extreme prematurity due to prior purulent peritonitis with laparotomy and repair of lacerated colon.

Histology

The heart was regularly developed, and without any congenital abnormity. The coronary arteries and valves were inconspicuous. Especially in the inner two-thirds of the left ventricular muscle layer, numerous extensive landmap-like areas with pale myocardial nuclei and partially dissolved cytoplasm were noted (Fig. 2b). Particularly in the outer portions there were pronounced flaky calcifications predominantly associated with necrotic myocardiocytes. The lungs were immature and showed overinflated areas with focal reticular interstitial fibrosis (bronchopulmonary dysplasia) and aggregated macrophages. In a few small arteries and capillaries sparse, partially organized and calcified microthrombi were detected. The mucosa of the larynx and trachea showed circumscribed necrotic areas extending to the depth of the submucosa. Focally calcified areas of necrosis were found in the striated muscles of the larynx, the hyaline cartilage tissue, and also in the glandular structures of the mucosa. The liver (weight 53 g) showed severe acute and subacute congestion with disseminated necrotic areas. Calcifications were not found. Splenic tissue presented microscopically extensive, geographical areas of necrosis with pronounced iron-containing calcifications as well as a resorptive inflammatory reaction and partly calcified vascular thromboses. The kidneys were regularly developed and showed a subtotal infarction of approximately 80 % of the renal tissue with extensive areas of necrosis with calcifications involving mainly peripheral parts of the necrotic areas and the tubular lumina, thus suggesting significant renal impairment prior to death (which may in turn have led to a not insignificant hormonal imbalance affecting calcium homeostasis). Focal partly calcified arterial thrombi were also found. A histological specimen of retroperitoneal fat tissue showed multiple, partially calcified fat tissue necrosis.

In summary, the histological report gave no evidence for any congenital organic abnormality, congenital metabolic disease or primary intrauterine infection. The child was expected to have been born in about the 5th month of pregnancy. The predominant histological changes were summarized as severe organ damage with secondary extensive necrosis with focal but marked calcifications in heart, spleen, kidneys, fatty tissue and also the gastro-intestinal tract,

suggesting that the necrosis were due to shock-induced disruption of perfusion immediately after birth. A superinfection of the gastro-intestinal tract necrosis with bacteria and fungi and pronounced chronic purulent inflammation of mesenteric fatty tissue and peritoneum led to a septic multiple organ failure which was considered as the final cause of death with underlying extreme prematurity.

Case 2

A 5-month-old boy was found unconscious by his parents. They immediately initiated CPR and called emergency personnel to the scene who continued CPR during transportation to the hospital. On admission to the Emergency Room (ER), the boy was unconscious, artificially ventilated, and pulseless despite own myocardial activity. The pupils were fixed and non-reactive to light. He was admitted to PICU where intensive medical care was able to stabilize the boy's circulatory system however his poor neurological condition did not improve. At day 10 after the incident, brain death was confirmed with formal testing, and the parents agreed to multiple organ donations (heart, liver, pancreas, kidneys). Echocardiography showed minor myocardial wall motion disturbances, however no clear contraindications for organ donation were identified. Organ harvesting was performed 10 days after the initial cardiac arrest. During the organ harvesting surgery the aortic cannula was placed incorrectly, and the cardioplegic solution could not be funnelled in an appropriate timeframe, thus the heart could not be used for transplantation and was returned to the body.

The boy was reported to have been born after an uneventful second pregnancy with all antenatal medical examinations and screening tests being normal. There was neither a family history of cardiac events nor a medical history except for a complication-free surgical correction of an inguinal hernia in the 2nd month of life. Medico-legal autopsy was ordered by the public prosecutor to clarify the cause of death and to exclude external violence.

Autopsy

Autopsy of the body (weight 6.7 kg, length 65 cm) confirmed multiple organ donations with surgical removal of heart, liver, kidneys and pancreas, in addition to signs of prolonged invasive PICU therapy. No fresh or older resuscitation-related or other injuries were obtained. The brain (weight 700 g) was remarkably pale and edematous, and the corticomedullary junction was blurred. All cut surfaces of the heart (weight 50 g) showed circumscribed hemorrhagic and calcified necrotic areas between 1.0 and 2.2 cm in diameter (Fig. 1a). All other available organs were macroscopically unremarkable with no further calcifications or hemorrhages. Cause of death was macroscopically assessed as either suspected Sudden Infant Death Syndrome (SIDS) with cardiac changes associated with previous cardiac arrest or as sudden cardiac death as a result of these myocardial changes. Additional toxicological and microbiological investigations were unremarkable.

