13 Coronary Sclerosis, Myocardial Infarction, Myocarditis, Cardiomyopathy, Coronary Anomalies, and the Cardiac Conduction System

Sudden unexpected deaths occur frequently in forensic autopsy practice. In such cases, pathological findings in the heart can often explain the acuteness of death (Fineschi et al. 2006; Fineschi and Pomara 2004). In addition to ruptured myocardial infarcts, these pathological changes include rare diseases, such as a primary heart tumor (atrial myxoma, rhabdomyosarcoma, *cardiac fibroma*; Ventura et al. 2012; Pusta et al. 2015) or pericardial tamponade in the case of a dissecting aortic aneurysm. Pathological changes also include:

- Acute coronary insufficiency in the case of stenosing coronary sclerosis
- Myocardial infarction
- All forms of myocarditis
- Cardiomyopathies of varying etiology
- Hereditary anomalies of coronary artery development
- Lesions of the cardiac conduction system
- Primary cardiac tumors

Histological and/or immunohistochemical findings of varying severity can be expected in all of the abovementioned pathological changes to the heart, on the one hand, confirming the macroscopically suspected diagnosis and, on the other, only then enabling the crucial differential diagnosis. Primary cardiac tumors are extremely rare as a cause of sudden death (Jiang et al. 2009). Sudden cardiac death (SCD) is one of the most common causes of death, and an important number of sudden deaths, especially in the young, are due to genetic heart disorders, both with structural and arrhythmogenic abnormalities (Rodríguez-Calvo et al. 2008). TUNEL can be a useful screening method in sudden cardiac death (Edston et al. 2002). There are a number of different terms for sudden cardiac death in the absence of coronary atherosclerosis: *Pokkuri death syndrome* (PDS) in Japan, "Lai Tai" in Thailand, "bangungut" in the Philippines, "dream disease" in Hawaii, and "sudden unexpected nocturnal death syndrome" among South Asian immigrants in the USA. Lipid metabolism disorders, for instance, are discussed as a possible cause (Takeichi et al. 2001). In order to document the various diseases underlying the phenomenon of sudden cardiac death, the Association for European Cardiovascular Pathology published their "Guidelines for autopsy investigation of sudden cardiac death" (Basso et al. 2008a, b). Finally, the literature describes comparatively rare findings that are seen in rare diseases or that infrequently occur following medical procedures. For example, calcified myocardial necrosis in pediatric patients following cardiopulmonary reanimation has been reported (Buschmann et al. 2013), as well as a combination of arrhythmogenic right ventricular cardiomyopathy and cystic tumor of the atrioventricular (AV) node (Cavanaugh and Prahlow 2013).

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13.1 Sudden Coronary Death

Autopsy frequently shows a stenosing coronary sclerosis of varying severity in subjects with acute or sudden death, also in defined patient collectives such as adolescents (Weiler and Knieriem 1975; Weiler and Risse 1981; Janssen 1968; Walthard 1942) or young women (Althoff 1983) *or smokers* (Leone 2014). On the one hand, autopsies have shown severe forms of arteriosclerotic stenosing coronary scleroses—partly infected with *Chlamydia pneumoniae* (Dettmeyer et al. 2006a)—in people who, until death, had had sufficient cardiac function. On the other hand, autopsies have also shown partially isolated coronary scleroses with only moderate stenoses of the vascular opening, which are given as the cause of death. In such cases, evidence of acute or protracted ischemia of the myocardium is crucial, either in extensive areas of the myocardium as a myocardial infarction or in the form of fresh and possibly focal myocardial ischemia under stress.

In conventional histology, a morphological equivalent of clinically indicated acute lethal coronary insufficiency is often difficult to identify; at best small scarred areas can be found as an indication of older, preceding local ischemia with circumscribed myocardial necrosis and scarring. Occasionally, single necrosis with homogeneous eosinophilia, myofibrillar degenerations, contraction bands, and thick cytoplasm accompanied by interstitial edema are also found. Acute myocardial ischemia can be displayed immunohistochemically by means of a wide range of primary antibodies (Xiaohong et al. 2002; Xu et al. 2001; Zhang and Riddick 1996; Brinkmann et al. 1993; Greve et al. 1990; Shekhonin et al. 1990; Steenbergen et al. 1987). Unlike circumscribed myocardial infarction, immunohistochemical investigations in cases of subtotal obturating thrombosis and coronary sclerosis show a rather diffuse pattern of damage (Brinkmann et al. 1993). Additionally, there are cases of sudden cardiac death in non-atherosclerotic and noninflammatory intimal cellular proliferations usually affecting small and medium caliber arteries (Dermengiu et al. 2010a, b, c). Fibromuscular dysplasia (FMD) was first described in 1958 by McCormack who reported its histological appearance in four patients with renovascular hypertension. Meanwhile, FMD is defined as an idiopathic, segmentary, noninflammatory, and non-atherosclerotic condition of the arterial walls, leading to stenosis in small and medium arteries (Dermengiu et al. 2010c with definitions for non-atherosclerotic histological alterations of the intima).

Coronary Thrombosis

Occasionally, it is difficult to macroscopically differentiate postmortem blood clots from intravascular thrombosis. Very small thromboses, for example, in a disrupted atheroma bed, may be overlooked. Histological evaluation of coronary thrombosis, which also serves as evidence, is often necessary, especially in the context of a legal expert opinion.

A note on dissection: Opening the coronary arteries longitudinally is not recommended, but rather lamellar cuts should be made perpendicular to the axis of the vessel and their localization from proximal to distal recorded. Postmortem coronary angiography might also be helpful. Tissue cross sections of the coronary vessels should include the arterial adventitia and adjacent soft tissue.

Coronary thrombosis (Fig. 13.1) normally involves white thrombi (see Chap. 9). The histological findings in the coronary arterial wall regularly show pathological arteriosclerotic changes, which are considered to be the cause of the wall-adherent thrombosis and early organization. In individual cases, a primarily inflammatory vascular disease (e.g., coronaritis, Kawasaki disease) might be the cause of coronary thrombosis; in extremely rare cases, the cause may be previous trauma (cardiac contusion). Staining methods recommended for diagnosis are as follows: HE, Elastica van Gieson, PTAH, and Prussian blue. Nuclear

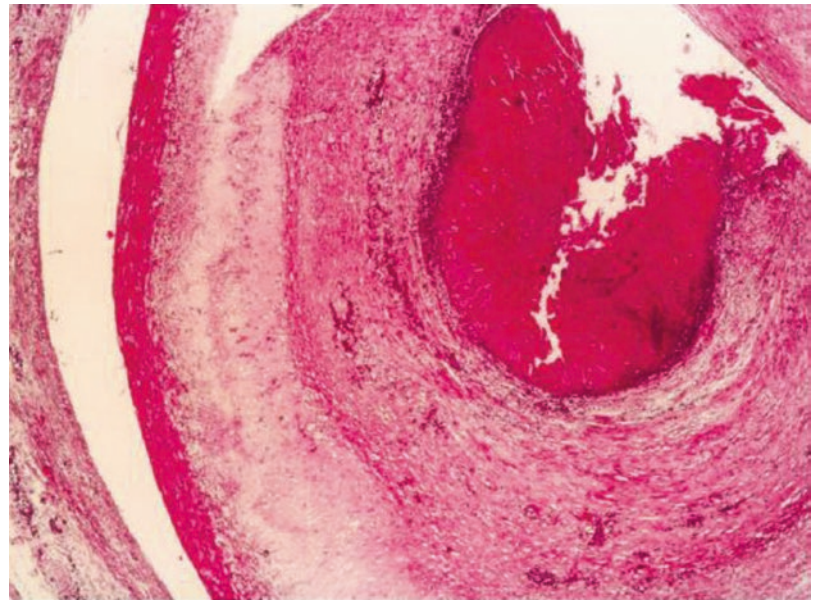

Fig. 13.1 Obturating coronary thrombosis in the setting of coronary sclerosis as a cause of acute myocardial infarction: atherosclerotic stenosis with fresh, central thrombosis (H&E ×40) (see Chap. 9 for determination of thrombus age)

morphometry of the myocardial cells as a diagnostic tool in cases of sudden death due to coronary thrombosis was investigated (Lazaros et al. 1998).

Meanwhile, immunohistochemical techniques have been widely utilized in the study and diagnosis of early myocardial ischemia. Large numbers of experiments indicate that myoglobin or desmin depletion, for example, can be used as morphologic parameters to diagnose early myocardial ischemia. Other authors investigated the immunohistochemical distributions of myocardial hypoxia-inducible factor (HIF)-1-α and its downstream factors, erythropoietin (Epo) and vascular endothelial growth factor (VEGF), in cardiac deaths. HIF-1-α was found weakly positive in cardiomyocytes in the cardiac necrotic region and intensely positive in the nuclei of cardiomyocytes showing eosinophilic change. Epo and VEGF were weakly positive in cardiomyocytes in the necrotic region, but intensely positive in the cytoplasm with eosinophilic change. Additionally, Epo was shown to be positive in macrophages of necrotic areas (Zhu et al. 2008). The diagnostic value of selected histological staining and immunohistochemical markers can be seen in Table 13.1. However, the spectrum of possible immunohistochemical markers to prove fresh myocardial infarction is more extensive, based in part also on animal models. The following markers, although not all adequately supported by studies, have been mentioned: myoglobin, C1, C3, C8, C9, CD59, α-actinin, vinculin, FABP, HIF-1α, PHD2, PHD3, CT-I, dystrophin, SORBS2, S100A1, npCX-43, CX-43, GAL-1, dityrosine, IL-15, MCP-1, GAL-3, CTn1, H-FABP, and Jun B. Here, positive evidence of antigen expression is in some cases significant and in others its loss, and thus the failure to detect it is relevant to diagnosis (Sabatasso et al. 2016).

Contraction band necrosis (*CBN*), *myofibrillary degeneration* (*MFD*). Histologically, this form of myocardial necrosis is characterized by:

- Irreversible hypercontraction of cardiomyocytes
- Markedly thickened Z-lines
- Extremely short sarcomeres
- Breakdown of the whole contractile apparatus
- Irregular pathological and eosinophilic cross-bands consisting of segments with hypercontracted or coagulated sarcomeres
- Total disruption of myofibrils
- A granular aspect of the whole cell without clear-cut pathological bands

Table 13.1 Conventional histological and immunohistochemical staining methods or techniques used to diagnose early myocardial damage in cases of cardiac and noncardiac perfusion damage (selection)

Conventional histological staining	Immunohistochemical markers
H&E and H&E in combination with fluorescence (Saukko and Knight 1989; Badir and Knight 1987; Fechner and Sivaloganathan 1987; Al-Rufaie et al. 1983; Carle 1981)	Complement C5b-$9_{(m)}$: positive reaction in the case of macroscopically visible myocardial infarction and in borderline cases (Thomsen and Held 1995; Thomsen et al. 1990; Schäfer et al. 1986; Knight 1967); also for the detection of group necroses; if C5b-$9_{(m)}$-positive, then also fibrinogen-positive reaction; early necrosis marker with positive reaction especially in desmin-negative areas; detectability may vanish after the acute stage; C5b-$9_{(m)}$ should only be positive if contraction bands can be detected in the chromotrope aniline blue stain (CAB) (Amberg 1995)
After approximately 30 min first visible contraction bands as a consequence of the collapse of the myofibril apparatus (Amberg 1995)	
Luxol fast blue (LFB) staining (Oehmichen et al. 1990a, b; Pedal and Oehmichen 1990; Arnold et al. 1985)	Fibronectin: positive detection in the case of macroscopically visible myocardial infarction and in borderline cases (Shekhonin et al. 1990); also for the detection of group necroses (Fischbein et al. 1986)
Hematoxylin basic fuchsin picric acid (HBFP staining) (Janssen 1984; Lie et al. 1971; Lie 1968): shows early myocardial ischemia; staining is very sensitive but not very specific (Amberg 1995)	Desmin (structural protein) + myoglobin (functional protein)—in both cases negative reaction, i.e., no desmin and no myoglobin in the acute ischemic area (Chumachenko and Vikkert 1991; Leadbetter et al. 1989, 1990; Ishiyama et al. 1982), possible focal depletions in the case of diffuse myocardial ischemia
Chromotrope aniline blue (CAB) stain (Zollinger 1983): presents visible contraction bands due to the collapse of the myofibril apparatus after approximately 30 min (Amberg 1995)	Troponin I: early negative reaction in the case of myocardial infarction (Hansen and Rossen 1999)
Alizarin complex stain: detection of early hypoxic myocardial damage by determining free oxygen radicals may be possible (Amberg 1995)	Fibrinogen: positive detection in the case of macroscopically visible myocardial infarction and in borderline cases (Shekhonin et al. 1990)
	HIF-1-α (hypoxia-inducible factor 1α)—stains necrotic areas within the first 2 h (Pampín et al. 2006)

Data is based on animal experiments and/or studies on human myocardium

Contraction band necrosis (Fig. 13.2), defined as above, can be observed in many human pathologies (Curca et al. 2011; Oehmichen et al. 1990a, b) and is reproduced experimentally by intravenous infusion of catecholamines. It does not represent an ischemic change (Baroldi et al. 2001; Todd et al. 1985a, b). Conditions associated with contraction band necrosis are (according to Karch 2009 and modified from Karch and Billingham 1986) reperfusion, steroid therapy, electrocution, defibrillation, cardiopulmonary resuscitation (Curca et al. 2011), drowning, cocaine, amphetamine, epinephrine, isoproterenol, norepinephrine, cobalt poisoning, starvation, myocardial infarction, free-radical injuries, brain death, phenylpropanolamine, intracerebral hemorrhage, and MDMA.

The detection of contraction bands or myofibrillar degeneration is carried out by means of H&E and PTAH staining methods, particularly with the modified Luxol fast blue staining method according to Arnold et al. (1985). Corresponding lesions, however, are found in multiple causes of death (e.g., drowning, shock, intoxication, hanging). CBN or MFD are therefore unspecific phenomena, which are indicative of asphyxia and are taken as evidence of an event during life (Oehmichen et al. 1990b).

Frequently, no histomorphological findings (neither macroscopic nor obtained using conventional histological staining) which could have led to heart failure or acute lethal cardiac arrhythmia can be seen to explain, e.g., local myocardial ischemia. Exceptions include findings in the

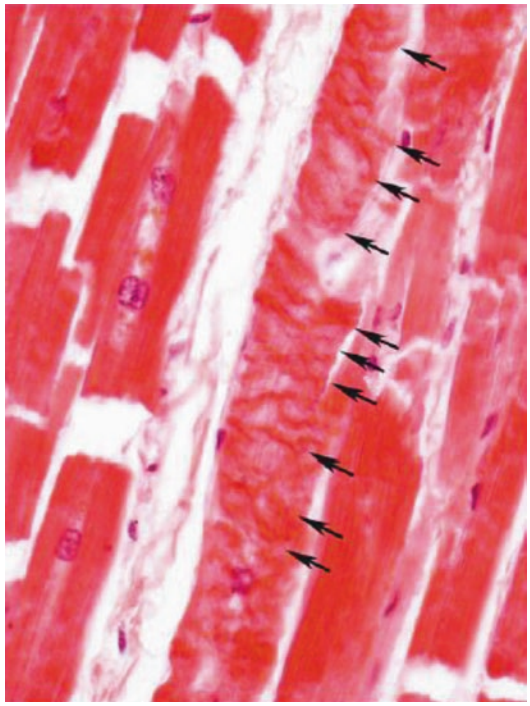

Fig. 13.2 Contraction band necrosis—myofibrillary degeneration (H&E ×400)

cardiac conduction system, for example, at the sinoatrial node; however, the significance of these findings is controversial. What is crucial in many cases is that a limit has been exceeded (e.g., physical and/or emotional stress, postprandial myocardial ischemia in the case of a full stomach), resulting in localized or diffuse myocardial ischemia. These diagnostic problems have resulted in a range of immunohistochemically usable myocardial ischemia markers now being recommended (Brinkmann et al. 1993).

If these immunohistochemical findings, along with anamnesis and macroscopic findings in the coronary arteries and myocardium, reveal a similar pattern, a diagnosis of acute lethal coronary insufficiency in the setting of stenosing coronary sclerosis is indicated. The degree of severity is less meaningful, however, in some cases. This applies to all cases where competing causes of death need to be excluded.

The conventional histological and immunohistochemical ischemia markers which have been recommended in the literature can also be used in cases of perfusion disturbance of noncardiac origin. Some immunohistochemical markers for the diagnosis of myocardial ischemia are explained here in more detail.

C5b-9$_{(m)}$. This is activated complement C5 with one C6–C8 molecule and six C9 molecules. Ischemically damaged cell membranes cause C5 activation. Complete myocardial necrosis can be clearly differentiated using an antibody against activated C5b-9$_{(m)}$.

C5b-9$_{(m)}$ forms transmembrane channels that accelerate the effect of calcium ions and thus lead to a direct toxic effect on myofibrils, or they trigger damaging secondary reactions. Thomsen and Held (1995) reported that they were unable to demonstrate C5b-9$_{(m)}$ in the myocardium of any of their cases of myocardial injury not caused by infarction. This means that C5b-9$_{(m)}$ was negative in cases with direct myocardial lesions, especially those caused by external trauma and with diseases directly affecting the myocardium. Additionally, C5b-9$_{(m)}$ seems to also be negative in indirect myocardial lesions due to systemic factors affecting the entire organism. For the early diagnosis of myocardial infarction, reference is made to the immunohistochemical identification of complement C9 (Piercecchi-Marti et al. 2001).

A note on microscopic analysis: Deeper wall portions of arteries show positive detection of C5b-9$_{(m)}$ in non-ischemic or non-necrotic areas, such that this reaction can be used as an "internal positive control" (Thomsen and Held 1995; Thomsen et al. 1990).

Creatine Kinase MM

Creatine kinase-type MM (CK-MM) for fast energy supply is predominantly found in the myocardium. In animal experiments, a significant decrease in creatine phosphate was detected as early as 30 s after ligating a coronary artery (Osuna et al. 1990). Immunohistochemically, CK-MM is normally represented homogeneously. Detection may be patchy or completely absent, depending on

the duration of ischemia; this also applies to circumscribed perfusion disturbances. Parallel to this, the detectability of desmin drops off (Amberg 1995).

Desmin

Desmin is a structural protein which is topographically associated with Z-lines of the muscle cell. Hypoxia-based activations of proteases are said to change the structure of desmin in such a way that the immunohistochemically used antibody no longer recognizes the antigen, while desmin can be well represented immunohistochemically in normally perfused heart muscle tissue (Wick and Siegal 1988). The result is that desmin is no longer identifiable in ischemically damaged myocardium (Fig. 13.3).

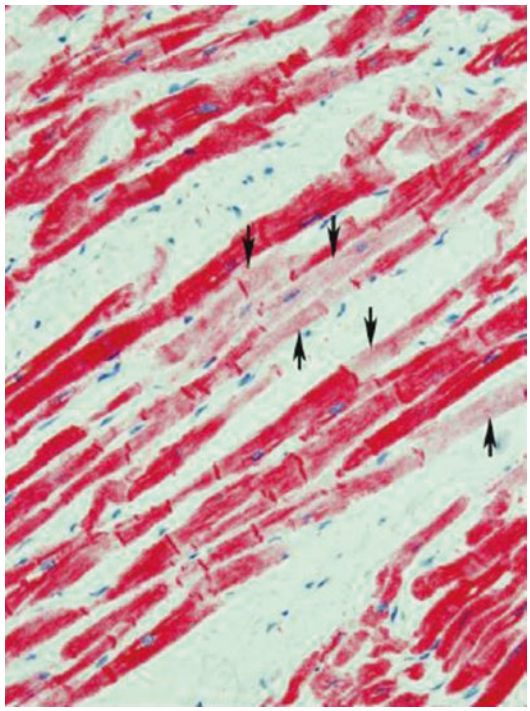

Fig. 13.3 Ischemically damaged cardiomyocytes—immunohistochemically detectable loss of desmin (*arrows*) (×400)

Fibrinogen

In an experimental rat model, fibrinogen seemed to increase 30 min after coronary artery ligation (Xiaohong et al. 2002), while fibrinogen staining extended in accordance with changes in myoglobin depletion 2–3 h after ligation.