Histology

In the left side of the heart, there were multiple areas with fresh hemorrhages, necrosis and extensive areas of calcification and—at the edges—intense histiocytic and macrophage infiltrations. The coronary arteries and valves were slight, and there was no evidence of pre-existing hypoxic, ischemic or inflammatory myocardial processes. Due to cardiac arrest most likely in the setting of SIDS, a global

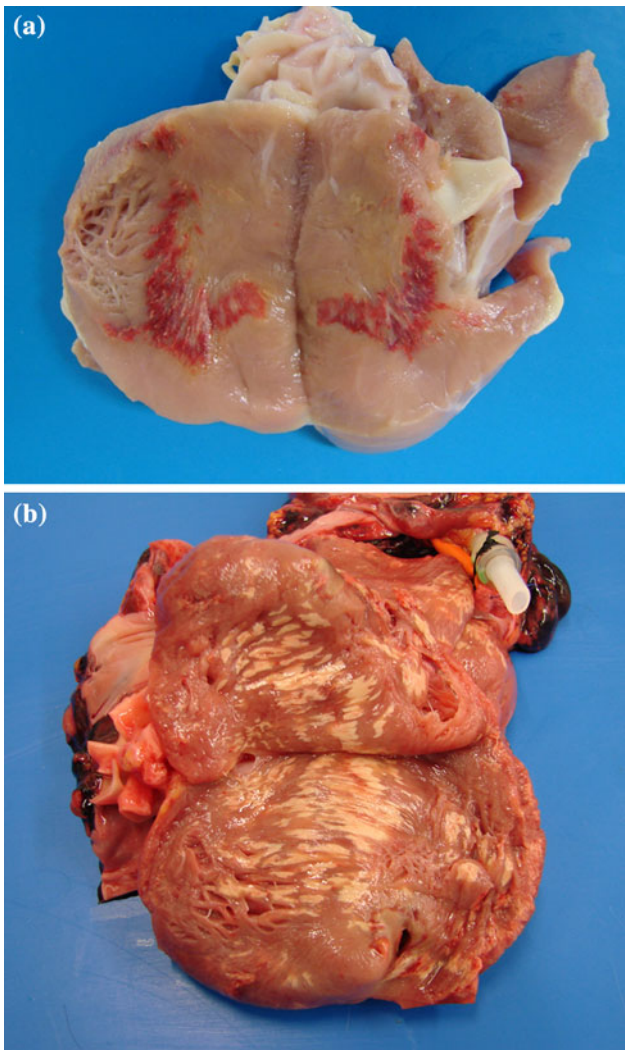

Fig. 1 **a** (Case 2) and **b** (Case 3): Macroscopic aspect of excessive calcified myocardial necrosis with a patchy/stripe-like aspect

cerebral edema (weight 700 g) with severe nerve cell loss, compatible with massive hypoxic brain tissue damage, was identified. The histiocytic and mesenchymal reactions indicated an age of about 10 days. All other organs studied were unremarkable. Further diagnostics, e.g., for genetically determined channelopathies or ultrastructural analyses, were not performed.

Case 3

Two unattended girls (2 and 2.5 years old) broke through the ice of a lake into the cold water and were rescued a few minutes after the accident by the supervising kindergarten teacher. While the 2-year-old girl remained uninjured, the 2.5-year old girl was unconscious. She received immediate CPR by emergency physicians and was transferred to hospital. On admission to the ER, the body temperature was 24.4 °C with cardiocirculatory insufficiency as well as wide, non-reactive pupils. The girl was moved to PICU and surgically connected to the heart–lung machine. With rewarming but persistent neurological deficiency, cerebral death diagnostics were performed, and the child was pronounced dead 9 days after the incident. Organ donations were not made. The clinical cause of death was cerebral death due to hypoxia after near-drowning. There was neither a family history of cardiac events nor other significant medical history. Medico-legal autopsy was ordered by the public prosecutor to clarify the cause of death, to exclude external violence and to evaluate if the child could have survived the near-drowning if the kindergarten teachers would have paid correct attention to the children.