Fibronectin

Fibronectin is a protein situated at the cell surface, also appearing in the serum. It is produced in fibroblasts, monocytes, and epithelial cells and apparently plays a role in fibrillogenesis in heart muscle cells. Fibronectin cannot be detected immunohistochemically in the normally oxygenated adult myocardium (Casscells et al. 1990) and is currently considered to be the earliest immunohistochemical necrosis marker, which, in terms of time, is identifiable even before $C5b\text{-}9_{(m)}$ (Hu et al. 2002).

Myoglobin

Myoglobin is a myocardial cytoplasmic component, and local and incomplete myoglobin depletion occurred in the subendocardial cells in front of the left ventricle after 30 min of myocardial ischemia (animal experiment; Xiaohong et al. 2002).

Troponin I

Cardiac troponin I is like myoglobin, myosin, and other muscle protein components of normal myocardial cells and appears elevated in serum after acute myocardial infarction due to leakage from the damaged myocardial cells (Adams et al. 1993).

Troponin I is specific for heart muscle cells and not found in other tissues. Cases of definite myocardial infarction show a well-defined area with loss of troponin I (Hansen and Rossen 1999; Leadbetter et al. 1989). Autolytic areas show a diffuse reduction in troponin I.

In cases of acute diffuse perfusion disturbance of the myocardium, there is no localized ischemia in terms of myocardial infarction. The abovementioned conventional histological stainings and immunohistochemical markers can show findings or absence of findings in all areas of the myocardium. This supports the assumption of acute coronary insufficiency. However, conclusions on the chronology of acute cardiac death must be drawn very cautiously.

For further information on the abovementioned and other immunohistochemical ischemia markers, please refer to the appropriate literature. There are several animal models and studies on autopsy tissue performed in order to determine the age of ischemia in cases of myocardial findings. However, to date, no reliable and generally accepted spectrum of reproducible immunohistochemical markers has been found. This also applies to age determination of myocardial infarction, even if in this case a concentration on certain immunohistochemical examinations is apparent.

Small Vessel Disease. This remains an umbrella term for various disorders of the small arteries in the heart (myocardial atherosclerosis). Sclerosis of the arterioles and small arteries are likely to be the most common forms; having said that, hereditary medial necrosis, fibromuscular dysplasia, amyloid deposits, and vasculitis have also been described. There is no proven correlation between small vessel disease and hypertension. A narrow vessel lumen in myocardial samples taken at autopsy does not reflect antemortem vessel width, but rather an artifact arising from the fact that the arteries were not fixated under physiological pressure (Hort 2000). In terms of histological changes, focal or diffuse loss of smooth muscle cells in the arterial media and their replacement by a fibrous tissue have been described in addition to narrowing of the vessel lumen. Hyperelastosis of the vessel wall and degenerative changes are also seen (Rahlf 1980). It is only with great caution that a diagnosis of small vessel disease as the cause of death should be made on the basis of lesions of this kind and only if an alternative cause of death has been ruled out and if the circumstances of death tally with the patient history.

13.2 Myocardial Infarction

Acute myocardial ischemia leads to myocardial necrosis which will be reabsorbed and fibrously organized if the patient survives. Since ischemia is normally considered to be the consequence of an incident such as coronary sclerosis with insufficient blood supply to the myocardium, smaller ischemic areas (up to 1 cm) are also called coronary insufficiency scars. Such coronary insufficiency scars may coalesce to larger scar zones. If the diameter of the ischemia-based myocardial necrosis is more than 1 cm, this can be considered a myocardial infarction. If the coronary arteries are narrowed, relative anemia following blood loss due to injury can lead to myocardial ischemia or myocardial infarction.

Conventional Histology
The hemorrhagic halo which occurs in fresh myocardial infarction and which is macroscopically visible, as well as the leukocytic demarcation which develops later, can be detected histologically.

In cases of coronary insufficiency calluses or myocardial infarctions, the age of the lesion can be determined histologically. In this context, conventional histology with various stainings and methods is still relied upon (Mihatsch 1988; Sahai 1976; Bouchardy and Majno 1974; McVie 1970; Knight 1967), but immunohistochemical techniques are increasingly used (Piercecchi-Marti et al. 2001; Brinkmann et al. 1993; Leadbetter et al. 1989, 1990). However, the detection of very fresh myocardial infarction is sometimes impossible, both macroscopically and using conventional histology. In such cases, improved diagnosis was initially achieved in the past using enzyme-histochemical methods.

Enzyme Histochemistry

Over 40 years ago, it was demonstrated that myocardial infarction can be detected with enzyme-histochemical methods in cases where there are no pathological findings in conventional histology. It was found that cytochrome oxidase activity is an early indicator of fresh myocardial infarction, showing a marked reduction even before the reduction of succinate dehydrogenase activity (Jääskeläinen 1968). Enzyme-histochemical methods have only been partially accepted in histological practice, while immunohistochemical techniques are now widespread.

Immunohistochemistry

By means of immunohistochemical control of structural and repair proteins, it is possible to provide evidence of a myocardial infarction even before it is visible macroscopically or detectable histologically. Primary antibodies have proven to be effective as infarction markers against the repair proteins fibronectin, C5b-$9_{(m)}$, and fibrinogen, as well as against the structural protein myoglobin, all of which can also display diffuse myocardial ischemia (see Table 13.1). Positive findings in repair proteins can in part also be seen in traumatic myocardial damage and in the case of fibrinogen in other organs (Raza-Ahmad 1994). Along with immunohistochemical detection of repair proteins, the loss of structural proteins is evidence of myocardial ischemia also in cases of myocardial infarction, such as the loss of troponin I (Hansen and Rossen 1999) and desmin. On the other hand, immunohistochemical analysis in animal models showed increased expression of *dityrosine*, a protein product in oxidative stress, in the affected ischemic and infarcted myocardial areas after only a very short ischemia time (approximately 5 min; Mayer et al. 2014, 2016). The angiotensin type 2 receptor was proposed as a marker of acute myocardial infarction with positive detection in the peripheral region of the infarcted myocardium after 12–24 h (Rentea et al. 2016; Mondello et al. 2017).

Coagulative necrosis and contraction band necrosis are microscopically visible using H&E/autofluorescence staining, diffuse myofibrillar degeneration is visible using Luxol fast blue staining (LFB) (Arnold et al. 1985), and contraction bands are also visible using chromotrope aniline blue staining (Zollinger 1983). Details on the chronology of myocardial infarction or on age determination of an infarction can be seen in Table 13.2 (see also Figs. 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, and 13.10).

Table 13.2 Chronology of microscopic findings of myocardial infarction

Time	Microscopic findings
From 15 min	Measuring distances between horizontal stripes in myocardial fibers in unstained sections: several myocardial sections are compared using an eyepiece micrometer on a phase contrast microscope; extension is evidence of myocardial infarction (Hort 1965)
Up to 30 min	Electron microscopic changes to the mitochondria with swelling and dissolution of the cristae mitochondriales (Büchner and Onishi 1968)
30–60 min	Edema of the myocardial fibers; decrease in glycogen; in animal studies immunohistochemical loss of myoglobin and early detection of fibrinogen (Xiaohong et al. 2002); in cases of ischemia of at least 30 min, contraction bands can be seen in the chromotrope aniline blue staining (CAB) as an expression of collapse of the myofibril apparatus (Amberg 1995)
From 60 min	Positive tartaric acid cresyl violet inclusion staining: preserved musculature, blue-violet to red-violet; damaged musculature, pale blue to sky blue (Holczabek 1970, 1973)
2–3 h	First homogeneous eosin red hyalinized myocardial fibers (Fig. 13.4) in peripheral areas of myocardial infarction (Janssen 1977); the stain according to Lie: dark red ischemic myocardial fibers (Tausch 1974)
	Unfixed tissue sections: Fluorochromization with acridine orange can represent damaged myocardium by means of bright green fluorescence (Korb and Knorr 1962)
3–4 h	First agglutinated sarcolemma tubes, discrete fatty degeneration of the myocardial fibers; possible hemorrhagic demarcation of the infarction with hyperemic edges (can also be present at an earlier stage), first tamping cell nuclei of the cardiomyocytes
4–5 h	Immunohistochemical representation of the infarct area with the early necrosis markers fibronectin and C5b-9(m) (Fig. 13.6); fibrinogen is also positive; visible loss of desmin and myoglobin
4–7 h	Necrosis in the infarct area, first peripheral leukocyte reaction, gradual general eosinophilia of the myocardial fibers, and shrinkage of the heart muscle cells in the infarct area, nuclear dyeability (Fig. 13.5) (Janssen 1977)
9 h	Pronounced necrosis in the infarct area, strong leukocyte reaction—now also in the infarct area, nuclear dyeability of the cardiomyocytes no longer possible, cell nuclei of the interstitial connective tissue can be dyed for somewhat longer (Fig. 13.7)
18–24 h	Pronounced necrosis, further leukocyte penetration of the infarct area
5–6 days	Continued leukocyte penetration of the infarct area, abscess-like dissolutions are possible with myocytolysis and rupture of the heart chamber wall (Fig. 13.8) (Janssen 1977)
2–3 weeks	More pronounced peripheral granulation tissue with sprouted capillary blood vessels, fibrocytes, fibroblasts, lymphocytes, few plasma cells, macrophages, possibly siderophages, few granulocytes
5 weeks to 2–3 months	Collagen fiber or scar tissue with endothelially coated capillary blood vessels of varying density (Mallory et al. 1939), siderophages still possible, loose infiltration with lymphocytes, few plasma cells, scant granulocytes (Fig. 13.9)
3–6 months	Scar tissue with fewer cells, few capillary blood vessels, scant siderophages
6–12 months	Scar tissue with few cells (DiMaio and Dana 2007), dystrophic calcification with basophilic calcium salt deposits is possible later (Fig. 13.10)

Summary according to the literature, own experience, and in line with Sandritter and Thomas (1977)

13.3 Acute and Chronic Viral Myocarditis

Myocarditis of varying etiology is often the explanation for sudden and unexpected death (Kiryakova et al. 2016; Kittulwatte et al. 2010; Dettmeyer et al. 2002a). A variety of causes may trigger myocarditises, from infection to the involvement of the myocardium in cases of systemic diseases (Table 13.3).

The most frequent and frequently unrecognized myocarditis is viral myocarditis (Fairley et al. 1996; Friman et al. 1995; Friman and Fohlman 1993; Karjalainen et al. 1980). Bacterial purulent myocarditises, tuberculous or rheumatoid myocarditis, fungal myocarditis, as well as

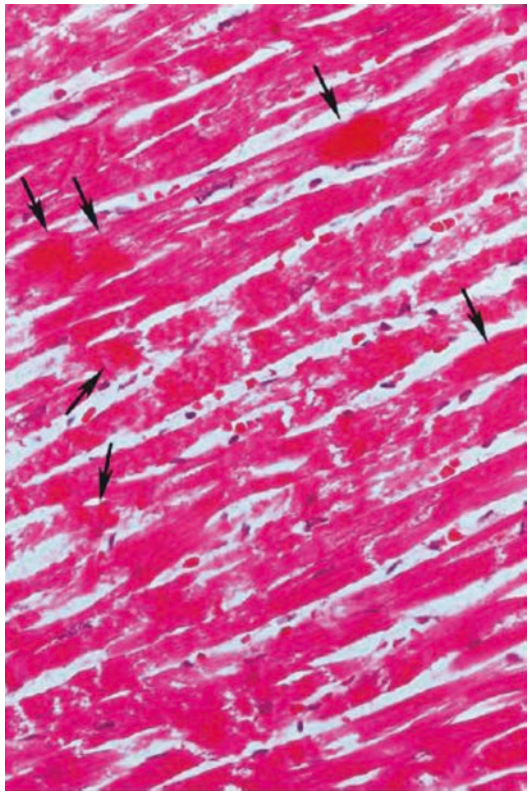

Fig. 13.4 Fresh myocardial infarction with homogeneous eosin red hyalinized myocardial fibers (*arrows*), fiber breaks, intensive myocardial decay, tamping cell nuclei, and interstitial edema—infarct age, approximately 2–4 h (H&E ×400)

inflammatory myocardium involvement in cases of systemic diseases or sarcoidosis are all very rare. Other rare diagnoses include myocarditises which respond well to medication (see Chap. 5), which frequently show pronounced infiltration with eosinophil leukocytes (Aoki et al. 1996), and giant-cell myocarditis.

It is remarkable that viral myocarditis can present clinically as ischemic heart disease (IHE), the ECG-mimicking myocardial infarction (Bültmann et al. 2003a; Kühl et al. 2003; Lauer et al. 1998; Tyson et al. 1989; Miller et al. 1973). The (viral) inflammation is said to act as an arrhythmia trigger, such that sudden and unexpected death in the case of viral myocarditis can be explained by acute cardiac arrhythmia with only discrete histological and immunohistochemical findings (Klein et al. 1995, 2000). Viral myocarditis should be considered in the case of sudden unexpected death when taking exercise or without any known physical strain (Bux et al. 2002; Byard 2002; Karjalainen and Heikkila 1999; McCaffrey et al. 1991; Drory and Hiss 1991; Philips et al. 1986).

Improved immunohistochemical methods in connection with the molecular pathological evidence of viruses in the myocardium allow a

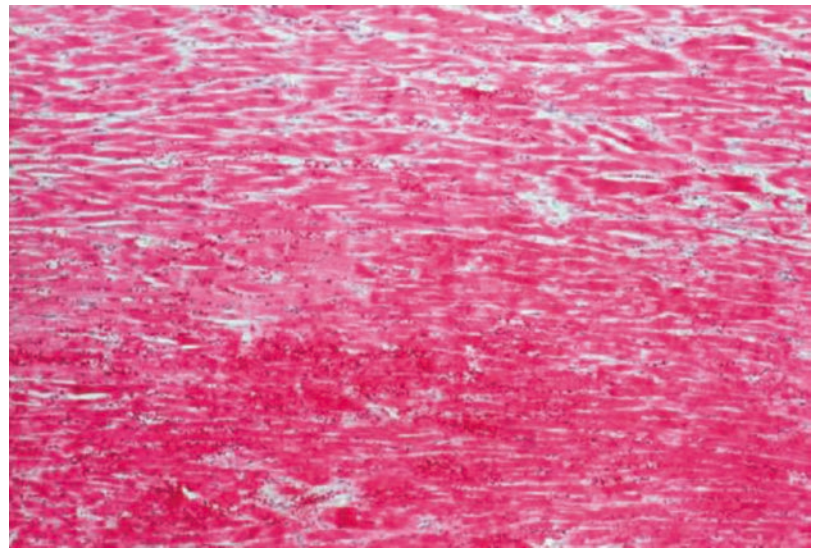

Fig. 13.5 Fresh myocardial infarction with hemorrhagic edges (*bottom*) and largely preserved nuclear dyeability of the cardiomyocytes—infarct age <7 h (H&E ×40)

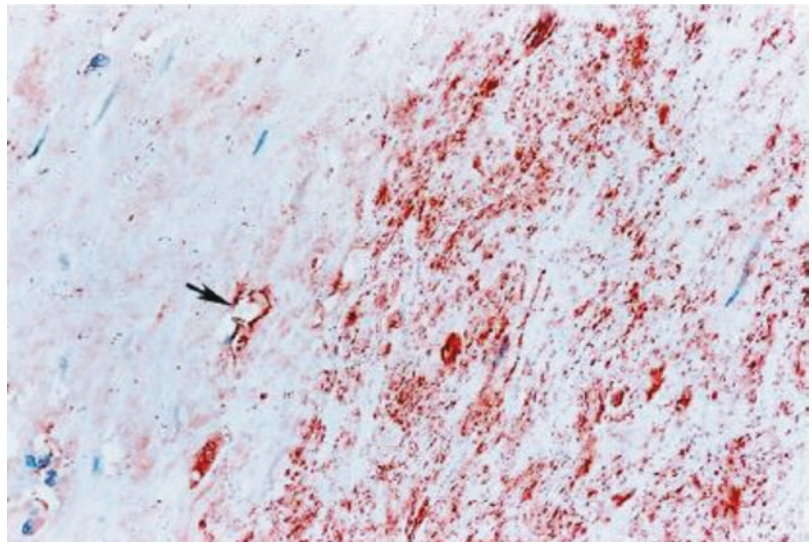

Fig. 13.6 Fresh myocardial infarction with evidence of the early ischemia marker C5b-9$_{(m)}$. Note: C5b-9$_{(m)}$ expression in the wall of a neighboring artery as "internal positive control" (*arrow*) (×200)

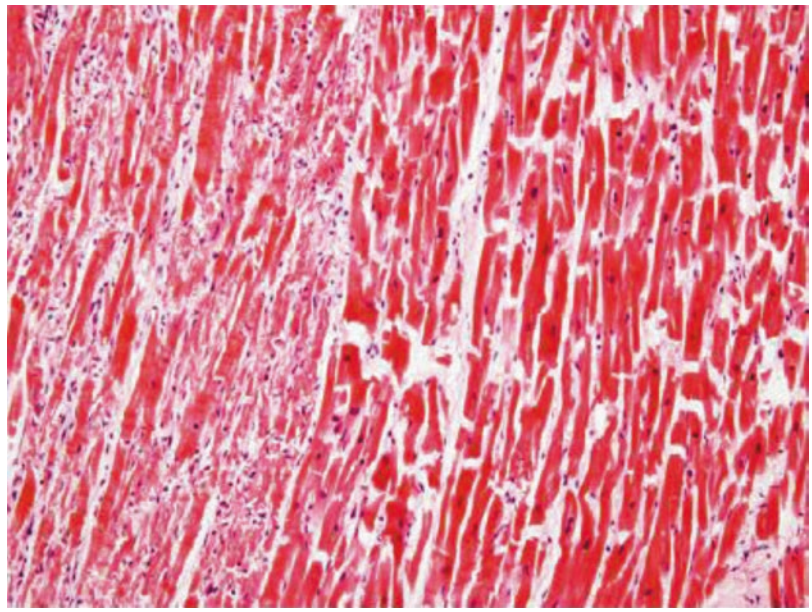

Fig. 13.7 Peripheral region of a myocardial infarction with lost heart muscle fibers, diffuse leukocyte infiltration, absent or almost completely tamped cell nuclei (*left*) adjacent to unaffected myocardium (*right*)—infarct age at least 7–9 h (H&E ×100)

better understanding of pathophysiological mechanisms in the case of acute and chronic myocarditis, even if a lot of questions remain unanswered (Liu and Mason 2001). Immunohistochemical staining first enabled the quantification of interstitial inflammatory cells in the myocardium (Klages and Gerken 1972) and more recently enabled the qualification of individual cell types (Noutsias et al. 2002; Kühl et al. 1994, 1997). Despite advances in the diagnosis of myocarditis, there is still controversy about how to judge small, focal inflammatory infiltrates in the myocardium in terms of their significance to the cause of death. Focal

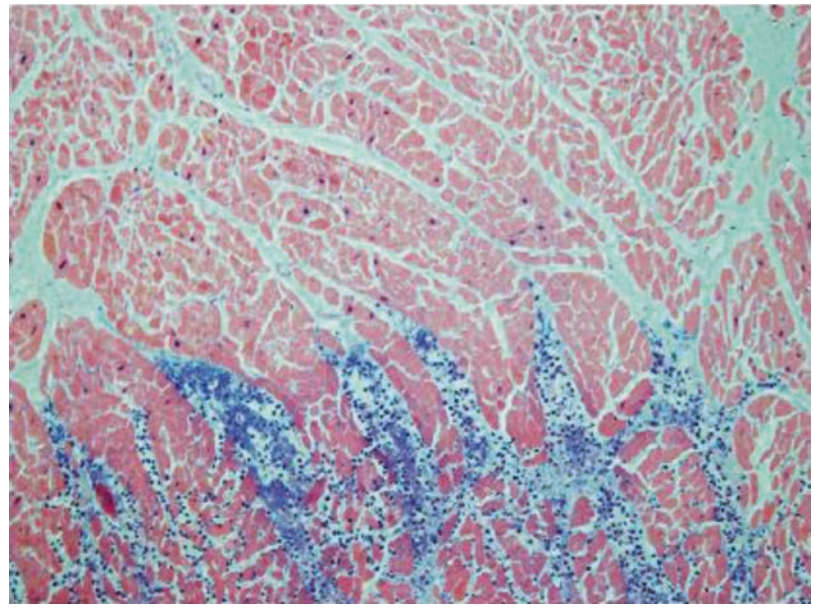

Fig. 13.8 Myocardial infarction, abscess-like leukocyte penetration of the infarct area—infarct age, approximately 24–48 h, few days (H&E ×100)

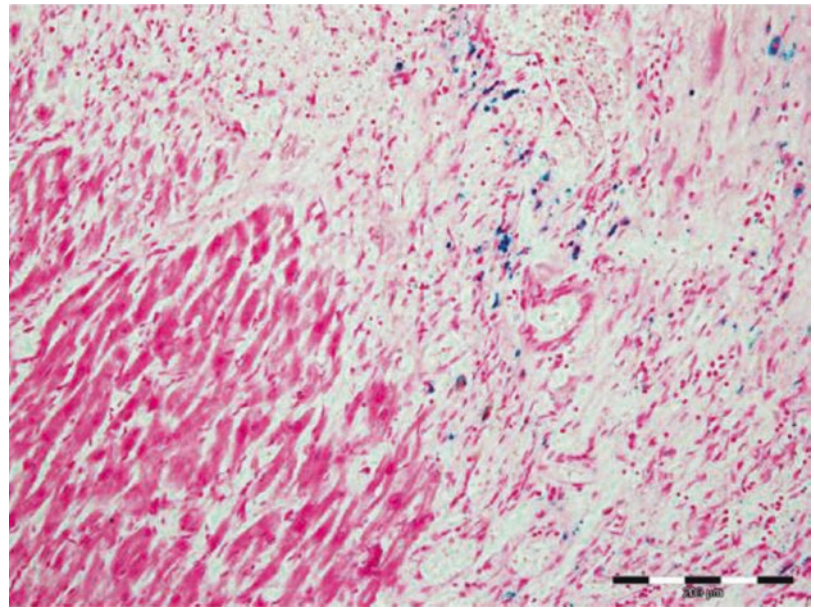

Fig. 13.9 Myocardial infarction which is no longer fresh with substituting granulation tissue: collagen fiber tissue with fibroblasts and fibrocytes, sprouted capillary blood vessels, a large number of siderophages as residuals of intramyocardial bleeding (Prussian blue ×200)—infarct age, approximately 3 weeks or older

infiltrates with inflammatory cells are occasionally seen in the myocardium in adults, evidently more frequently as a reactive event following the use of a wide variety of drugs, e.g., antibiotics (Zhang et al. 2013). Findings of this kind cannot necessarily be deemed relevant to death. Myocardial inflammatory infiltrates in the infant heart are of greater significance in terms of cause of death (see Chap. 17).

13.3.1 Acute Viral Myocarditis

The diagnosis of acute, subacute, or abating myocarditis is made partly with the help of conventional histological methods, as well as by using immunohistochemical myocarditis diagnostics established in the 1990s. This is currently supplemented by molecular pathological detection of viruses in the myocardium.

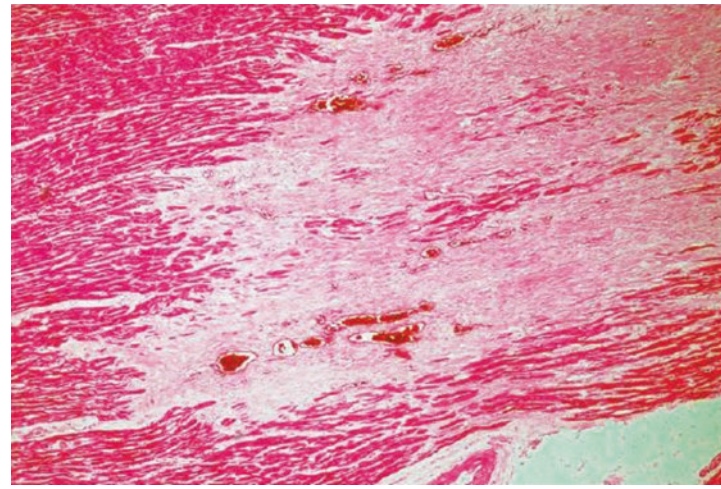

Fig. 13.10 Old myocardial infarction scar with dense collagen fiber tissue, partially revascularized with capillary blood vessels, and no inflammatory infiltrates (H&E×100)—infarct age, at least 6 months

Table 13.3 Classification of the etiology of myocarditis

Etiology	Triggering agent (selection)
Infection	Viruses (in particular enteroviruses, coxsackieviruses B1–B5, coxsackieviruses A4 and A16, echoviruses 9 and 22, polioviruses, parvovirus B19, adenoviruses, human herpes virus 6, Epstein–Barr virus, human cytomegaly virus, influenza viruses, mumps virus, herpes simplex virus, varicella-zoster virus, respiratory syncytial virus, measles virus, rubella virus, human immunodeficiency virus)
	Bacteria [staphylococci, *Pseudomonas*, *Proteus*, *Klebsiella*, pneumococci, mycobacteria (Tbc), meningococci, mycoplasma pneumoniae, *Borrelia burgdorferi* (Lyme carditis)]
	Fungi (candida, aspergilla)
	Protozoans (*Trypanosoma cruzi*–Chagas disease, *Toxoplasma gondii*)
Allergic/autoimmune	Immune reaction (autoimmune or eosinophilic myocarditis, rheumatic carditis, myocarditis which responds well to medication, e.g., antibiotics, diuretics, anticonvulsives, neuroleptics)
Pharmacological/toxic	Anthracyclines, amphetamines, catecholamines, cocaine, *Corynebacterium diphtheriae* (exotoxin), drugs
Systemic diseases	For example, lupus erythematodes (LE)
Physical	For example, radiotherapy
Rare forms	Giant-cell myocarditis, sarcoidosis, hypereosinophilic syndrome, Kawasaki disease with myocardium involvement, transplant rejection

Conventional Histological Myocarditis Diagnostics

With the exception of more rare forms of myocarditis, microscopic diagnosis was and still is performed using conventional histological staining methods (in particular H&E, LFB, Elastica van Gieson, Mallory's stain, Giemsa stain), according to the Dallas criteria in the first instance (Aretz 1987; Aretz et al. 1987; Table 13.4). Descriptions of histological findings include, e.g., inflammatory infiltrates and fibrosis:

Table 13.4 Conventional histological diagnosis of myocarditis according to the Dallas criteria (Aretz 1987)

First myocardial biopsy	Findings
Active myocarditis	Myocytolysis, lymphomonocytic interstitial inflammatory infiltrate in the myocardium, interstitial edema (Fig. 13.11)
Borderline myocarditis	Sparse accumulation of lymphocytes, subsequent control biopsy
Control biopsy	Findings
Persistent myocarditis	Unchanged evidence of a myocarditis
Healing myocarditis	Decrease in lymphomonocytic infiltration
Healed myocarditis	No myocytolysis, no necrosis, no increase in lymphomonocytic cells

1. Inflammatory infiltrates
   (a) Focal, confluent, and diffuse
   (b) Mild, moderate, and severe
   (c) Lymphocytic, eosinophilic, granulomatous, giant cells, neutrophilic, and mixed
2. Fibrosis
   (a) Endocardial
   (b) Mild, moderate
   (c) Perivascular and replacement

The complete picture of viral myocarditis shows dense, diffuse lymphomonocytic interstitial infiltrates, necrosis of single cardiomyocytes, more extensive group necrosis, interstitial edema, empty sarcolemma tubes, and leukocytes adhering to the vascular endothelium in the vascular space (Fig. 13.11). A 2013 consensus statement emphasized the diagnostic value of *endomyocardial biopsy (EMB)* in the diagnosis of myocarditis and highlighted the diagnostic possibilities presented by immunohistochemistry and molecular pathology testing for viruses (Thiene et al. 2013).

In the case of purulent myocarditis, granulocyte infiltration may lead to microabscesses, or a focal abscess may be induced by embolic spread of bacterial colonies. In cases of myocarditis responsive to drug treatment, relatively well-demarcated focal lymphomonocytic infiltrates with plasma cells and eosinophil granulocytes may appear (see Chap. 5). Within the scope of a removal reaction, macrophages may occur en masse; fibrocytes and fibroblasts will then drive the replacement of eliminated cardiomyocytes with collagenous connective tissue. However, with regard to myocarditis, the tissue is rather diffuse and not within a well-demarcated area as seen with myocardial infarct. It is possible that myocarditis is followed to some extent by circular perivascular fibrosis.

Two disadvantages of myocarditis diagnostics according to the Dallas criteria were already highlighted early on:

1. Questionable representativeness of the myocardial samples examined, hence the sampling error (Hauck et al. 1989)
2. Significantly different diagnoses from individual observers, hence the "interobserver variability" (Shanes et al. 1987)

Nevertheless, clarification of myocarditis according to the Dallas criteria is the first step in myocarditis diagnosis. If the findings for myocarditis according to the Dallas criteria listed in Table 13.4 are absent, viral infection of the myocardium is not in any way excluded, and

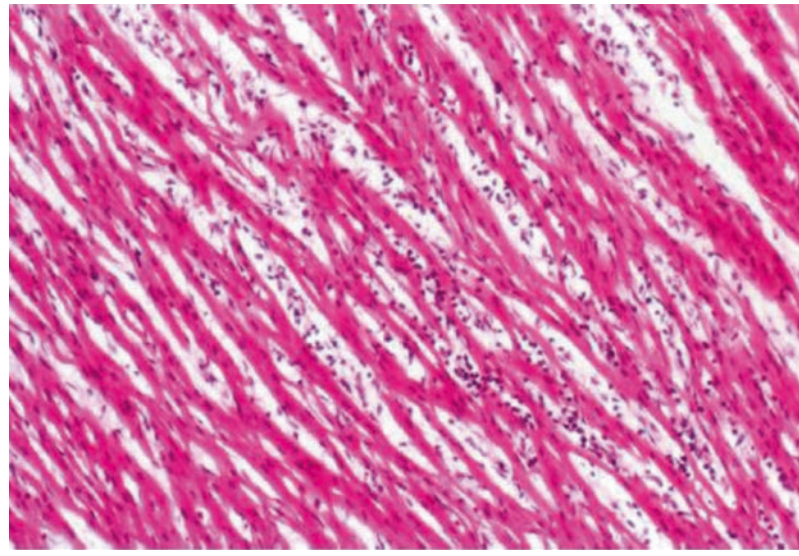

Fig. 13.11 Acute lymphomonocytic viral myocarditis according to the Dallas criteria with myocardial necrosis, myocytolyses, leukocyte infiltration, and interstitial edema (H&E ×100)

immunohistochemical examinations may be needed. Investigations to differentiate fatal myocarditis from incidental myocarditis show that myocardial necrosis is not necessarily required to establish the diagnosis of myocarditis (Casali et al. 2012). The molecular genetic detection of viral genomes in myocardial samples taken at autopsy remains methodologically complex, and conflicting results have been presented. Especially retrospective studies in old myocardial samples stored for long periods of time seem to yield more virus-negative findings (Nielsen et al. 2014a, b).

In the case of acute death and macroscopically normal findings at autopsy, conventional histological examinations may largely show normal findings despite myocarditis. Since viral myocarditis only offers a circumscribed focal interstitial lymphomonocytic inflammatory infiltrate, a sufficiently high number of tissue samples are needed for microscopic diagnosis to ensure detectability of these focal infiltrates.

According to personal experience, a minimum of eight myocardial samples from a defined area should be examined (localization of the specimens; see Chap. 17) concerning babies. For adults, other authors ask for eight samples from the right and eight samples from the left myocardium, additionally samples from the cardiac conduction system, a reasonable proposal (Janssen 1977). If indications of myocarditis are found, e.g., a focal inflammatory infiltrate, step sections of all tissue samples may lead to the detection of additional focal leukocyte infiltrates, thus supporting the diagnosis of myocarditis.

The anamnesis of patients with myocarditis often reveals a viral infection of the respiratory system or gastrointestinal tract which may have been perceived as insignificant in the preceding weeks. At forensic autopsy and particularly in the case of sudden death in relatively young subjects due to physical stress, myocarditis should be considered once other cardiac diseases have been excluded. This includes death while participating in sports (e.g., soccer), swimming, military duty, or in cases of sudden cardiac death.

The chronology of acute myocarditis corresponds to electron-microscopic, immunohistochemical, and conventional histological findings. The conventional histological diagnosis, however, is no longer reliable during the early phase and while the myocarditis is subsiding. Thus, with no virus detected in the myocardium, only a histomorphologically justified suspected diagnosis remains (Table 13.5).

Table 13.5 Diagnostic phases of acute viral myocarditis: postinfection findings

Phase	Findings
Early phase (hours following infection)	Ultrastructural and molecular pathological diagnosis: evidence of ultrastructural changes (electron microscopy); molecular pathological evidence of a virus
From approx. 24–48 h	Immunohistochemical diagnosis: growing immunohistochemically provable findings with expression of proinflammatory molecules; adhesion molecules, cytokines, leukocyte infiltration, expression of non-cellular proinflammatory molecules
From approx. 24–48 h	Conventional histological diagnosis: possible development of myocarditis according to the Dallas criteria

Note: When the immune system is intact, possible early elimination of the virus in the myocardium may be considered, such that the myocardium may be affected only temporarily and in a confined area
According to Feldmann and McNamara (2000) and Mall (1995)

Finally, it is not clear to what extent viral infections impact the myocardium, but cardiotropic viruses, including certain enteroviruses, may have a greater impact than other viruses. Currently, there is no research into the interplay between rapid elimination of the viral genome and the organism's immune defense, the intensity and duration of the viral infection and a possible genetic variation, or into whether chronic myocarditis with viral persistence often develops when the number of viral copies is extremely low. A reduction in interstitial and especially perivascular fibroses is occasionally proposed as an indication of healed, viral myocarditis. If there are zones of fibrosis with a discrete lymphomonocytic inflammatory infiltrate and myocardial single-cell necrosis, a transition to chronic myocarditis or inflammatory cardiomyopathy should be considered.

Immunohistochemical Diagnosis of Myocarditis

One improvement in the diagnosis of myocarditis was based on immunohistochemical methods (Noutsias et al. 2002; Yazaki et al. 1998; Kühl et al. 1996, 1997; Maisch et al. 1995; Mall 1995; Schwartzkopff et al. 1995; Maisch 1994, among others). Due to significant interobserver variability (Shanes et al. 1987) and also because the examined myocardial samples are not sufficiently representative with low sample counts when myocardium particles are very small, immunohistochemical methods were established to demonstrate inflammatory processes in the myocardium. In this context, interstitial leukocytes, T-lymphocytes, and macrophages are qualified and quantified, proinflammatory molecules are immunohistochemically expressed, and the degree of expression is semiquantitatively determined. This process, which has been an established part of the diagnostic work-up in adult myocarditis since the 1990s, has since been transferred to cases of sudden infant death (Dettmeyer and Kandolf 2009, Dettmeyer et al. 2004a, 2006c; Dettmeyer and Madea 2004; see Chap. 17).

According to personal experience, it is remarkable that with expression of proinflammatory MHC class II molecules, the myocardium apparently reacts as a whole; relatively even expression of this proinflammatory marker can also be found when cellular infiltration is only detectable focally.

A larger spectrum of immunohistochemical markers has meanwhile been proposed for the diagnosis of myocarditis. However, the focus remains on the extent of cellular infiltration of the myocardial interstitium, oriented to empirically derived limit values for adults and cases of sudden infant death. Thus for adults, a T-lymphocyte number (marker CD3; Figs. 13.12 and 13.13) of >2.0 cells/visual field (high power field; ×400) or >7.0 cells/mm^2 is regarded as a pathological finding, as well as <14 T-lymphocytes and macrophages (CD68; Fig. 13.14) per mm^2, marked expression of MHC class I and II molecules (Fig. 13.15), or adhesion molecules (CD18, CD54, VLA-4) on cells and the vascular endothelium (Fig. 13.16) (Kühl et al. 1997). Other studies propose a threshold value of 11–16 T-lymphocytes/mm^2, whereas the quantification of intramyocardial macrophages using the CD68 macrophage marker is deemed infeasible (Nielsen et al. 2014a, b).

If these limit values are exceeded, the diagnosis of myocarditis is definite or highly probable,

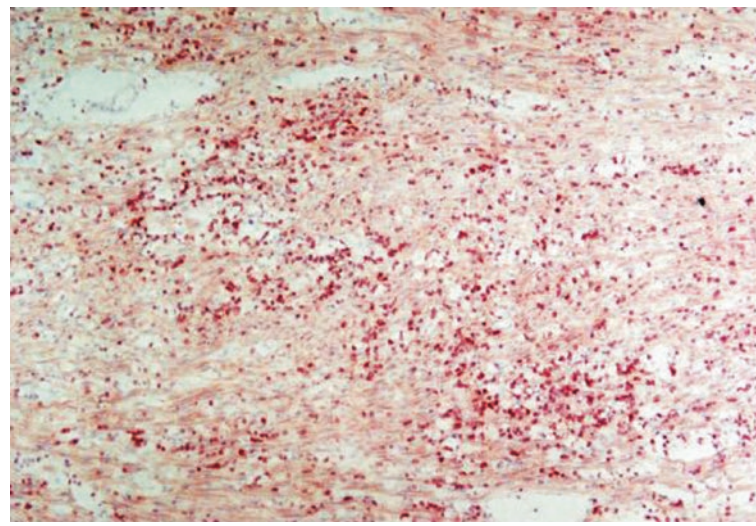

Fig. 13.12 Myocarditis with diffusely increased infiltration by CD3$^+$-T-lymphocytes (×100)

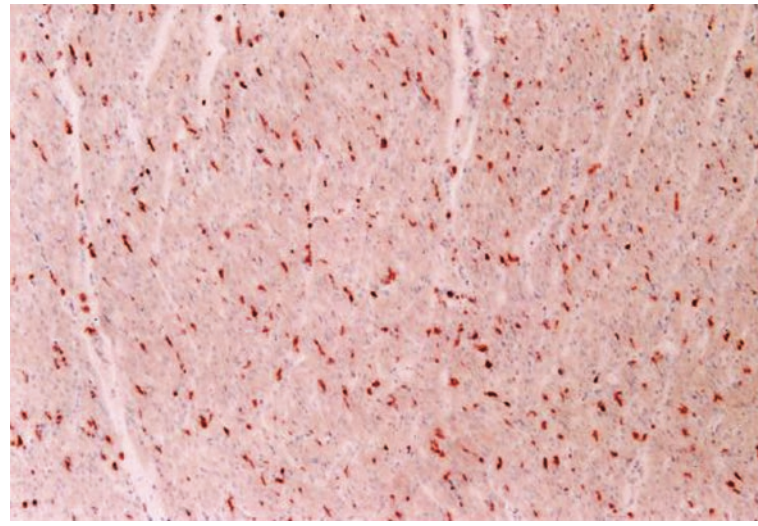

Fig. 13.13 Myocarditis with diffusely increased infiltration by $CD45R0^+$-T-lymphocytes (×100)

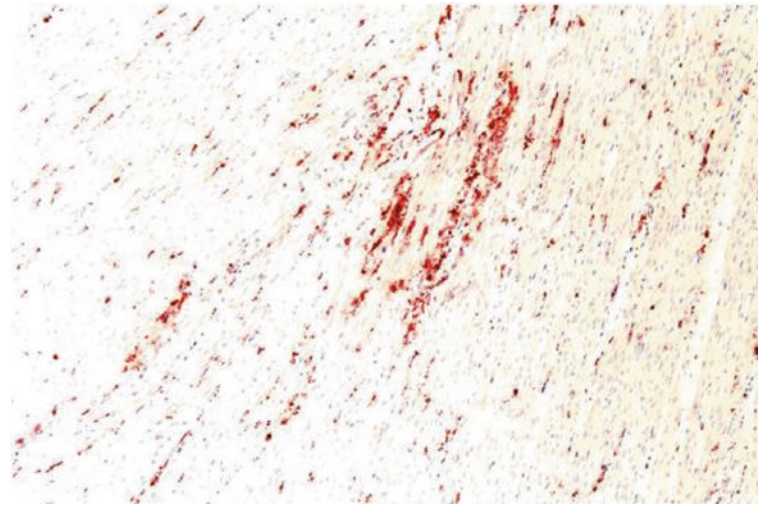

Fig. 13.14 Focally dense infiltration by $CD68^+$ macrophages in the posterior wall of the left ventricular myocardium (×100)