Autopsy

The body was 93 cm tall and weighed 16 kg. Apart from evidence of prolonged invasive PICU therapy, external examination of the body yielded no evidence of external injuries or violence; there were no fresh or older resuscitation injuries. Macroscopic autopsy findings revealed severe brain edema (weight 1,330 g). Shock lungs (left 140 g, right 209 g) were noted with probable early onset of hepatic necrosis (liver weight 650 g). The heart (not weighted because of surgically adapted parts of the heart–lung-apparatus in situ) showed striped, parallel, horizontally arranged, partially confluent beige-colored areas of pallor between 0.3 and 1.2 cm in diameter in the apical and basic parts of the anterior wall and also in the entirety of the posterior wall (Fig. 1b). No marked changes were observed in the other organs, especially there being no further calcifications. Cause of death was near-drowning with subsequent cerebral death. Femoral venous blood and urine were collected for toxicological analysis, but toxicological examinations revealed no specific findings. Further diagnostics were not carried out.

Histology

The left ventricular anterior and posterior walls showed large, infarct-like hypoxic-necrotic areas with uniform partly striped, partly focal and confluent myocardial necrosis, hypereosinophilia and marked calcification (Fig. 2a), especially impressive with von Kossa's staining (Fig. 3). In semi-thin sections calcification appeared to be localized intracellularly and also as an extracellular deposit (Fig. 4). The coronary arteries and valves were unremarkable. Indicating an underlying event a few days prior, there was an accentuated histiocytic response (migrating from peripheral to central), and a lymphohistiocytic reaction extending into the inner sections of the necrotic areas. In between, remnants of normal myocardium were found.

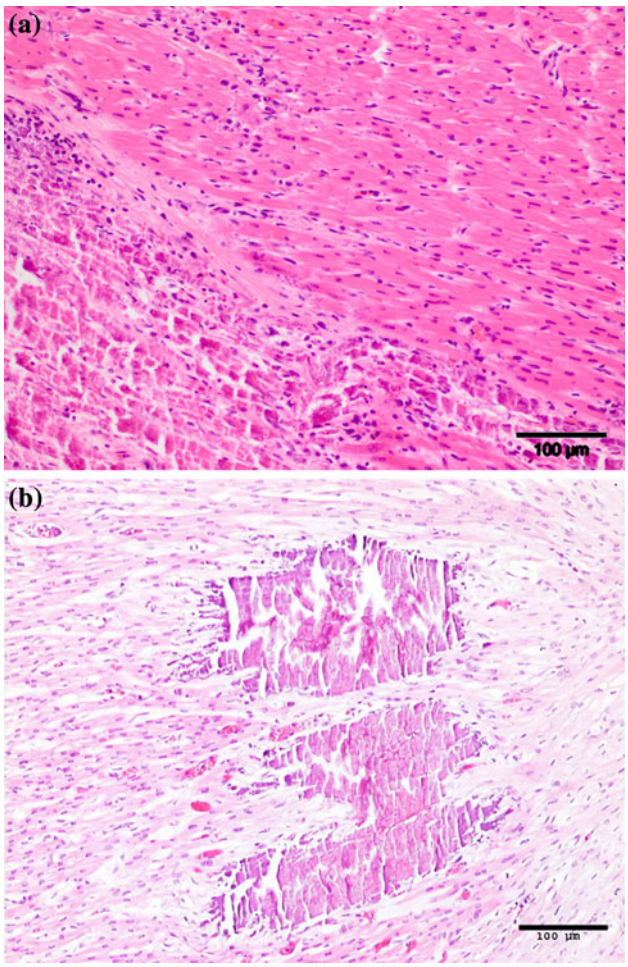

Fig. 2 **a** (Case 3) and **b** (Case 1): Microscopic aspect of calcified necrosis in the myocardium which appears in large confluent areas (**a**) and in the papillary muscles (**b**). Hematoxylin eosin staining, original magnification ×200