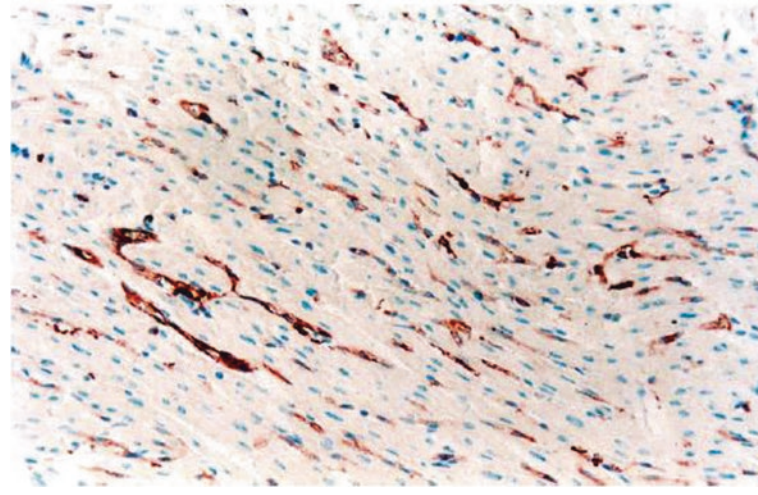

Fig. 13.15 Diffusely marked expression of the MHC class II molecules (+++) in the presence of viral myocarditis in myocardial samples taken from various locations (×100)

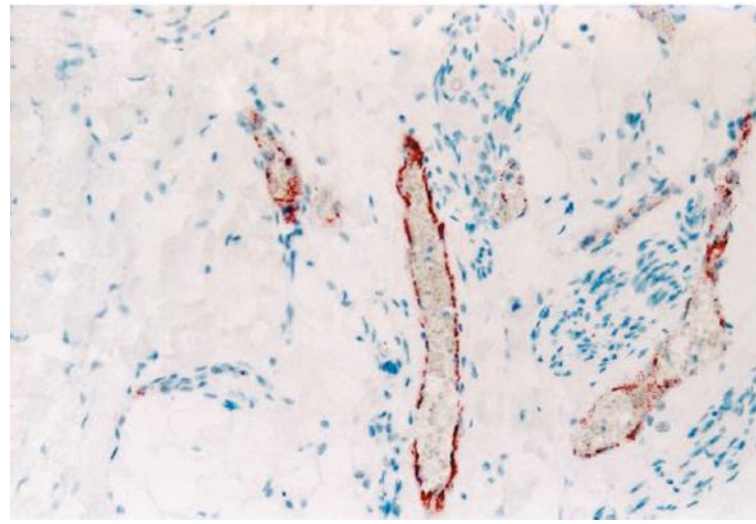

Fig. 13.16 Marked endothelial expression of E-selectin in peripheral arterial branches of the myocardium in the presence of myocarditis (×200)

Table 13.6 The spectrum of cellular and non-cellular inflammatory markers in immunohistochemical diagnosis of myocarditis (selection)

Marker	Antigen
Leukocytes	Leukocyte common antigen (LCA)
T-lymphocytes	CD2, CD3
B-lymphocytes	CD19-CD22
Macrophages	CD68
Natural killer cells	CD57
Lymphocyte subpopulations	
Helper-inducer cells	CD4
Suppressor-cytotoxic cells	CD8
Activated cells	
Lymphocytes	CD25, CD71, CD45R0 (Fig. 13.13)
Macrophages	27E10, RM3/1, 25 F9
Vascular endothelial cells	HLA-I/DR, CD54
Other inflammatory molecules	
Major histocompatibility complex	MHC-I (A,B,C), MHC-II (DP,DQ,DR)
Adhesion molecules, cytokines, etc.	CD18, CD54, VLA-4, E-selectin, etc.

According to Dettmeyer et al. (2006b)

but as with suspicious cases, molecular genetic evidence of a viral presence in the myocardium is desirable to support the diagnosis. In addition, the literature mentions a spectrum of immunohistochemical markers which are used within the scope of myocarditis diagnosis (Table 13.6). Other immunohistochemical antigens were tested, e.g., ICAM-1 (Wojnicz et al. 1998); the increase in number of T-lymphocytes in the myocardial interstitium is of the greatest diagnostic importance.

Given that the quality of immunohistochemical diagnosis depends to a large extent on the methodical approach, the guidelines given in Table 13.7 should be followed for the diagnosis of myocarditis. This method refers in particular to the selection of the fixative and the duration of fixation, while some flexibility remains in the selection of immunohistochemical markers, in addition to the antibodies needed for the qualification and quantification of interstitial leukocytes; new proinflammatory antibodies are being tested.

The immunohistochemical diagnosis of myocarditis is initially based on the qualification and quantification of interstitial leukocytes, T-lymphocytes, and macrophages within the scope of empirically determined standard values for adults (Kühl et al. 1997; Azzawi et al. 1997; Milei et al. 1990; Chow et al. 1989; Schnitt et al. 1987; Steenbergen et al. 1986; Cassling et al. 1985; Linder et al. 1985; Edwards et al. 1982). For the expression of proinflammatory endothelial markers and non-cellular molecules, a semiquantitative evaluation (0, +, ++, +++) is recommended, also against the background of empirically determined levels of expression, e.g., for MHC class I and II molecules (Daar et al. 1984a, b) and other proinflammatory markers

Table 13.7 Method of recommended conventional histological, immunohistochemical, and molecular genetic investigations for the diagnosis of myocarditis

Method	Important points requiring attention
Fixative	Neutrally buffered formaldehyde (pH-control) or an acceptable alternative fixative
Duration of fixation	Up to 36–48 h
Routine histology	Hemalaun–eosin staining of representative samples for all internal organs
Conventional histology of the myocardium	Hemalaun–eosin staining, additionally Mallory, LFB, and EvG staining; taking at least eight myocardial samples from defined locations is recommended for postmortem diagnosis
Immunohistochemistry	Qualification and quantification of interstitial leukocytes, T-lymphocytes, and macrophages (marker: e.g., LCA, CD45R0, CD68, CD3): count 20 high power fields (hpf) at ×400 or per mm^2; then determine average value
Immunohistochemistry	Detection and semiquantitative evaluation of proinflammatory, e.g., endothelial proteins or molecules (e.g., MHC class I and II, selectin, cytokine, necrosis marker-like fibronectin and C5b-9(m), ICAM-1, etc.)
Molecular genetic agent diagnosis	The myocardial samples with more pronounced lymphomonocytic infiltrates are preferred: PCR and rt-PCR on DNA and RNA viruses [especially enteroviruses (EV), coxsackieviruses, belonging in particular to Group B (CVB; especially CVB3), adenoviruses (AV), Epstein–Barr virus (EBV), parvovirus B19 (PVB19), Herpes simplex viruses, especially Type 6 (HHSV-6), cytomegaly viruses (CMV), etc.]

(Noutsias et al. 1999; Hufnagel and Maisch 1991). In addition, the significance of such markers is partially proven in animal experiments, especially in connection with Group B coxsackievirus infection (Seko et al. 1990).

An immunohistochemical antibody against the enterovirus envelope protein VP1 can provide immediate microscopic evidence of enteroviruses in the myocardium (Li et al. 2000). According to personal experience with these antibodies, the findings could not be reliably reproduced and led to incorrect positive results, as shown by a molecular pathological control.

Molecular and Pathological Evidence of a Viral Presence in the Myocardium

In tissue samples adequately treated with formalin and embedded in paraffin, virus genomes can be found in connection with conventional, histological, and immunohistochemical diagnosis of myocarditis including RNA viruses like the enteroviruses and DNA viruses such as adenoviruses, Epstein–Barr viruses, parvovirus B19, etc. (Dettmeyer et al. 2003, 2004a, b, 2006b, c; Baasner et al. 2003a, b; Chia and Jackson 1996; Zell et al. 1995; Cassinotti et al. 1993; Jin et al. 1990). According to personal experience, evidence of viruses in the myocardium is possible, even when histological and immunohistochemical findings show rather discrete deviations from the standard.

Enteroviruses are common pathogens of myocarditis, particularly cardiotropic Group B coxsackievirus (Gaaloul et al. 2011; Dettmeyer et al. 2006c; Bendig et al. 2001; Huber et al. 1999; Lau 1994; Kandolf et al. 1993; Muir 1993; Jin et al. 1990; Bowles et al. 1986; Lau 1983), but also cytomegaly virus (Kytö et al. 2005; Maisch et al. 1993), Epstein–Barr virus (Lentini et al. 2001; Hebert et al. 1995), adenovirus (Lozinski et al. 1994), influenza virus (Drescher et al. 1987), and parvovirus B19 (Klingel and Kandolf 2009; Bültmann et al. 2003a, b; Dettmeyer et al. 2003; Murry et al. 2001; Enders et al. 1998; Orth et al. 1997). Especially in cases of drug addicts with known hepatitis B or C, myocarditis caused by hepatitis virus should be taken into consideration. Coinfections with two

or more pathogens of a myocarditis exist but are relatively rare (Rohayem et al. 2001). The most common pathogens of acute and chronic myocarditis or inflammatory cardiomyopathy are various types of the enterovirus, whereby the Group B coxsackieviruses, specifically CVB3, are considered as particularly cardiotropic (Lang et al. 2008; Klingel et al. 2000; Klump et al. 1990; Pauschinger et al. 1994, 1998; Martino et al. 1995; Kandolf 1995; Klingel et al. 1992a, b; Kandolf et al. 1987).

Enteroviruses (EV)

To determine the importance of detecting enteroviruses in the human myocardium, both pathophysiological aspects and epidemiological findings should be taken into consideration. Based on epidemiological investigations, enteroviruses are recognized as the most common pathogens of viral myocarditis; the coxsackieviruses B1–B5 (CVB), of which the CVB3 is recognized to be particularly cardiotropic (Chrysohoou et al. 2009; Priemer et al. 1999; Klump et al. 1990). Enteroviral infections show seasonal variability (Moral et al. 1993), appearing more often in the summer (Druyts-Voets et al. 1993; Grady and Costanzo-Nordin 1989), while occasional epidemics are reported (Braun et al. 2002; Dettmeyer and Madea 2002; Mounts et al. 2001; Philipps et al. 1980). Human pathogenic enteroviruses are one of the most examined virus systems (Kandolf 1995). Genetic factors not yet identified are assumed to be responsible; for most people, spontaneous elimination of the virus from the myocardium is possible. This effective virus elimination is supposedly associated with an adequate, natural killer cell response, elimination of the virus-infected cell with the help of T-cells, as well as suppression of histocompatible antigens (MHC class). In addition, cytokine-mediated activation of phagocytic macrophages and the induction of apoptotic cell death of virus-infected cells (Ventéo et al. 2010; Schaper et al. 1999; Narula et al. 1996; Kawano et al. 1994) are assumed. Meanwhile, a coxsackievirus and adenovirus receptor (CAR) has been isolated, suggesting a molecular basis for the particular cardiotropic nature of certain viruses (Bergelson et al. 1997; Noutsias et al. 2001). Although a rare exception, enteroviral myocarditis that follows a fulminant course with severe clinical symptoms and rapid death has been described (Oka et al. 2005).

In the early phase of enteroviral myocarditis, endocytic invasion of cardiomyocytes is followed by virus replication with only electron microscopically detectable intracytoplasmic vesicle formation (Klingel et al. 2000; Kandolf 1993, 1995). As part of this process, the number of virus components inside the infected cell may rapidly replicate. If the cell has viral proteins and RNA genomes in sufficient numbers, these components are assembled into infectious viruses (self-assembly). Viral proteins include, for example, envelope proteins of the enteroviruses and capsid proteins 1–4 (VP1–4). The enteroviral proteinase 2A destroys the dystrophin-glycoprotein complex, an extra-sarcomeric protein of the cardiomyocyte cytoskeleton, and thus attacks the contractile apparatus of the host cell. Molecular biological investigations led to the exact breakpoint, and the “Hinge 3” region could be localized (Noutsias et al. 2002; Badorff et al. 1999, 2000a, b).

Increased expression of proinflammatory cytokines, however, should already have a proarrhythmogenic effect (Klein et al. 1995). Within the scope of comprehensive observation and based on current knowledge, it is assumed that detection of enteroviruses in the myocardium should be seen as a pathological diagnosis in its own right.

Parvovirus B19 (PVB19)

According to current investigations, parvovirus B19 in the myocardium should not necessarily be regarded as a less significant finding and irrelevant in terms of cause of death. PVB19 preferentially affects the endothelial cells of peripheral arterioles and capillaries and may lead to acute endothelial dysfunction (Bock et al. 2010; Klingel and Kandolf 2009; Bültmann et al. 2003a, b; Schwartzkopff et al. 1998). According to personal experience, histologically and immunohistochemically diagnosed chronic myocarditis may be caused by PVB19 infection (Dettmeyer and Madea 2003; Dettmeyer et al. 2003). In an older study, a PVB19 variant led to the sudden death of young dogs as a result of myocarditis (Hayes et al. 1979).

Epstein–Barr Virus (EBV)

Epstein–Barr viruses are known as potential pathogens of viral myocarditis; in the context of infectious mononucleosis (Pfeifer's mononucleosis, "kissing disease"), sudden unexpected death may occur (Ishikawa et al. 2005; Byard 2002). EVB-induced myocarditis and pericarditis are rarely observed in the clinical setting, despite the fact that the incidence of EBV infection increases with age and is high in adults. However, death in infancy can occur (Hebert et al. 1995). Knowledge of molecular EBV pathology is limited. According to individual cases, EBV-induced myocarditis may clinically and echocardiographically simulate acute myocardial infarction with cardiogenic shock (Lentini et al. 2001; Tyson et al. 1989; Miller et al. 1973), but the exact mechanism of damage remains unknown.

Adenoviruses (AV)

Of the pathogens of viral myocarditis, adenoviruses are often mentioned second to enteroviruses, in particular adenoviruses 2 and 5 (Oyer et al. 2000; Bergelson et al. 1997; Lozinski et al. 1994; Martin et al. 1994). Meanwhile, common membrane-linked receptors for coxsackie- and adenoviruses (Liu and Mason 2001; Bergelson et al. 1997) have been successfully identified. This coxsackievirus and adenovirus receptor (CAR) belongs to the immunoglobulin superfamily and is able to react with other viruses of the enteroviruses group (Liu and Mason 2001). CAR is an embryonic gene product with high expression levels during embryonic development, as well as early downregulation already in the neonatal phase. Under physiological conditions, the receptor is absent on adult cardiomyocytes (Noutsias et al. 2002; Bergelson et al. 1997). At least in immature newborns and preterm infants, postnatal, initially persistent, and relatively high expression levels of the CAR gene could represent a molecular basis for the increased cardiotropic nature of coxsackie- and adenoviruses, but possibly also of enteroviruses.

Cytomegalovirus (CMV)

Cytomegaloviruses are regarded as relatively rare pathogens of myocarditis; they are occasionally found in babies and children in the glandular epithelia of the salivary glands, particularly the parotid gland (Cecchi et al. 1995; Cremer and Althoff 1991). More recent investigations suggest a greater role for cytomegalovirus-induced myocarditis in the case of fatal outcome (Dettmeyer et al. 2006d; Kytö et al. 2005).

Influenza A H1N1-Associated Myocarditis
During the 2009/2010 A/H1N1 influenza pandemic, fatal cases were seen showing molecular pathological evidence of infection and interstitial myocarditis accompanied by myocardial necrosis in the absence of significant respiratory tract and pulmonary infection (Gdynia et al. 2011).

Autoimmune Myocarditis. This involves an immune reaction to endogenous cardiac myosin producing the histological picture of lymphocytic myocarditis. It is not uncommon for this entity to be preceded by viral myocarditis, with the immune reaction developing in a delayed manner once the virus has already been eliminated. Therefore, in such cases of postviral myocarditis, the viral genome is no longer detectable in myocardial samples. However, our knowledge of the basics of immunopathology is still patchy. Autoimmune myocarditis is challenging to differentiate from chronic myocarditis with at least partial but often undetectable viral persistence. For this reason, chronic myocarditis is sometimes also referred to as autoimmune myocarditis.

13.3.2 Chronic Myocarditis

Acute myocarditis may either heal or become chronic. In particular, immunohistochemical and molecular pathological investigations over the past 20 years have shown that most of the macroscopically diagnosed dilative cardiomyopathies are the result of chronic myocarditis; evidence of virus persistence is only possible in some cases. It is clear that, despite successful elimination of the virus, the result may be an autoimmune response with persistent myocardial inflammation (autoimmune myocarditis). In some cases, diagnostic differentiation from concomitant myocarditis may be difficult following microscopic diagnosis, but this is usually still possible within the scope of a comprehensive histological examination of all internal organs.

Conventional staining will result in diagnostic findings which already indicate a chronic inflammatory process; if necessary, further immunohistochemical diagnostic tests should follow (see Table 13.8). Following death of a heart muscle cell, there is increased cellular infiltration in the myocardial interstitium, accompanied by partially interstitial, partially perivascular fibrosis, as well as some streaky fibrosis (Fig. 13.17). Studies to date have focused on myocarditis and its transition to a chronic inflammatory process (D'Ambrosio et al. 2001; Strauer et al. 2001; Maisch et al. 2000; Kawai 1999; Noutsias et al. 1996; Martino et al. 1994; Schultheiß 1993; Klingel et al. 1992a, b; Herzum and Maisch 1988; Kawai et al. 1987).

Table 13.8 Histological and immunohistochemical diagnosis of chronic myocarditis, dilated myocarditis, or dilated cardiomyopathy, inflammatory type (DCMi)

Histology	Immunohistochemistry/molecular pathology
Focal, interstitial edema, fiber structures with partially and somewhat irregular appearance	Often only a moderate increase in leukocytes, T-lymphocytes, and macrophages
Interstitial fibrosis, caliber deviation of the cardiomyocytes, differences in size of nuclei	Somewhat increased expression of MHC class I and II molecules
Pronounced perivascular fibrosis (EvG stains)	Sign of progressive restructuring with expression of tenascin at the margin of microscopically small zones of fibrosis
Myocardial single-cell necrosis	Focal loss of desmin detectability
Single, empty sarcolemma tubes	Myocardial single-cell necrosis, seldom group necrosis (fibronectin, C5b-$9_{(m)}$)
Potential microscopically small zones of scarring	Expression of additional proinflammatory markers (see Table 13.6)
Circumscribed endocardial fibroses	Molecular pathology (PCR, rt-PCR), possible detection of viral genome with typically small number of viral copies (Bowles et al. 1989; Arola et al. 1998)

The differentiation between chronic myocarditis and inflammatory cardiomyopathy has been discussed in the literature (Kühl et al. 1992)

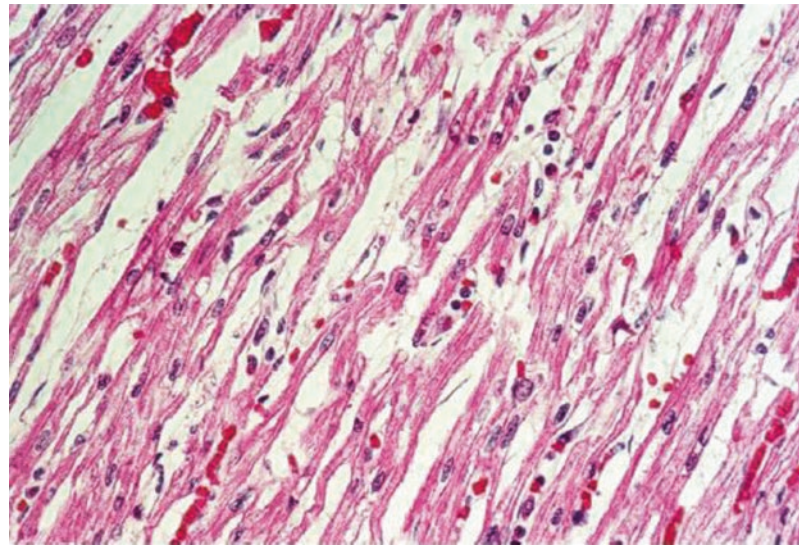

Fig. 13.17 Chronic myocarditis with somewhat increased cellular infiltration, interstitial edema, and degeneration of heart muscle fibers (H&E ×400)

The term "chronic myocarditis" is appropriate for a macroscopically normal heart with the microscopic diagnosis of a chronic inflammatory process. If dilated cardiomyopathy is present macroscopically, in addition to a histologically or immunohistochemically observed inflammatory process, the term "dilated cardiomyopathy, inflammatory type (DCMi)" may be used. The spectrum of possible viruses responsible remains unknown, although according to more recent tests, the virus PVB19, for example, is being considered (Bock et al. 2005; Klingel et al. 2004).

Apoptosis

Apoptosis is a form of programmed cell death with cell shrinkage and dismantling of the DNA into defined fragments by endonucleases, which may be detected with the help of the TUNEL method (Chap. 2). From the histological perspective, the affected cell separates from the cell environment and becomes increasingly eosinophilic and smaller. The cell nucleus becomes small and compact. Effector caspases, primarily caspases 3, 6, and 7, lead to apoptotic cell death. Investigations into apoptosis from a forensic perspective are currently being undertaken in only a few studies. Nevertheless, cardiomyocyte apoptosis, a key pathologic feature of heart failure, may play a critical role in patients with acute myocarditis (Abbate et al. 2009; Kawano et al. 1994) and in cases of dilated cardiomyopathy (Schaper et al. 1999).

13.4 Non-virus-Based Myocarditis

Rare forms of non-virus-based myocarditis sometimes appear at autopsy. For example, *Chagas disease*, a disorder widespread in some areas of South America and involving an intracellular parasite (*Trypanosoma cruzi*), can cause chronic lymphocytic myocarditis (de Lourdes Higuchi et al. 1993). Since these findings often explain sudden death due to natural causes and are histologically characteristic, brief explanations should be sufficient here to cover the different forms.

13.4.1 Bacterial Myocarditis

In the context of bacterial infection, which usually involves sepsis accompanying bacteremia, partially diffuse and partially granulocytic infiltrates with focal emphasis can be found in the myocardium (Figs. 13.18 and 13.19). At the same time, some cases may show basophilic colonies of bacteria (cocci, coccoid rods) which are more effectively detected using specialized stains. In addition, histological findings, such as septic shock, are made on a regular basis. Particularly in cases of focal infection with purulent abscess and central bacterial colonies, embolic spread of pathogens should be taken into consideration.

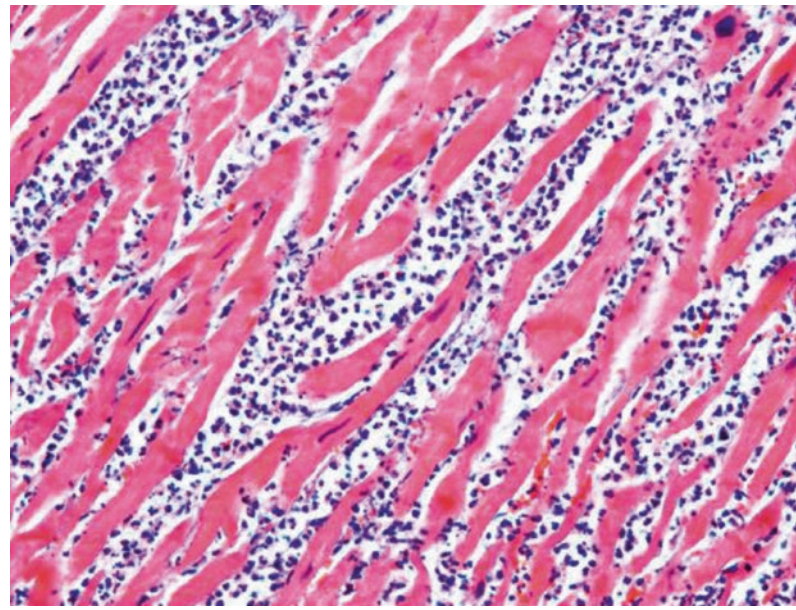

Fig. 13.18 Acute purulent myocarditis with multiple granulocytes (H&E ×200)

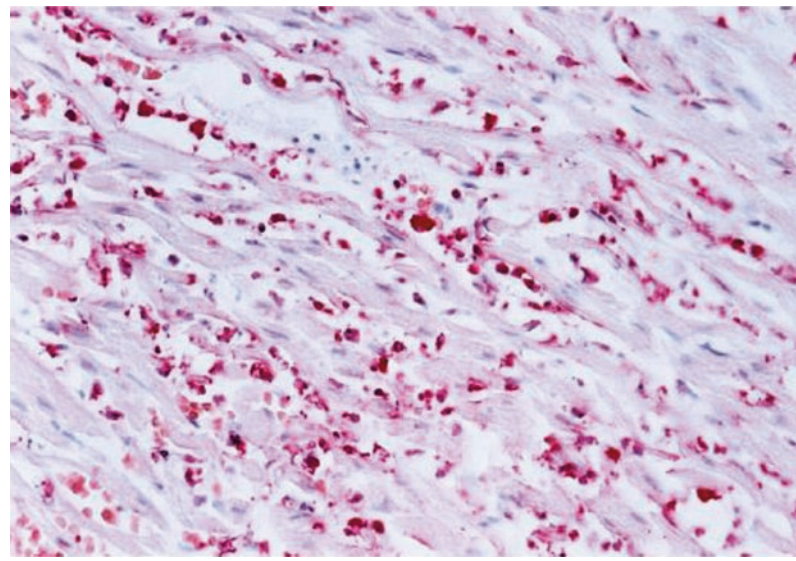

Fig. 13.19 Acute purulent myocarditis with enzyme-histochemical detection of granulocytes (*red*) in the interventricular septal myocardium and bulky degeneration of individual cardiomyocytes, interstitial edema, and drifting apart of heart muscle fibers (ASD ×400)

13.4.2 Tuberculous Myocarditis

Tuberculosis rarely involves the myocardium (Dada et al. 2000). At autopsy, decedents with a weakened immune system (e.g., chronic alcoholics) should be examined for the possibility of cardiac tuberculosis, followed by investigations to establish whether other organs are affected (particularly the lung). Tuberculosis pathogens can be seen using Ziehl–Neelsen staining (oil immersion microscopy ×1000); however, this method is frequently unsuccessful. Tuberculous bacteria are often found in the peripheral region of caseous necrosis, adjacent to the lymphocyte wall and Langerhans giant cells. However, diagnosis may easily be based on classic histological diagnosis with no detection of agents: Necrotic zone with a lymphocytic border, peripheral fibrosis, multinucleated Langhans giant cells, and the cores of these giant cells are frequently arranged in a horseshoe form.

13.4.3 Fungal Myocarditis

When using conventional stains under microscopy, an experienced pathologist may recognize fungal components in the myocardium, often with marked surrounding inflammation. Grocott stains (Fig. 13.20) are usually used to show fungal spores and hyphae. The entry site often remains undetected, as with other myocarditis pathogens. However, sources of infection can regularly be observed in other organs (lungs, liver, kidney).

13.4.4 Rheumatoid Myocarditis

Diagnosis of rheumatoid myocarditis as the cause of premature sudden death is extremely rare. Map-like necrotic zones with dense, raised margins full of inflammatory cells with no multinucleated Langhans giant cells appear next to Aschoff nodules (Fig. 13.21) (Fraser et al. 1995). There have also been reports of seasonal variations in myocardial involvement in rheumatism (Metze et al. 1993). Sudden death in the setting of rheumatic heart disease in children is seen in extremely rare cases (Rérolle et al. 2016).

13.4.5 Giant-Cell Myocarditis

Giant-cell myocarditis (Fig. 13.22) is a special form of myocarditis, which has been described

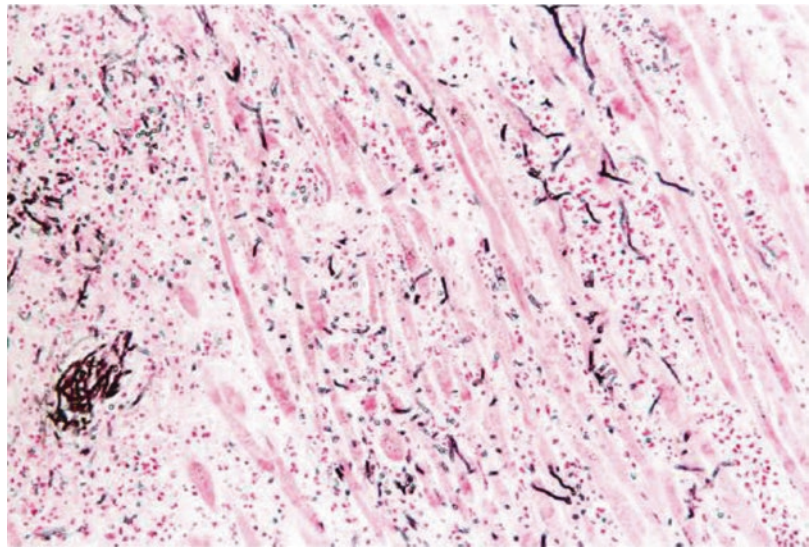

Fig. 13.20 Fungal hyphae demarcated by inflammatory cells in the myocardium in the presence of fungal myocarditis (Grocott ×200)

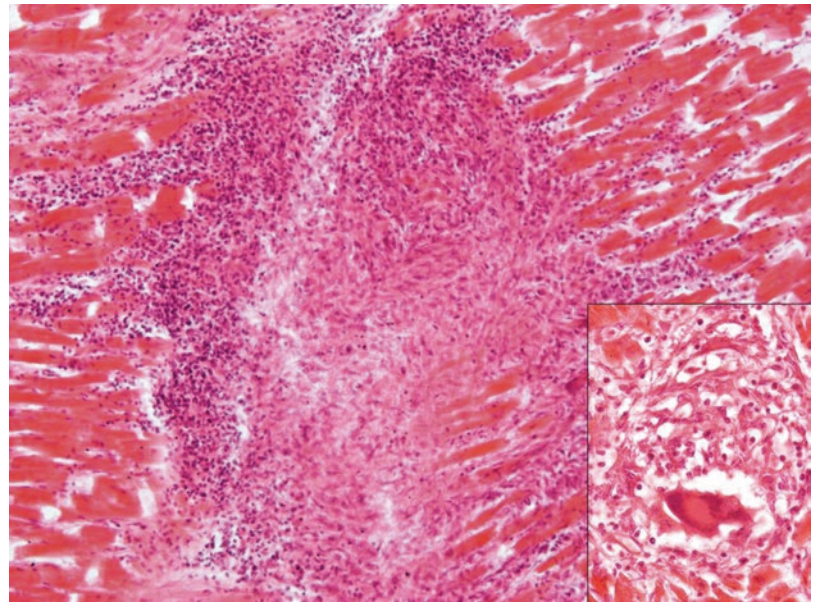

Fig. 13.21 Rheumatoid myocarditis with central necrosis and a dense wall of inflammatory cells as the cause of unexpected sudden death (H&E ×100; ×400)

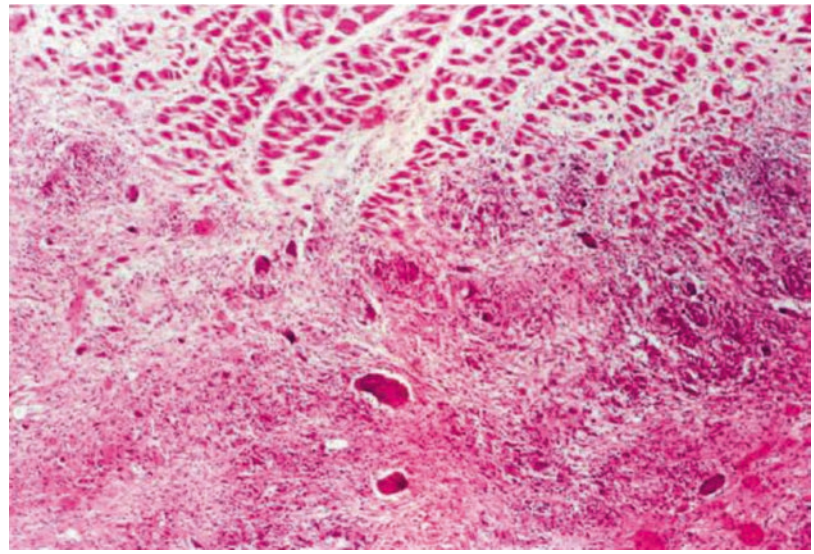

Fig. 13.22 Acute giant-cell myocarditis with significant fibrous components (H&E ×100)

as a cause of sudden death (Martinez et al. 2013; Matejic et al. 2010; Blauwet and Cooper 2010; Langlois 2009; Murty 2008; Hamilton et al. 2007). Microscopically, the myocardium is frequently replaced by extensive collagen connective tissue with a lymphohistiocytic inflammatory infiltrate, which often includes numerous multinucleated giant cells with no characteristic alignment of cell nuclei. Epithelioid and granulomatous structures are absent, and other organs are not involved. Healed, fibrous areas occur alongside reparative processes. Young adults are particularly affected by giant-cell myocarditis. An autoimmune process as a possible cause is under investigation.

13.4.6 Myocardial Involvement in Sarcoidosis

Sarcoidosis may affect internal organs (Bernstein et al. 1929), and systemic sarcoidosis may cause myocardial inflammation. In this case, sarcoidosis is often detectable in other organs, particularly in the lungs. The forensic literature reports undetected myocardial involvement in sarcoidosis, which remained undiagnosed up to the point of autopsy, as the cause of sudden death (Ginellinová et al.; Bagwan et al. 2011; Riezzo et al. 2009; Byard et al. 2008; Riße et al. 2008; Veinot and Johnston 1998; Ogbuihi et al. 1993).

With the help of microscopic investigations, scattered foci of granulomatous inflammation with epithelioid giant cells, lymphocytes, mononuclear cells, and foci of myocytic necrosis can be found (Fig. 13.23). Specific stains for fungi and acid fast bacilli are always negative. In addition to multinucleated giant cells and noncaseating epithelioid granulomas, there have been occasional reports of intracytoplasmic inclusions in sarcoidosis: so-called Hamazaki-Wesenberg bodies, Schaumann bodies (as laminated proteinaceous concretions), birefringent calcium oxalate crystals under polarized light microscopy, and asteroid bodies (as stellate-shaped inclusions within giant cells) (Ginellinová et al. 2016). The diagnostic differentiation from idiopathic giant-cell myocarditis can be challenging. Myocardial necrosis and increased eosinophilic granulocytes suggest giant-cell myocarditis.

13.4.7 Eosinophilic Myocarditis

The literature mentions idiopathic eosinophilic endocarditis and myocarditis (Janík and Hejna 2017; Fragkouli et al. 2011); however, in individual cases, allergic myocarditis, in particular myocarditis responsive to drug therapy, should also be considered when histological accumulations of eosinophilic granulocytes can be detected in the myocardium (Fineschi et al. 2004; Burke et al. 1991; Löffler 1936; see Chap. 5, Fig. 4.13).

In certain cases, immunohistochemical stains may provide additional evidence of IgE and an allergic-responsive cause, for example, in increased mast cells in lung tissue. If possible, evidence of the trigger allergen should be provided. Eosinophilic myocarditis can be part of "drug-induced hypersensitivity syndrome (DIHS)," also called "drug rash with eosinophilia and systemic symptoms (DRESS)," and is a

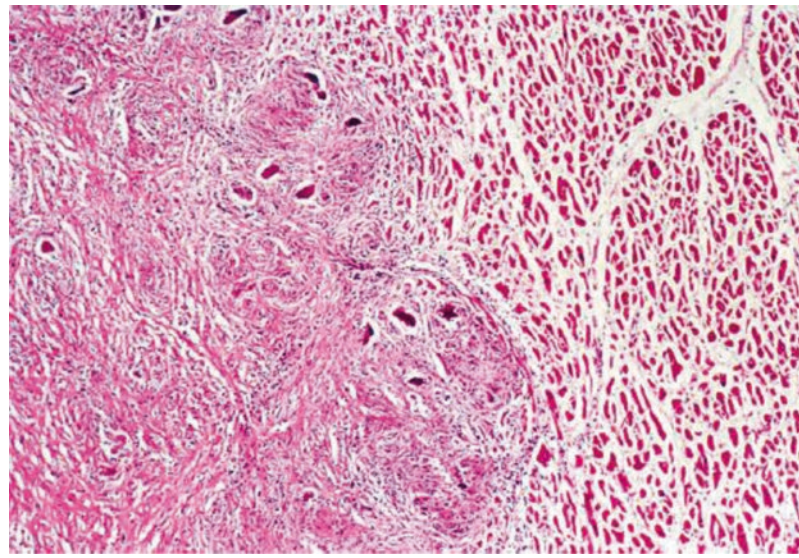

Fig. 13.23 Myocardial involvement in sarcoidosis (H&E ×100)

severe reaction usually characterized by fever, rash, and multiorgan failure, occurring 1–8 weeks after drug introduction. It is an immune-mediated reaction involving macrophage and T-lymphocyte activation and cytokine release, although no consensus has been reached as to its etiology (Ben m'rad et al. 2009).

13.5 Cardiomyopathy

The term cardiomyopathy includes various diseases of the heart muscle, with a distinction between primary and secondary cardiomyopathies. The expert consensus panel proposes a definition (Maron et al. 2006):

> Cardiomyopathies are a heterogenous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-relatively disability.

Cardiomyopathy is a disease of the heart muscle which has not been caused by coronary artery disease, mechanical stress through congenital heart disease, a coronary anomaly, or hypertension in the large and small circulation.

Primary cardiopathy types are classified according to the revised version (Maron et al. 2006) of the 1996 American Heart Association (AHA) definitions (Richardson et al. 1996). In addition, the European Society of Cardiology Working Group produced a statement on myocardial and pericardial types (Elliott et al. 2008). Hypertrophic cardiomyopathy and other forms of cardiomyopathy which may become symptomatic in infants have a genetic cause (Schwartz et al. 1996; Seidman et al. 1992; Takahashi et al. 2008). A modified classification of cardiomyopathy is given in Table 13.9 (for additional details, please refer to the relevant literature).

As with nonviral myocarditis, only the classic histology of the most important forms of cardiomyopathy in forensics will be discussed here. Microscopic diagnosis is suitable for the investigation of a suspicious macroscopic diagnosis; in some cases, immunohistochemical findings may provide additional diagnostic confirmation.

13.5.1 Hypertrophic Cardiomyopathy

Evidence of hypertrophic cardiomyopathy can be detected at autopsy in both children and adults; however, this condition may also affect children with less conspicuous macroscopic findings (Bryant 1999). In this case, myocardial samples should be specifically taken from

Table 13.9 Modified classification of cardiomyopathy types

Genetic forms	Mixed forms	Acquired forms
Hypertrophic cardiomyopathy (HCM), e.g., as idiopathic, hypertrophic subaortic stenosis (IHSS)	Dilative cardiomyopathy (DCM)	Inflammatory dilative cardiomyopathy (DCMi)
Arrhythmogenic right ventricular cardiomyopathy (ARVCM)	Restrictive cardiomyopathy	Stress-induced cardiomyopathy
		Takotsubo cardiomyopathy
Glycogen reservoir diseases		Periportal cardiomyopathy
Transition defects		Tachycardia-induced cardiomyopathy
Mitochondrial cardiomyopathy		Acquired in children with insulin-dependent diabetic mothers
Ion channel defects		Thyrogenic cardiomyopathy
Isolated noncompaction cardiomyopathy (NCCM)		Drug-induced forms, e.g., cocaine cardiomyopathy

There are other rare forms of acquired cardiomyopathy

the affected area for investigation (primarily H&E, van Gieson staining). For example, samples should be taken from the portion of the interventricular septum below the aortic valve, as well as the left ventricular wall in cases of idiopathic hypertrophic subaortic stenosis (IHSS).