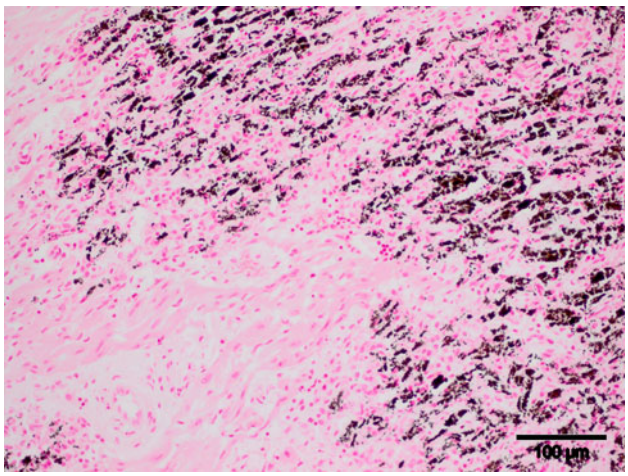

Fig. 3 (Case 3): Von Kossa's staining specifically illustrates calcified tissue within the necrotic myocardium. Original magnification, ×200

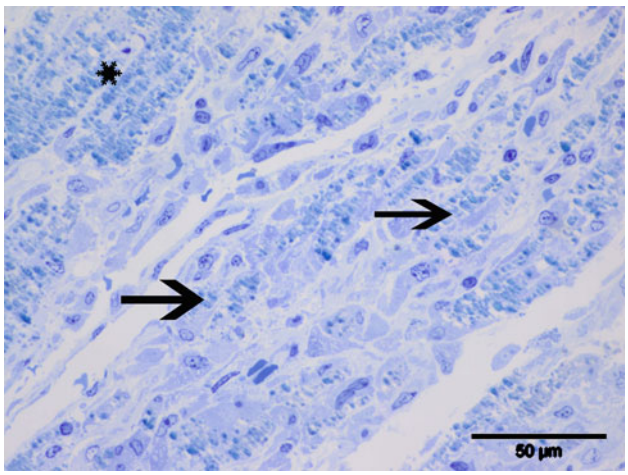

Fig. 4 (Case 3): In semi-thin-sections, Richardson's methylene blue staining ×600, calcification appears to be localized intracellularly (*arrows*) and also as an extracellular deposit (*star*)

There was no evidence of pre-existing hypoxic, ischemic or inflammatory processes. Further ultrastructural analysis of the myocardium showed large foci of calcifications within cardiomyocytes. The calcifications were not linked to mitochondria. Mitochondrial morphology was unremarkable; notably no calcification was found (Fig. 5). All other organs revealed no further calcifications. In accordance with the macroscopic autopsy findings, death was considered to have occurred as a direct consequence of the near drowning incident 9 days prior and subsequent cerebral death.

Discussion

We present three pediatric autopsy cases with wide-spread dystrophic myocardial calcifications. To the best of our

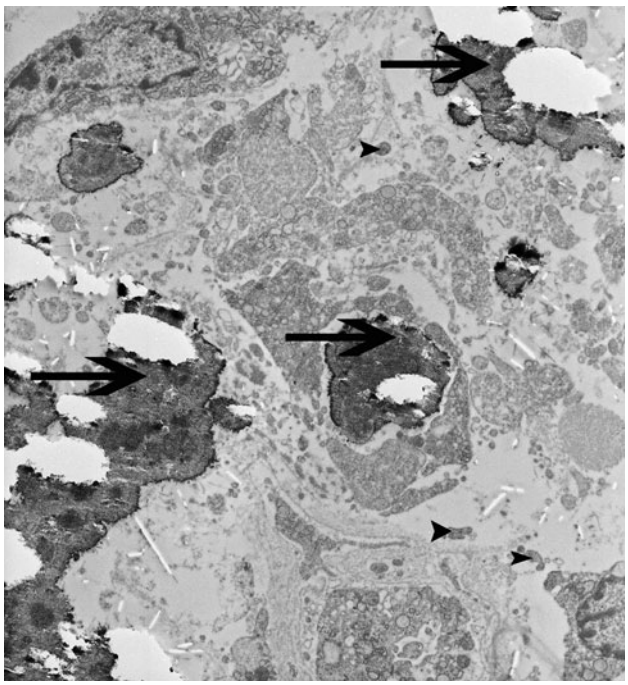

Fig. 5 (Case 3): Ultrastructural analysis of the myocardium shows large foci of calcifications (*arrows*) within cardiomyocytes. These are not linked to mitochondria (*arrowheads*). Mitochondrial morphology is unremarkable; especially no calcification can be detected in these organelles. Original magnification, ×13,000

knowledge, such findings have not been reported in the context of primarily successful CPR and indicate that only a few days of survival after a hypoxic-ischemic condition are required for formation of such reperfusion injuries in pediatric patients. The degree of calcification in other organs apparently depends on the time of survival; the heart seems to be a primary target. Although cause of death was not cardiac failure in any of the cases, a connection between the cardiac autopsy findings and death at any given point of time may exist. Whereas there might be alternative etiopathological explanations for the extensive calcifications (e.g., loop diuretics such as furosemide during PICU treatment may lead to calciuresis and profound nephrocalcinosis in case 1, potential "subclinical myocarditis" may lead to excretion of dystrophin and intracardiac "scarring," secondary hyperparathyroidism), all reported cases have in common that the patients survived hypoxic-ischemic conditions by CPR but died days, weeks, or months, later. However, due to longer survival time and extreme prematurity in case 1, the pathogenetic mechanism of myocardial calcification in case 1 is possibly not the same as in the cases 2 and 3.

Generally, in coagulative or liquefactive necrosis there are calcified areas which are not absorbed or cicatrized: Infarcted muscular tissues with calcification occurring after reperfusion have been described, and calcified areas of

necrosis are well recognized in gynecological and bony tumors. Further clinical examples are calcifications of teratomas, tuberculous tissue with caseating necrosis, lithopaidion (calcification of a dead fetus in utero) and phleboliths (calcification of venous blood clots). Dystrophic calcifications are deposits of calcium in necrosis, hemorrhages, and/or with fibrosis. This pathology is explained by the fact that with nullified perfusion in the affected tissue, the mitochondrial adenosinetriphosphate (ATP) synthesis is also inhibited, leading to cessation of the ATP-dependent calcium transport via the cell membrane ("swelling necrosis"). If the tissue is reperfused after a prolonged period of ischemia, Ca^{2+} and water will then influx into the cell and into the mitochondria where Ca^{2+} is intercepted in the mitochondria. Furthermore, upon reperfusion, essential substrates for the generation of ATP will influx into the cell, and rapid normalization of the extracellular pH will occur, creating an H^+ gradient across the plasma membrane. Thus the Na^+/H^+-exchange and a Na^+-influx is triggered, instantly activating the surface Na^+/Ca^{2+}-exchanger which absorbs Na^+ via excretion but accumulates Ca^{2+} in the cell [1, 7]. Beyond that, oxidative stress may result in cellular alterations including a depression in the activity of sarcolemmal Ca^{2+}-pump ATPase and Na^+-K^+-ATPase activities. These changes lead to decreased Ca^{2+}-efflux and increased Ca^{2+}-influx, respectively. Oxidative stress has also been reported to depress the sarcoplasmic reticulum Ca^{2+}-pump-ATPase and thus inhibits Ca^{2+}-sequestration from the cytoplasm in cardiomyocytes [14, 15]. Finally, accumulation of calcium and phosphate in the mitochondria finally results in mitochondrial rupture and consecutive calcification of the whole cytoplasm [16].

Calcified myocardial necrosis in infants have been reported after birth-related hypoxia, idiopathic arterial calcification and other conditions with decreased perfusion and reduced oxygen supply due to maternal collagenosis, myocarditis, and intrauterine infection [17–21]. Cocaine-induced vasospastic hypoxia in maternal chronic cocaine abuse, the "congenital heart block" (auto-immunological process of maternal Ro/La antibodies that irreversibly damage the cardiac conduction tissue of the child) and trisomy 13 and trisomy 21 also predispose to myocardial (papillary) calcifications of the child [22–25]. Moreover, myocardial calcifications have been seen after cardiac surgery, especially in infants, and are also ascribed to prolonged ischemic conditions during the surgical procedure; the grade of the resulting myocardial ischemia-related tissue damage depends on the length of ischemia. All these differential diagnosis should be taken into account by the forensic pathologist when confronted with pediatric myocardial calcifications at autopsy.