The histological picture varies between children and adults (Wigle et al. 1985; Frenzel et al. 1987; Maron 2002), whereby the following are frequent:

- Manifest disturbance of the texture of the left ventricular myocardial tissue partially with storiform patterns (disarray) (Fig. 13.24)
- Circumscribed hypertrophic cardiomyocytes (myofiber hypertrophy) with partially bizarre cell nuclei (Fig. 13.25)

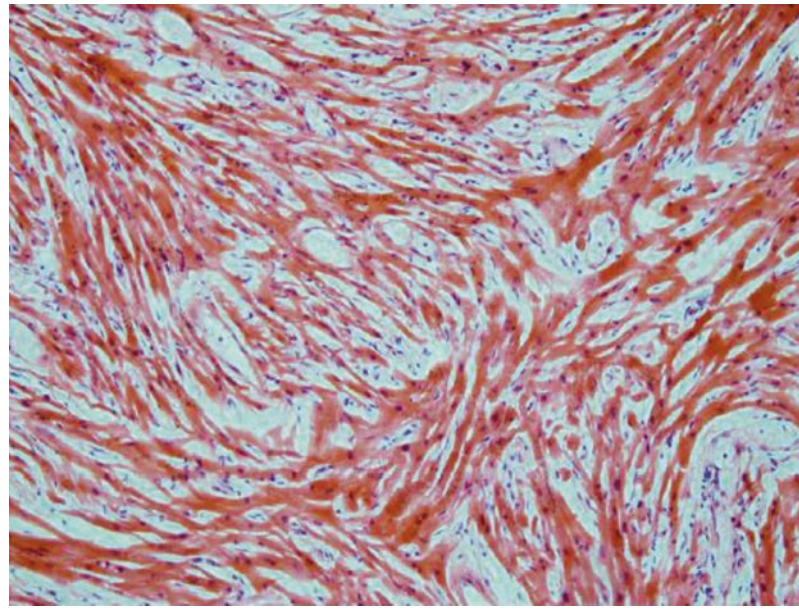

Fig. 13.24 Histologically irregular dendritic texture of heart muscle fibers with a denoted storiform basic pattern in hypertrophic cardiomyopathy (Elastica van Gieson ×100)

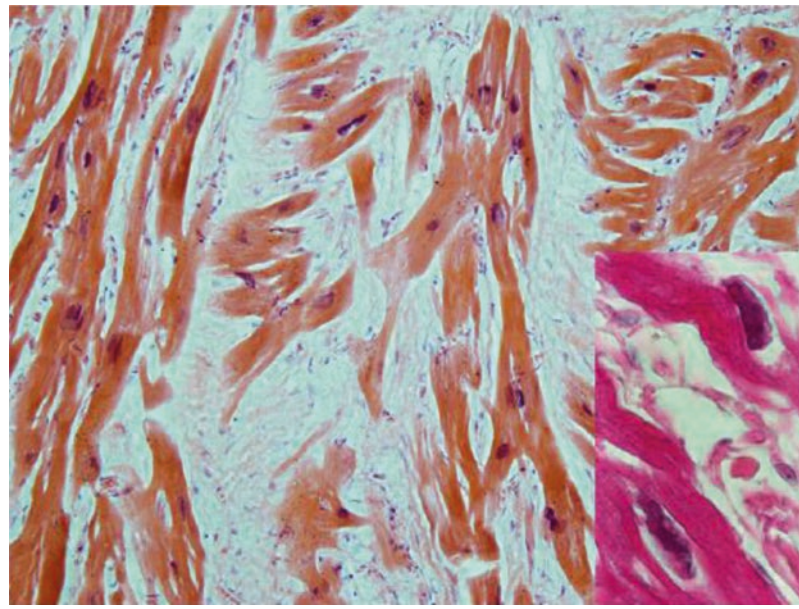

Fig. 13.25 Irregular dendritic heart muscle fibers in hypertrophic cardiomyopathy with enlarged cell nuclei (van Gieson ×100; Insert: H&E ×1000)

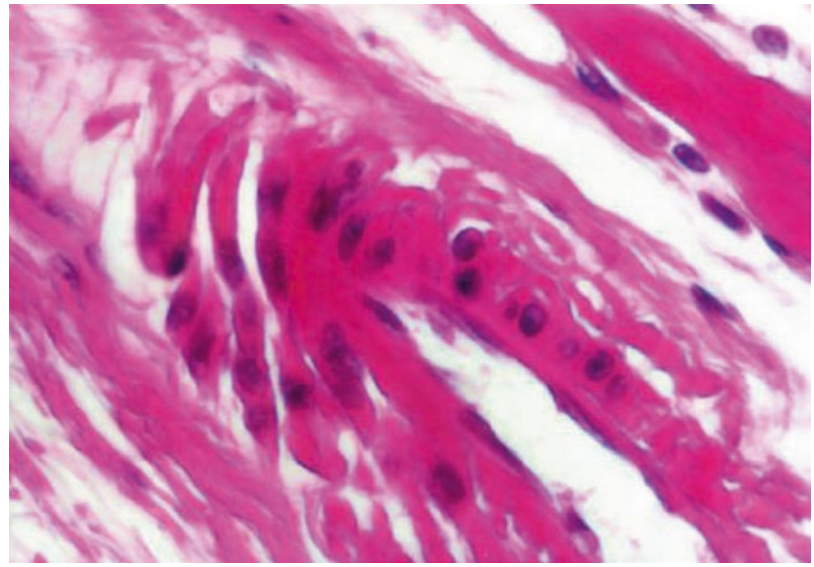

Fig. 13.26 Hypertrophic cardiomyopathy: dysplastic vessels with increased thickness of the wall and enlarged hyperchromatic nuclei of vascular smooth muscle cells (H&E ×400)

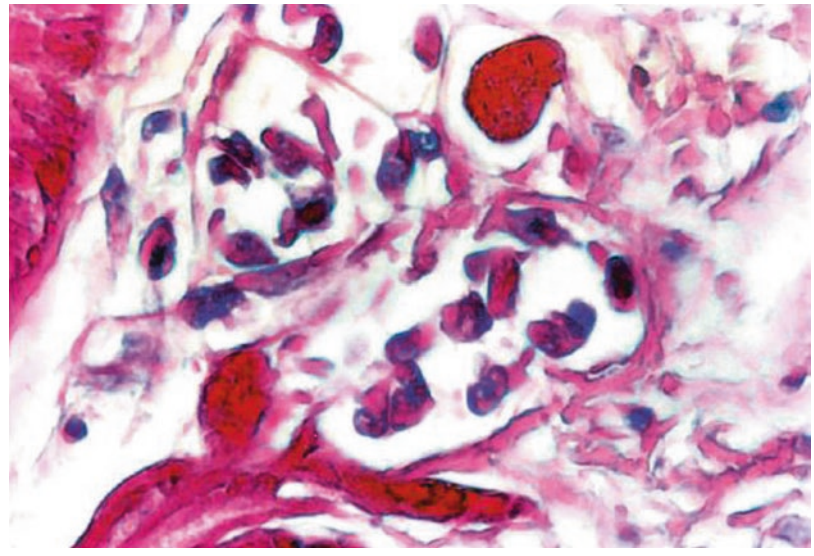

Fig. 13.27 Hypertrophic cardiomyopathy with empty sarcolemma tubes in which accumulations of enlarged hyperchromatic heart muscle cell nuclei are found (H&E ×1000)

- Cardiomyocytes with irregular myofibril structure
- Peripheral vessels with thickened walls and smooth muscle cells showing enlarged and hyperchromatic nuclei (Fig. 13.26)
- Occasional focal accumulation of $CD68^+$ macrophages
- In isolated cases, empty sarcolemma tubes can be present in which accumulated cell nuclei can be seen (Fig. 13.27)
- Interstitial fibrosis may appear in places

In the case of confirmed hypertrophic cardiomyopathy, a genetic diagnosis is recommended in cases where this could be of therapeutic significance for relatives and where such an examination is desired (Maron et al. 1997). After an often longer course, hypertrophic cardiomyopathy may appear macroscopically as dilative cardiomyopathy (Riedel et al. 1997; Lin et al. 1998) and in some cases may be difficult to differentiate from inflammatory cardiomyopathy (Dettmeyer et al. 2004b).

13.5.2 Dilative Cardiomyopathy (DCM)

Dilative cardiomyopathy is characterized by dilation and enlargement of the left ventricle with a partially thickened, partially normal, and partially thinning ventricle wall which shows reduced motility. Histopathologically, degeneratively modified cardiomyocytes as well as hypertrophic heart muscle fibers with enlarged, and occasionally abnormally shaped, cell nuclei are found. Additionally, there are zones of interstitial fibrosis which can be found particularly in subendocardial sections. The extracellular matrix contains collagen, proteoglycan, and glycoprotein, which may be involved in fibrotic restructuring. Components of the extracellular matrix also include glycoprotein tenascin, for example, which is more significantly expressed at the margin of relatively discrete zones of fibrosis, but also in enlarged cardiomyocytes and next to necrotic heart muscle cells (see alcoholic cardiomyopathy; Chap. 6). Tenascin expression is seen as a continuous, progressive restructuring process in the myocardium (Tamura et al. 1996), connexin (Cx), especially the relationship between Cx43, and sudden death in patients with dilated cardiomyopathy was examined (Chen and Zhang 2006).

Both primary obstructive hypertrophic cardiomyopathy and the resulting secondary dilative cardiomyopathy show a similar histological picture. If dilative cardiomyopathy is a chronic inflammatory process (termed dilative inflammatory cardiomyopathy), chronic myocarditis is involved, often of viral genesis (Figulla 2004; Kühl et al. 1994, 1996; see also above). Attention should be paid to perivascular fibrosis (Fig. 13.28) in addition to moderately increased cellular infiltration. Increased mRNA expression of *coxsackievirus and adenovirus receptor (CAR)*, whose pathophysiological role remains the subject of discussion, has been observed in both dilated and ischemic cardiomyopathy (Tatrai et al. 2011). CAR can perhaps be regarded as a novel modifier of ventricular conduction and arrhythmia vulnerability in the setting of myocardial ischemia. Genetic determinants of arrhythmia susceptibility, such as CAR, may constitute future targets for risk stratification of potentially lethal ventricular arrhythmias in patients with coronary artery disease (Marsman et al. 2014).

13.5.3 Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia (ARVCM)

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVCM) may be the cause of sudden unexpected death, for example, under

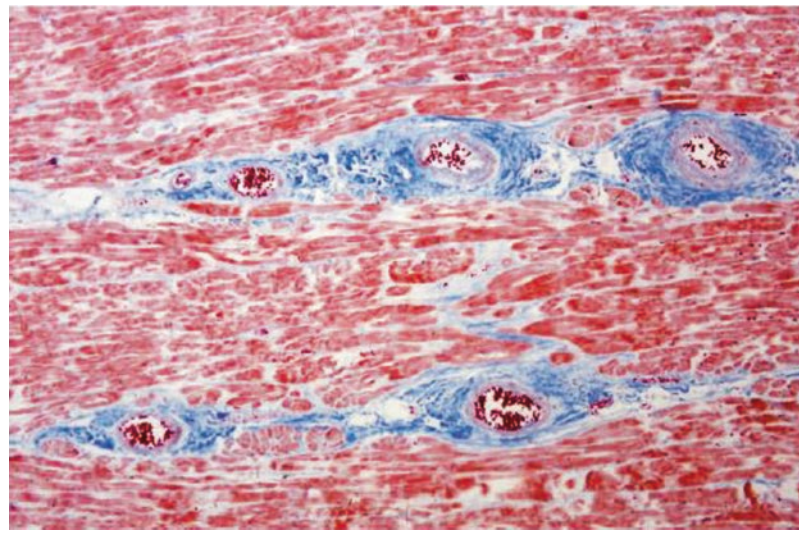

Fig. 13.28 Dilative cardiomyopathy with multifocal, perivascular fibrosis—most likely inflammatory dilative cardiomyopathy (DCMi) (Mallory ×125)

physical stress (Wingenfeld et al. 2010; Mund et al. 2002). A prevalence of 1:2500 to 1:5000 has been indicated for ARVCM (Basso et al. 2009), but considerable regional variation has been described. It is inherited in a predominantly autosomal dominant manner; 11 different genotypes are currently known. In the case of ARVCM, progressive adiposis of mainly the right ventricular myocardium is present; heart muscle fibers are replaced by adipose and connective tissue (Fig. 13.29) (Basso et al. 2008a, b; Angelini et al. 1996; Angelini et al. 1993). The remaining myocardium often is partially hypertrophied but may appear atrophic as well. Cardiomyocytes can appear vacuolated or may show coagulation necroses. Sometimes they are surrounded by inflammatory, mostly lymphocytic infiltrates (Huckenbeck and Papadomanolakis 2005). Although there are a number of reports concerning histologically detectable adipose and fibrous infiltrations of the left ventricular myocardium with left ventricular functional disorders, in all these cases, a concomitant infiltration of the right ventricle was present. The literature contains criteria for diagnosis which also include clinical data and family anamnesis (McKenna et al. 1994). Evidence of transmural replacement of myocardium by fat and connective tissue with fat cell nests reaching as far as under the right ventricular endocardium is histologically significant (Lobo et al. 1992). These changes, however, can only be detected in localized areas of the right ventricular wall and, alone, are not sufficiently specific (Basso et al. 2008a, b; Angelini et al. 1993). Similar findings can also be seen in older hearts (Basso and Thiene 2005; Tansey et al. 2005). For this reason, a histomorphometric method was suggested to determine the percentage of fat and connective tissue in seven visual fields at a 400× magnification using a diagram analysis system (Angelini et al. 1993). Diagnosis of ARVCM requires a minimum of 3% fat tissue on average and more than 40% fibrotic tissue. Other investigators regard 5–20% fat tissue as suspicious (Hort 2000; Dalal et al. 1994). In 2010, a modified method was introduced to evaluate digital microphotographs treating five myocardial regions, each with seven fields of view, together with Elastica van Gieson staining and Sudan III staining (Hagemeier et al. 2010). Patients with ARVCM may suffer from a myocardial viral infection, which may at least in part explain interstitial fibrosis and accompanying inflammatory infiltrates (Bowles et al. 2002). It was shown that ARVCM in children coexists with chronic myocarditis, as was shown with the aid of immunocytochemical staining for markers for T-lymphocytes (CD3, CD4, CD8)

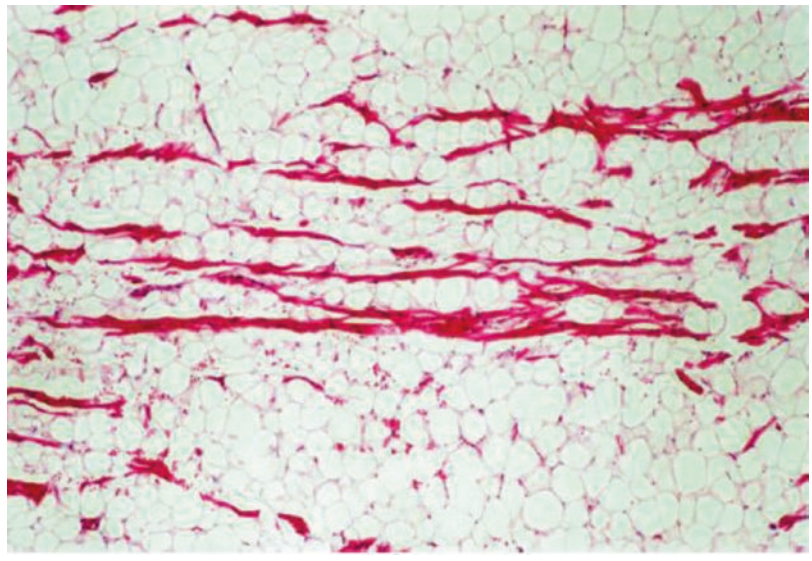

Fig. 13.29 Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVCM) with a fatty replacement of cardiac muscle in the right ventricular myocardium. Adipose tissue infiltration is associated with atrophic heart muscle cells (H&E ×40)

B-lymphocytes (CD22), and macrophages (CD68) and for adhesion molecules (ICAM-1, VCAM, ELAM) and endothelial marker (CD31/PECAM-1) (Woźniewicz et al. 1998). Clinically, the arrythmogenic right ventricular cardiomyopathy may lead to cardial arrhythmias. However, the disease is often asymptomatic until the diagnosis is made by an autopsy performed for the analysis of a sudden unexpected death. Recent investigations propose mutations believed to occur more frequently in patients with ARVCM, despite the fact that histological findings in the cases investigated were not typical for ARVCM (Sato et al. 2015). Plakoglobin is believed to be a suitable immunohistochemical diagnostic marker for ARVCM (Munkholm et al. 2015).

13.5.4 Isolated Noncompaction Cardiomyopathy

Isolated noncompaction cardiomyopathy (NCCM) was first described in 1984 (Engberding and Bender 1984). Fatal cases are usually seen in the pediatric population (Handlos et al. 2017; Lim and Langlois 2016; Buschmann et al. 2006). The term "isolated noncompaction of left ventricular myocardium" was suggested later (Chin et al. 1990). The clinical picture of NCCM varies greatly. In addition to heart insufficiency, intraventricular thrombosis and thromboembolic events occur (Binz et al. 2003; Bleyl et al. 1997a, b), including microcirculation imbalance (Jenni et al. 2002). It is reported to be the third most frequent form in children, after dilative cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) (Andrews et al. 2008; Arola et al. 1997), and carries a serious prognosis (Oechslin et al. 2000).

There are sporadic cases as well as cases showing familial prevalence (Ichida et al. 2001). Meanwhile, a genetic basis for the disease has been identified (Rodríguez-Calvo et al. 2008; Hermido-Prieto et al. 2004; Kenton et al. 2004; Sasse-Klaassen et al. 2003, 2004; Ichida et al. 2001; Bleyl et al. 1997a, b).

Histologically, there are sinusoidal recesses with an immunohistochemically CD34-positive endothelial or endocardial lining in the affected myocardial area which run deep into the left ventricular myocardium (Fig. 13.30) (Chin et al. 1990; Burke et al. 2005). In the right ventricle, it is almost impossible to distinguish this type of change from the regular trabecula system; thus NCCM is considered as localized, pathological left ventricular trabeculation. The corresponding endocardium may show subendocardial fibrosis (Jenni et al. 2002). In sudden infant death, NCCM may be considered in the differential diagnosis; it is possible that some cases of sudden infant death can be explained in this way (Dettmeyer and Kandolf 2009).

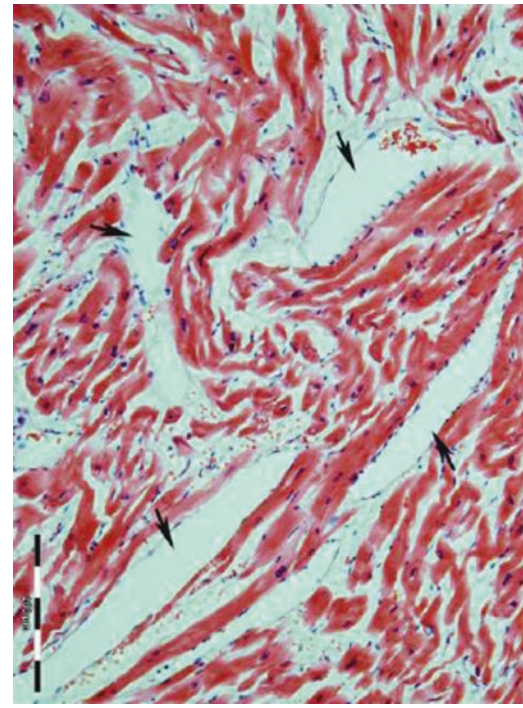

Fig. 13.30 Noncompaction cardiomyopathy: cross section of trabeculations (*arrows*) focally reaching far into the myocardium (H&E ×200)

13.5.5 Alcoholic Cardiomyopathy

Alcoholic cardiomyopathy belongs to the group of toxic cardiomyopathies (Bulloch et al. 1972). In addition to alcohol consumption reported during anamnesis, alcoholic cardiomyopathy

appears macroscopically as dilative cardiomyopathy. It is under discussion whether at least some cases of presumed alcoholic cardiomyopathy should actually be categorized as inflammatory dilative cardiomyopathy (DCMi) (Dettmeyer et al. 2002b). For more information, see Chap. 6.

13.5.6 Rare Forms of Cardiomyopathy

Rare forms of cardiomyopathy include:

- Thyrogenic cardiomyopathy
- Histiocytoid/oncocytic cardiomyopathy
- Takotsubo cardiomyopathy

Thyrogenic Cardiomyopathy

Hyperthyreosis may lead to cardiomyopathy with an eccentric myocardial hypertrophy, including necrosis, focal fibroses, and fine adiposis of the heart muscle fibers. Thyrotoxicosis of long standing may lead to the diagnosis of dilative cardiomyopathy (Santer 2004). Diagnosis always requires evidence of hyperthyreosis that has existed over a longer period of time (see Chap. 16).

Histiocytic/Oncocytic Cardiomyopathy

This rare childhood disease affects girls more often than boys. Microscopically, transformed muscle cells can be detected with partially vacuolized, partially eosinophilic and granular cytoplasm. Necrosis and an inflammatory response are absent (Stahl et al. 1997; Ruszkiewicz and Vernon-Roberts 1993; Ferrans et al. 1976). Eston and Perskvist (2009) reported on the association between histiocytoid cardiomyopathy and left ventricular hypertrabeculation in the death of a female infant. Histiocytoid cardiomyopathy and noncompaction cardiomyopathy are occasionally associated with mitochondrial disease (Finsterer and Stöllberger 2009; Finsterer 2008; Finsterer et al. 2007; Vallance et al. 2004).

Takotsubo Cardiomyopathy. Stress-Induced Cardiomyopathy (SICM)

Takotsubo cardiomyopathy (also called transient apical ballooning and stress cardiomyopathy; Angelini 2016; Indorato and Bartolini 2016; Indorato et al. 2015; Prasad et al. 2008; Cebelin and Hirsch 1980) is characterized by transient left ventricular dysfunction, electrocardiographic changes, and minimal release of myocardial enzymes (modest elevation of cardiac troponin), which mimic acute myocardial infarction. Patients do not present with coronary artery disease, and the pathomechanism is unknown. Takotsubo cardiomyopathy occurs primarily in postmenopausal women (Stöllberger et al. 2010; Fineschi et al. 2010; Bybee and Prasad 2008; Hansen 2007). Currently, there is no consensus on the diagnostic criteria for Takotsubo cardiomyopathy; some investigators proposed diagnostic criteria in 2004, which included the absence of pheochromocytoma and myocarditis (Akashi et al. 2008). The expert consensus panel (Maron et al. 2006) proposes a definition about stress cardiomyopathy:

> … a recently described clinical entity characterized by acute but rapidly reversible LV systolic dysfunction in the absence of atherosclerotic coronary artery disease, triggered by profound psychological stress. This distinctive form of ventricular stunning typically affects older women and preferentially involves the distal portion of the LV chamber ("atypical ballooning"), with the basal LV hypercontractile. Although presentation often mimics ST-segment-elevation myocardial infarction, outcome is favorable with an appropriate medical therapy.

There is no known specific histomorphologic correlate for Takotsubo cardiomyopathy, and a more precise histological documentation is needed for all cases with different kinds of behavior who suddenly died following emotional stress. Of the patients who underwent endomyocardial biopsy, interstitial infiltrates consisting primarily of mononuclear lymphocytes and macrophages and contraction bands without myocyte necrosis were observed (Wittstein et al. 2005). Myocardial contraction band necrosis is the pathognomonic lesion of myocardial catecholamine damage linked with peroxidation (Fineschi et al. 2010). Other investigations revealed intensely increased expression of β_1-adrenergic receptors in subendocardial as well as deeper layers of the cardiac musculature. At the same time, areas of myocardial damage and cellular apoptosis (TUNEL assay) were found (D'Errico et al. 2011). Other authors describe lymphocytic infiltrates, macrophages, contraction band necrosis, as well as endocardial myoelastofibrosis, smaller myocardial infarctions, hypereosinophilia, and myocardial fibrosis (Angelini 2016; Indorato and Bartolini 2016; Kammal et al. 2015).

Toxic Cardiomyopathies

Numerous toxins are essentially capable of causing cardiomyopathies, including drugs, poisons, and narcotic drugs, such as cocaine (see Chap. 5) or amphetamines (Karch 2011). Cobalt-beer cardiomyopathy became known after cobalt chloride started being added to beer.

13.6 Coronary Anomalies

Anomalies of the coronary arteries that have been classified and studied at autopsy and by clinical angiography can be divided into minor and major forms (Lipsett et al. 1994; Pedal and Teufel 1993; Taylor et al. 1992; Roberts 1986; Pedal 1976; Alexander and Griffith 1956). Descriptions of the various forms cover a wide range of entirely asymptomatic courses up to cases with sudden cardiac death. The incidence of the entire group of coronary anomalies is 0.036–6.5% (Thierauf et al. 2007; Yamanaka and Hobbs 1990). The most common anomaly is an aberrant course of the circumflex artery with an incidence of 0.16–0.35% (Barriales et al. 2001). The most common anomalous origin is the aberrant origin of the circumflex artery (Cx) from the right aortic sinus (RSV) with normal origin of the left anterior descending branch (LAD) (Cohle et al. 1986). Unexpected stimulation can work as a trigger of sudden cardiac death in the presence of a coronary abnormality (Kurosu et al. 2016).

A single coronary artery is rare in hearts without other congenital malformations (McConnell and Collins 1998). In about 0.4% of adults undergoing angiography, single coronary arteries are present (Thierauf et al. 2007). Clinical symptoms occur in 11–41% of patients with coronary anomalies (Eber et al. 1991). Angina pectoris, myocardial infarction, cardiac dysrhythmia, and acute cardiac death have all been reported as possible manifestations of coronary anomalies (Joswig et al. 1978). Major coronary anomalies often result in cardiac dysfunction and may cause cardiac failure and death. Minor anomalies tend to have no pathophysiological significance and include alterations in the number and location of coronary ostia. The anomalous origin of the left main coronary artery can be divided into four subtypes: intertruncal course, anterior free wall course before the right ventricular outflow, posterior course with the left coronary artery or one of the great branches passing behind the aorta, and an intertruncal–septal course through the crista supraventricularis (Aoki et al. 1999; Roberts and Shirami 1992).

In the case of insufficient perfusion of areas of the myocardium as a result of a coronary anomaly, there will often be areas of fibrosis of varying sizes replacing the myocardium, a finding highlighted by a Masson's trichrome stain. Surrounding myocytes exhibit hypertrophic changes with large hyperchromatic nuclei. At times, several foci of dystrophic calcifications with fibrosis may be noted, and often intimal

proliferations of intramyocardial vessels are evident (McConnell and Collins 1998). Additionally, sections of the cerebrum can reveal neuronal subacute hypoxic changes, and siderophages can be found within pulmonary alveoli.

There are rare cases where the right coronary artery departs from a Valsalva sinus aneurysm (Albalooshi et al. 2008) or cases with an initial anomaly of this artery with Roemheld syndrome (Hagemeier and Madea 2009). Radiological examinations are helpful to detect various forms of coronary anomaly (McConnell et al. 1995), including hypoplastic coronary arteries (McConnell and Collins 1998; Zugibe et al. 1993). The forensic literature contains various descriptions of coronary anomalies which lead to death (Hagemeier and Madea 2009; Albalooshi et al. 2008; Iino et al. 2007; Madea and Dettmeyer 1998); when young athletes die suddenly, a coronary anomaly should be considered (Tsung et al. 1982). Myocardial ischemia is also described in connection with abnormal continuous forms between the aorta and the departure of the pulmonary trunk (Roynard et al. 1994). In cases of abnormal origin of the left coronary artery (LCA) from the right sinus, the clinical significance is determined by the course of the artery. Cases of sudden death, especially in young people during exercise, are mainly reported in connection with an intertruncal course of the artery (Madea and Dettmeyer 1998; Janssen 1975). There have been individual cases which reported the presence of multiple coronary anomalies together with a borderline hypertrophic cardiomyopathy (Dermengiu et al. 2010a).

The following is valid in histological evaluation: Myocardial samples must be removed from the outer range of the supply areas of the coronary arteries. Confluent coronary insufficiency scars can be observed even macroscopically. Older collagen scar tissue can be seen which replaces the preexisting myocardium on the one hand, while partially fresh myocardial necrosis is detectable in an acute or subacute course on the other; this is partially a sign of organizing myocardial necrosis with alternating dense collagen connective tissue, macrophages, lymphocytes, fibrocytes, fibroblasts, and branched capillary blood vessels in the form of granulation tissue.

Myocardial Bridging

Myocardial bridging is a common coronary anomaly characterized by the presence of a muscle bridge above an epicardial artery (Srettabunjong 2016; Sunnassee et al. 2011; Weiler and Risse 1994; Ferreira et al. 1991). According to the literature, interstitial fibrosis (Brodsky et al. 2008), interstitial edema, and hypoxia-induced changes, particularly inside the left ventricular front wall (Dermengiu et al. 2010b), are often found in myocardial bridging (Riße and Weiler 1985). Individual studies report myocardial infarction in connection with myocardial bridging (Baldassarre et al. 1996; Bestetti et al. 1987; Bezerra et al. 1987). Nevertheless, controversy exists over whether myocardial bridging can actually cause sudden cardiac death (Biggs et al. 2008; Möhlenkamp et al. 2002).

13.7 Cardiac Conduction System (CCS)

When the cause of death remains unclear, and in those cases where the cause of death cannot be explained even after the case history and autopsy findings have been examined, one should also consider lesions of the cardiac conduction system, particularly of the sinoatrial node (Ogbuihi 1989; Doerr 1980; Smith and Davis 1997). However, up to now histological examinations of the cardiac conduction system are carried out too rarely in cases of sudden cardiac death caused by conduction disturbances (Zack and Wegener 1994). This is also valid for cases which do not demonstrate relevant microscopic myocardial or coronary findings. In this case, samples should be taken from various areas of the heart, which may lead to pathologic findings, as has been frequently the case. In addition, while histological examination of the cardiac conduction system is

useful, the findings require interpretation (Suarez-Mier and Aguilera 1998; Suarez-Mier et al. 1995) and are sometimes regarded as inconclusive (Pedersen 1980). Cystic tumors of the atrioventricular nodal region are a rare cause of sudden death (Patel and Sheppard 2011).

13.7.1 Examining the CCS

Earlier studies suggested methods to examine the cardiac conduction system, many of which required differentiated tissue work-up with between hundreds and thousands of tissue sections per case (Bharati and Lev 1995; Song et al. 1991; Okada and Kawai 1983; Hudson 1963; Lenègre and Chevalier 1951). Currently, there are suggestions for a modified and simplified method to examine the conduction system (Michaud et al. 2002; Sigrist and Germann 1998; Song et al. 1997; Charlton and Williams 1990; Chandrasiri 1985). Song et al. (1997, 1991) described a revised technique in which the sinoatrial node, the AV node, the distal part of the His bundle, and the bundle branches of the CCS are demonstrated in longitudinal sections by cutting between four and five blocks. This method reduces workload and can make examination of the CCS a routine procedure to some extent.

Sigrist and Germann (1998) described a further possible dissection approach:

1. Firstly, the coronary arteries are dissected, including the sinoatrial node and AV node arteries (Haas' artery).
2. Secondly, the coronary ventricles are opened either by cutting with scissors alongside the blood flow or by cutting with a knife vertically to the heart axis. The upper third of the interventricular septum must not be damaged.
3. Thirdly, starting at the left ventricular chamber, one can easily observe the membranous portion. Four radical incisions with the scalpel are made in this region:
   (a) Firstly, through the attachment of the frontal valvula mitralis at the septum interventriculare
   (b) Secondly, parallel to the first incision, approximately 1.5 cm before the membranous part
   (c) Thirdly, 1 cm above the membranous portion vertically through the vestibule septum
   (d) Fourthly, parallel to the third incision 2 cm below the membranous portion

With these four incisions, a tissue sample almost rectangular in shape has been removed which may be sliced into 2–3-mm-thick slices after formaldehyde fixation. These tissue slices can be used to prepare tissue sections suitable for histological examination. Occasionally, the cross section of the His bundle can be recognized as a light brown point structure inside the membranous portion. Other investigators have described a similar examination technique, in particular Michaud et al. (2002), Davies et al. (1975), and Hudson (1963).

13.7.2 Histopathologic Findings in the CCS

Histopathological changes such as a fibromuscular dysplasia (James and Marshall 1976), modular wall thickening, or thrombosis of the sinoatrial node artery are described in numerous publications (Zack et al. 2011). However, for some of these findings, there are no systematic investigations into their frequency or their relevance in terms of the cause of death. Some of the histological changes in the cardiac conduction system evidently occur more frequently than previously assumed and cannot necessarily be considered as pathological findings. For example, it was found that fibromuscular proliferation of the AV node artery is also seen relatively frequently in individuals free of cardiac disease (Zack et al. 2016). Fat cell nests, moderate lumen-narrowing proliferations in the wall of the sinus node artery, and discrete inflammatory infiltrates in the sinus node or surrounding area are found more commonly in individuals that died of a nonnatural cause of death (Zack et al. 2016). Therefore, findings of this type

should at most—if at all—only be considered in the diagnosis of cause of death once other causes of death have been ruled out. In this context, any coincidence of arrhythmogenic or cardiotoxic drugs and histopathological findings in the cardiac conduction system should prompt consideration of a cumulative cause of death, for instance, in pronounced lipomatosis of the atrioventricular node and simultaneous sertindole and pipamperone use (Zack et al. 2014a). Traumatic damage is possible in addition to degenerative changes and inflammatory infiltrates. Local fibrosis with degeneration of the specific musculature is also reported (Ogbuihi 1989). This fibrosis may explain sick sinus syndrome. However, previous studies have not proven that there is increased fibrosis of the sinoatrial node with increasing age (Hudson 1960; Doerr 1959), nor which degree of fibrosis can be regarded as a pathological finding at all (Song et al. 1999). However, examination of the conduction system in 150 Finnish subjects led to the result that an increase in fibrosis and adiposis of the cardiac conduction system (CCS) could be observed with increasing age (Song et al. 2001). In about half of the subjects examined, there were calcium deposits in the central fibrous body, membranous portion, and the top of the musculature in the interventricular septum. In seven cases, the AV node, His bundle, or bundle branches (right bundle branch, left bundle branch) were compressed by the calcium deposits. Hemorrhage, inflammation, amyloidosis, tumor, fatty infiltration, and development malformations were observed in 31 cases. Although 28 cases died of myocardial infarction, no involvement of the CCS was observed in these subjects (Song et al. 2001).

Arteriosclerotic changes, especially those of the sinoatrial node artery, can certainly lead to even fatal cardiac arrhythmia (Lev et al. 1970), including surgical and other trauma to the region of the conduction system (Cohle and Lie 1998; Titus et al. 1963). There is one case of elective fatty degeneration of the specific heart muscle cells in connection with digitoxin intoxication described in the literature (Doerr 1969).

Histological findings on the CCS after acute hypoxia such as perinuclear vacuoles and cavities next to the cell nuclei with fish bone-like deformation have been known for a long time. These findings include “tubular myopathy” with tube-shaped cavity formation and peripheral displacement of the cytoplasm, whereby the cross-sectional fibers retain a ring-like appearance (Büchner 1975; Pichotka 1942). These findings could also be proven at autopsy. A loss of specific heart muscle fibers is the result of chronic lack of oxygen (Sigrist and Germann 1998).

Pathologic changes in the cardiac conduction system may already be found intrauterine. Piercecchi-Marti et al. (2003) provide the description of a fetus in the 29th gestational week with histologically proven alterations of the AV node and the His bundle with fibrosis, calcification, endocardial fibroelastosis, and mononuclear inflammatory infiltration. Embolism caused by adiposis of the CCS is also described (Schwartz et al. 1988).

A correlation between histopathological changes and clinically diagnosed cardiac arrhythmias should be considered first, including fatal arrhythmias (Lev et al. 1979; Doerr 1975). Nevertheless, in individual cases, histopathologic findings in relation to their importance in terms of the time of death are often difficult to interpret, and other causes of death must be excluded first (Nishida et al. 2002; Zack and Wegener 1994; Ogbuihi 1989; Voigt 1976).

Sinus Node Fibrosis

In addition to histopathological lesions in the region of the AV node and bundle of His, findings made in the sinus node could explain death, assuming other causes have been excluded. Sinus node fibrosis is of particular relevance in this regard. As part of this process, the specific muscle fibers may be largely destroyed (Zack et al. 1996; Ogbuihi 1989). Individual fat cell nests have been reported, as have occasional lymphocytic infiltrates (Knieriem et al. 1979) (Fig. 13.31).

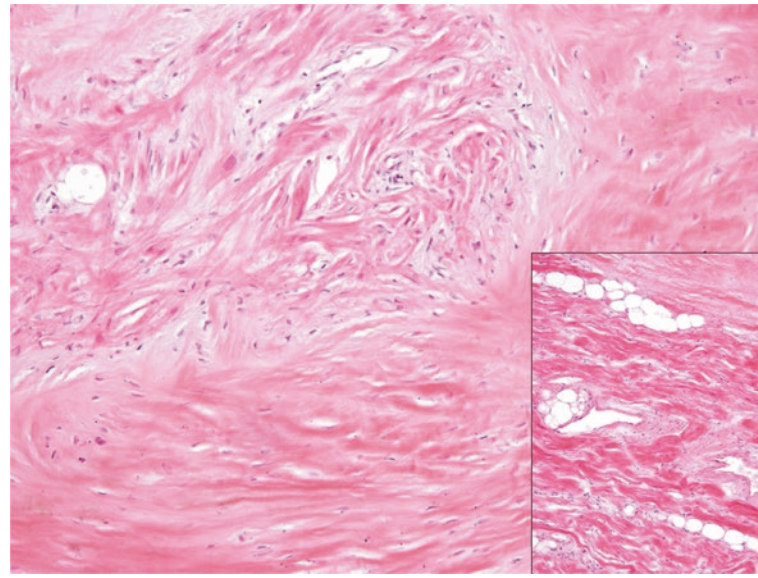

Fig. 13.31 Largely fibrosed sinus node region with peripheral fibrosis, scant lymphocytic infiltration, and tiny individual fat cell nests (H&E ×100)

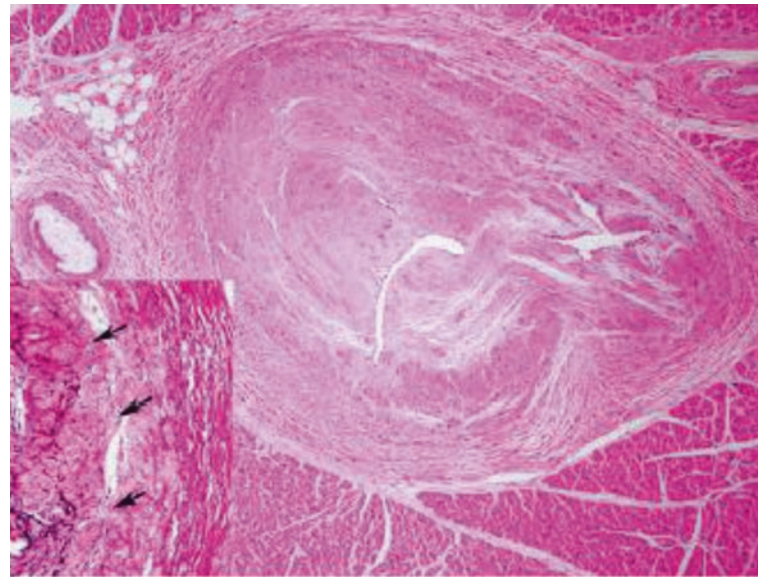

Fig. 13.32 AV node artery (AVNA) of the heart with strong thickening of the arterial wall, narrowing of the lumen (H&E ×100), and destruction of the internal elastic lamina (*arrows*; Elastica van Gieson ×400)

Fibromuscular Dysplasia

Intramyocardial small vessel anomalies are not commonly recognized. Small vessel disease has been reported as an isolated cardiac anomaly in individuals with sudden death. The best known anomaly is fibromuscular dysplasia (Fig. 13.32), involving the sinoatrial or AV nodal artery. Histological findings include prominent vascular dilatation, interstitial edema, and marked vascular narrowing of intramyocardial arterioles due to fibromuscular dysplasia. The vessel presents a thick media which is disorganized, causing narrowing of the vessel (Veinot et al. 2002).