Pulselessness naturally also represents a state of hypoxia when initially untreated by CPR—even with sufficient external cardiac massage a systemic blood pressure of about 30 % of the original systemic blood pressure can be achieved which then may lead to reperfusion of myocardial tissue and cardiac action again [26], but this is not to be considered as continuous satisfactory oxygen supply. Beyond that, studies have shown that the pediatric heart is more sensitive to ischemia and reperfusion injury compared with the adult heart [27–29]. For the etiopathology of the newborn heart's greater susceptibility to hypoxia reactive oxygen species, inflammation, accumulation of metabolic end products, tissue pH, immaturity and apoptosis may be responsible [13].

Myocardial damage following CPR has been reported in the context of external cardiac massage considered as blunt chest trauma with possible subsequent immediate or even later laceration of the myocardium [30, 31]. Calcification of the myocardium may follow such injuries [32–34], and ROSC elicits an array of damages to the cell, including membrane lipid peroxidation, cross-linking and degradation of proteins, and the nicking of DNA, resulting in the impairment of cellular integrity and function.

In our cases there was no CPR-related trauma, especially not to the myocardium. Also pre-existing myocardial damage was not found. All cases have in common that a

Table 1 Patient characteristics

Case	Sex	Age	Survival time after initially successful CPR (days)	Myocardial calcifications	Other calcifications	Cause of death	Pre-existing diseases
1	f	Newborn (extreme prematurity, 20th week of pregnancy)	60	Yes	Yes	Septic multi organ failure	Extreme prematurity
2	m	5 months	10	Yes	No	Sudden infant death syndrome	No
3	f	2.5 years	9	Yes	No	Near-drowning	No

significant time of generalized hypoxia was survived for at least several days. An overview of circumstantial features is given in Table 1. In case 1, CPR started after a longer period of time. In case 2, the incident was not witnessed and (delayed) CPR was conducted by parents (medical laymen). In case 3, the incident was not witnessed either and CPR was also started after a longer period of time. Thus, a significant time of hypoxia, i.e. several minutes, with relevant hypoxia-related tissue necrosis and continuous tissue demise, can be assumed in all three cases. Nonetheless, sufficient cardio-circulatory performance was regained by CPR, followed by in-hospital support measures. Calcification of the necrotic myocardial tissue must have taken place after initial CPR—there were no indications that the calcified necrosis were pre-existing, and their histological picture corresponded to the successful CPR efforts. Since pre-existing pathological conditions were not present in our cases, we must refer to the initially pulseless condition with subsequent hypoxia-related tissue necrosis, CPR and reperfusion thereafter as the cause for the massive myocardial calcifications. Interestingly, mitochondrial structures remained intact, at least in case 3. This doubts the suggested etiopathological pathway of mitochondrial rupture after ATP depletion with reperfusion and necessitates alternative paths of origin which are yet unclear. Despite the myocardial calcifications, none of the cases showed evidence of myocardial damage in the clinical course. The amount of calcification as well as its specific distribution (striped) is astonishing and apparently unique in infants. Probably this autopsy feature is seen more often than is published. Together with the insights into the pathophysiology, the short time course and the difference compared to adult pathology, this is worth a reminder.

Key points

1. If survived for a longer period of time (e.g., days/weeks/months), hypoxic episodes in children may lead to calcified areas of necrosis from reperfusion injury, especially in the myocardium.
2. Despite excessive myocardial calcification, mitochondrial structures may remain unaltered, despite mitochondrial rupture being proposed as an etiopathological pathway.
3. These myocardial calcifications may not be the direct cause of death in children after initially successful resuscitation; in the presented cases, death was caused by hypoxic-ischemic lesions of other organ systems.
4. After initially successful resuscitation with brain death pediatric patients should be evaluated carefully with regard to organ donation, especially with regard to the heart. This might include diagnostic tests such as cardiac CT before transplantation.

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Conflict of interests None.

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