Finally, in the case of sudden death with no histomorphological correlation to a plausible cause of death, rare genetic defects should be considered (e.g., ion channel defects). In order to clarify these defects, molecular genetic investigations are necessary (Michaud et al. 2011; Kauferstein et al. 2009). Doubts about the pathophysiological significance of fibromuscular dysplasia have been expressed, since this entity is not infrequently an incidental finding in the context of thorough investigations (Zack et al. 2014b, 2016). Evidently, the vessel lumen stenosis associated with fibromuscular dysplasia does not necessarily cause acute ischemia under strain; one assumes sufficient formation of collateral vessels. In the case of negative histopathological findings and assumed sudden cardiac death, molecular genetic testing is able to determine cardiac ion channel defects as the cause of death in some cases (Kauferstein et al. 2013; Campuzano et al. 2014).

References

Abbate A, Sinagra G, Bussani R, Hoke NN, Merlo M, Varma A, Toldo S, Salloum FN, Biondi-Zoccai GG, Vetrovec GW, Crea F, Silvestri F, Baldi A (2009) Apoptosis in patients with acute myocarditis. Am J Cardiol 104:995–1000

Adams JE, Bodor GS, Dávila-Román VG et al (1993) Cardiac troponin I: a marker with high specificity for cardiac injury. Circulation 88:101–106

Akashi YJ, Goldstein DS, Barbaro G, Ueyama T (2008) Takotsubo cardiomyopathy. A new form of acute, reversible heart failure. Circulation 118:2754–2762

Albalooshi Y, Hagemeier L, Doberentz E et al (2008) Abgang der rechten Herzkranzarterie aus einem Aneurysma des Sinus Valsalvae. Rechtsmedizin 18:437–440

Alexander RW, Griffith GC (1956) Anomalies of the coronary arteries and their clinical significance. Circulation 14:800–805

Al-Rufaie HK, Elorio RA, Olsen EGJ (1983) Comparison of the haematoxylin basic fuchsin picric acid method and the fluorescence of haematoxylin and eosin stained sections for the identification of early myocardial infarction. J Clin Pathol 36:646–649

Althoff H (1983) Zur morphologie des akuten koronartodes jüngerer frauen. Z Rechtsmed 91:85–99

Amberg R (1995) Immunmorphologische Reaktionsmuster des Myokard bei kardialen und nicht-kardialen Perfusionsstörungen. In: Bratzke H, Schröter A (eds) Immunhistochemie in der Rechtsmedizin. Hänsel-Hohenhausen, Egelsbach, pp 101–116

Andrews RE, Fenton MJ, Ridout DA, Burch M (2008) British congenital cardiac association. New onset heart failure due to heart muscle disease in childhood: a prospective study in the United Kingdom and Ireland. Circulation 117:79–84

Angelini A, Thiene G, Boffa GM et al (1993) Endomyocardial biopsy in right ventricular cardiomyopathy. Int J Cardiol 40:273–282

Angelini A, Basso C, Nava A, Thiene G (1996) Endomyocardial biopsy in arrhythmogenic right ventricular cardiomyopathy. Am Heart J 132:203–206

Angelini P (2016) Do pathologists agree on how to diagnose takotsubo cardiomyopathy? Forensic Sci Med Pathol 12:226

Aoki Y, Nata M, Hashiyada M, Sagisaka K (1996) Sudden unexpected death in childhood due to eosinophilic myocarditis. Int J Legal Med 108:221–224

Aoki Y, Saigusa K, Nakayama Y (1999) Sudden infant death with anomalous origin of the left coronary artery from the pulmonary artery. Legal Med 1:250–253

Aretz HT (1987) Myocarditis: the Dallas criteria. Hum Pathol 18:619–624

Aretz HT, Billingham ME, Edwards W, Factor SM, Falllon JT, Fenoglio JJ et al (1987) Myocarditis: a histopathologic definition and classification. Am J Cardiovasc Pathol 1:5–14

Arnold G, Kaiser C, Fischer R (1985) Myofibrilläre degeneration – a common type of myocardial lesion and its selective identification by a modified Luxol fast blue stain. Pathol Res Pract 180:405–415

Arola A, Jokinen E, Ruuskanen O, Saraste M, Pesonen E, Kuusela AL, Tikanojja T, Paavilainen T, Simell O (1997) Epidemiology of idiopathic cardiomyopathies in children and adolescents. A nationwide study in Finland. Am J Epidemiol 146:385–393

Arola A, Kallajoki M, Ruuskanen O, Hyypia T (1998) Detection of enteroviral RNA in end-stage dilated cardiomyopathy in children and adolescents. J Med Virol 56:364–371

Azzawi M, Hasleton PS, Kann SW, Hillier VF, Quigley A, Hutchinson IV (1997) Distribution of myocardial macrophages in the normal human heart. J Anat 191:417–423

Baasner A, Dettmeyer R, Graebe M, Madea B (2003a) PCR-based diagnosis of enterovirus and parvovirus B19 in paraffin-embedded heart tissue. In: Brinkmann B, Carracedo A (Hrsg.) Progress in Forensic Genetics 9, 19th International ISFG Congress, 28.08–01.09.2001, Münster, Germany; International Congress Series 1239, p. 715–717

Baasner A, Dettmeyer R, Graebe M, Rissland J, Madea B (2003b) PCR-based diagnosis of Enterovirus and Parvovirus B19 in paraffin embedded heart tissue of children with suspected sudden infant death syndrome. Lab Investig 83:1451–1455

Badir B, Knight B (1987) Fluorescence microscopy in the detection of early myocardial infarction. Forensic Sci Int 34:99–102

Badorff C, Lee GH, Lamphear BJ, Martone ME, Campbell KP, Rhoads RE, Knowlton KU (1999) Enteroviral protease 2A cleaves dystrophin: evidence of cytoskeletal disruption in an acquired cardiomyopathy. Nat Med 5:320–326

Badorff C, Berkeley N, Mehrotrar S, Talhouk JW, Rhoads RE, Knowlton KU (2000a) Enteroviral protease 2A directly cleaves dystrophin and is inhibited by a dystrophin-based analogue. J Biol Chem 275:1191–1197

Badorff C, Lee GH, Knowlton KU (2000b) Enteroviral cardiomyopathy: bad news for the dystrophin-glycoprotein-complex. Herz 25:227–232

Bagwan IN, Hooper LVB, Sheppard MN (2011) Cardiac sarcoidosis and sudden death. The heart may look normal or mimic other cardiomyopathies. Virchows Arch 458:671–678

Baldassarre S, Unger P, Renard M (1996) Acute myocardial infarction and myocardial bridging: a case report. Acta Cardiol 51:461–465

Baroldi G, Mittleman RE, Parolini M, Silver MD, Fineschi V (2001) Myocardial contraction bands. Definition, quantification and significance in forensic pathology. Int J Legal Med 115:142–151

Barriales R, Moris C, Lopz Muniz A, Hernandez LC, San Roman L, Barriales Alvarez V, Testa A, de la Hara J, Sammartin JC, Cortina A (2001) Anomalías congénitas de las arterias coronarias del adulto descritas en 31 años de estudios coronariográficos en el Principado de Asturias: principales características angiográficas y clínicas. Rev Esp Cardiol 54:269–281

Basso C, Thiene G (2005) Adipositas cordis, fatty infiltration of the right ventricle, and arrhythmogenic right ventricular cardiomyopathy. Just a matter of fat? Cardiovasc Pathol 14:37–41

Basso C, Burke M, Fornes P, Gallagher PJ, Henriques de Gouveia R, Sheppard M, Thiene G, van der Wal A (2008a) Guidelines for autopsy investigation of sudden cardiac death. Virchows Arch 452:11–18

Basso C, Ronco F, Marcus F et al (2008b) Quantitative assessment of endomyocardial biopsy in arrhythmogenic right ventricular cardiomyopathy/dysplasia: an in vitro validation of diagnostic criteria. Eur Heart J 29:2760–2771

Basso C, Corrado D, Marcus F et al (2009) Arrhythmogenic right ventricle cardiomyopathy. Lancet 373:1289–1300

Ben m'rad M, Leclerc-Mercier S, Blanche P, Franck N, Rozenberg F, Fulla Y, Guesmi M, Rollot F, Dehoux M, Guillevin L, Moachon L (2009) Drug-induced hypersensitivity syndrome: clinical and biologic disease patterns in 24 patients. Medicine 88:131–140

Bendig JWA, O'Brien PS, Muir P, Porter HJ, Caul EO (2001) Enterovirus sequences resembling coxsackievirus A2 detected in stool and spleen from a girl with fatal myocarditis. J Med Virol 64:482–486

Bergelson JM, Cunningham JA, Droguett G, Kurt-Jones EA, Krithivas A, Hong JS et al (1997) Isolation of a common receptor for coxsackie B viruses and adenoviruses 2 and 5. Science 275:1320–1323

Bernstein M, Konzelman FW, Sidlick DM (1929) Boeck's sarcoid: a report of a case with visceral involvement. Arch Intern Med 4:721–734

Bestetti RB, Finzi LA, Amaral FTV (1987) Myocardial bridging of coronary arteries associated with an impending acute myocardial infarction. Clin Cardiol 10:129–131

Bezerra AJC, Prates JC, DiDio LJA (1987) Incidence and clinical significance of bridges of myocardium over the coronary arteries and their branches. Surg Radiol Anat 9:273–280

Bharati S, Lev M (1995) Cardiac conduction system involvement in sudden death of obese young people. Am Heart J 129:273–281

Biggs MJ, Swift B, Sheppard MN (2008) Myocardial bridging: is it really a cause of sudden cardiac death? In: Tsokos M (ed) Forensic pathology reviews, vol 5. Humana, Totawa, pp 115–127

Binz G, Knirsch W, Lewin MA, Haas NA, Koch W, Kandolf R, Uhlemann F (2003) Isolated myocardial noncompaction in childhood – case report and review of the literature. Z Kardiol 92:1039–1044

Blauwet LA, Cooper LT (2010) Myocarditis. Prog Cardiovasc Dis 52:274–288

Bleyl SB, Mumford BR, Brown-Harrison MC, Pagotto LT, Carey JC, Pysher TJ, Ward K, Chin TK (1997a) Xq28-linked noncompaction of the left ventricular myocardium: prenatal diagnosis and pathologic analysis of affected individuals. Am J Med Genet 72:257–265

Bleyl SB, Mumford BR, Thompson V, Carey JC, Pysher JT, Chin TK, Ward K (1997b) Neonatal, lethal noncompaction of the left ventricular myocardium is allelic with Barth syndrome. Am J Hum Genet 61:868–872

Bock CT, Klingel K, Aberle S, Duechting A, Lupescu A, Lang F, Kandolf R (2005) Human parvovirus B19: a new emerging pathogen of inflammatory cardiomyopathy. J Vet Med B Infect Dis Vet Public Health 52:340–343

Bock CT, Klingel K, Kandolf R (2010) Human parvovirus B19-associated myocarditis. N Engl J Med 362:1248–1249

Bouchardy B, Majno G (1974) Histopathology of early myocardial infarcts. A new approach. Am J Pathol 74:301–330

Bowles NE, Richardson PJ, Olsen EGJ, Archard LC (1986) Detection of coxsackie-B-virus-specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy. Lancet 17:1120–1122

Bowles NE, Rose ML, Taylor P, Banner NR, Morgan-Capner P, Cunningham L et al (1989) End-stage dilated cardiomyopathy. Persistence of enterovirus RNA in myocardium at cardiac transplantation and lack of immune response. Circulation 80:1128–1136

Bowles NE, Ni J, Marcus F, Towbin JA (2002) The detection of cardiotropic viruses in the myocardium of patients with arrhythmogenic right ventricu-

lar dysplasia/cardiomyopathy. J Am Coll Cardiol 39:892–895
Braun R, Hassler D, Kimmig P (2002) Myokarditis durch Enteroviren in Griechenland – und bei uns? Dtsch Med Wochenschr 127:1364
Brinkmann B, Sepulchre MA, Fechner G (1993) The application of selected histochemical and immunohistochemical markers and procedures to the diagnosis of early myocardial damage. Int J Legal Med 106:135–141
Brodsky SV, Roh L, Ashar K, Braun A, Ramaswamy G (2008) Myocardial bridging of coronary arteries: a risk factor for myocardial fibrosis? Int J Cardiol 124:391–392
Bryant RM (1999) Hypertrophic cardiomyopathy in children. Cardiol Rev 7:92–100
Büchner F (1975) Strukturveränderungen durch allgemeinen Sauerstoffmangel, insbesondere bei der Höhenkrankheit. In: Grundmann E (ed) Hypoxie. Springer, Berlin
Büchner F, Onishi S (1968) Der Herzmuskel bei akuter Coronarinsuffizienz im elektronenmikroskopischen Bild. Urban & Schwarzenberg, München
Bulloch RT, Pearce MB, Murphy ML, Jenkins BJ, Davis JL (1972) Myocardial lesions in idiopathic and alcoholic cardiomyopathy. Study by ventricular septal biopsy. Am J Cardiol 29:15
Bültmann BD, Klingel K, Sotlar K, Bock CT, Baba HA, Sauter M, Kandolf R (2003a) Fatal parvovirus B19-associated myocarditis clinically mimicking ischemic heart disease: an endothelial cell-mediated disease. Hum Pathol 34:92–95
Bültmann BD, Klingel K, Sotlar K, Bock CT, Kandolf R (2003b) Parvovirus B19: a pathogen responsible for more than hematologic disorders. Virchows Arch 442:8–17
Burke AP, Saenger J, Mulick F, Virmani R (1991) Hypersensitivity myocarditis. Arch Pathol Lab Med 115:764–769
Burke A, Mont E, Kutys R, Virmani R (2005) Left ventricular noncompaction: a pathological study of 14 cases. Hum Pathol 36:403–411
Buschmann C, Stenzel W, Martin H, Heppner FL, Guddat SS, Tsokos M (2013) Calcified myocardial necrosis in pediatric patients after cardiopulmonary resuscitation. Forensic Sci Med Pathol 9:543–550
Buschmann C, Schäfer HJ, Püschel K, Schulz F (2006) Innate heart deformation as a cause of sudden death in a 7-year-old girl. Rechtsmedizin 16:64–68
Bux R, Bratzke H, Rothschild MA, Lutz FU (2002) Plötzlicher Tod einer 12-Jährigen mit klinisch inapparenter Myokarditis unter psychischer und physischer Belastung. Rechtsmedizin 12:229–232
Byard RW (2002) Unexpected death due to infectious mononucleosis. J Forensic Sci 47:202–204
Byard RW, Manton N, Tsokos M (2008) Sarcoidosis and mechanism of unexpected death. J Forensic Sci 53:460–464
Bybee KA, Prasad A (2008) Stress-related cardiomyopathy syndromes. Circulation 118:397–409
Campuzano O, Allegue C, Partemi S, Iglesias A, Oliva A, Brugada R (2014) Negative autopsy and sudden cardiac death. Int J Legal Med 128:599–606
Carle BN (1981) Autofluorescence in the identification of myocardial infarcts. Hum Pathol 12:643–646
Casali MB, Lazzaro A, Gentile G, Blandino A, Ronchi E, Zoja R (2012) Forensic grading of myocarditis: an experimental contribution to the distinction between lethal myocarditis and incidental myocarditis. Forensic Sci Int 223:78–86
Casscells W, Kimura H, Sanchez J, Yu Z, Ferrans VJ (1990) Immunohistochemical study of fibronectin in experimental myocardial infarction. Am J Pathol 137:801–810
Cassinotti P, Weitz M, Siegl G (1993) Human parvovirus B 19 infections: routine diagnosis by a new nested polymerase chain reaction assay. J Med Virol 40:228–234
Cassling RS, Linder J, Sears TD, Waller BF, Rogler WC, Wilson JE, Kugler JD, Kay DH, Dillon JC, Slack JD et al (1985) Quantitative evaluation of inflammation in biopsy specimen from idiopathically failing or irritable hearts: experience in 80 pediatric and adult patients. Am Heart J 110:713–720
Cavanaugh J, Prahlow JA (2013) Sudden cardiac death due to arrythmogenic right ventricular cardiomyopathy and cystic tumor of the AV node. Forensic Sci Med Pathol 9:407–412
Cebelin MS, Hirsch CS (1980) Human stress cardiomyopathy. Myocardial lesions in victims of homicidal assaults without internal injuries. Hum Pathol 11:123–132
Cecchi R, Bajanowski T, Kahl B, Wiegand P (1995) CMV-DNA detection in parenchymatous organs in cases of SIDS. Int J Legal Med 107:291–295
Chandrasiri N (1985) Histopathological re-study of the human cardiac conduction system. Med Sci Law 25:29–43
Charlton I, Williams R (1990) Cardiac conducting tissue: a simplified technique for examination of the SA and AV nodes. Am J Forensic Med Pathol 11:213–218
Chen X, Zhang Y (2006) Myocardial Cx43 expression in the cases of sudden death due to dilated cardiomyopathy. Forensic Sci Int 162:170–173
Chia JKS, Jackson B (1996) Myopericarditis due to parvovirus B19 in an adult. Clin Infect Dis 23:200–201
Chin TK, Perloff JK, Vuillemin M, Thompson RP, Anderson RH (1990) Isolated noncompaction of left ventricular myocardium. A study of eight cases. Circulation 82:507–513
Chow LH, Ye Y, Linder J, McManus BM (1989) Phenotypic analysis of infiltrating cells in human myocarditis. Arch Pathol Lab Med 113:1357–1362
Chrysohoou C, Tsiamis E, Brili S, Barbetseas J, Stefanadis C (2009) Acute myocarditis from coxsackie infection, mimicking subendocardial ischaemia. Hell J Cardiol 50:147–150
Chumachenko PV, Vikkert AM (1991) Immunomorphologic diagnosis of early myocardial

necrosis using monoclonal antibodies to desmin and vimentin. Arkh Patol 53:16–19
Cohle SD, Lie JT (1998) Histopathologic spectrum of the cardiac tissue in traumatic and noncardiac sudden death patients under 30 years of age: an analysis of 100 cases. Anat Pathol 3:53–76
Cohle SD, Graham MA, Pounder DJ (1986) Nonatherosclerotic sudden coronary death. Pathol Annu 21:217–249
Cremer U, Althoff H (1991) Nachweis und Inzidenz von Zytomegalievirusinfektionen bei plötzlichen Kindstodesfällen (SIDS). Rechtsmedizin 1:25–28
Curca GC, Dermengiu D, Ceausu M, Francisc A, Rusu MC, Hostiuc S (2011) Cardiac lesions associated with cardiopulmonary resuscitation. Rom J Legal Med 19:1–6
D'Ambrosio A, Patti G, Manzoli A, Sinagra G, Di Lenarda A, Silvestri F, Di Sciascio G (2001) The fate of acute myocarditis between spontaneous improvement and evolution to dilated cardiomyopathy: a review. Heart 85:499–504
Daar AS, Fuggle SV, Fabre JW, Ting A, Morris J (1984a) The detailed distribution of HLA-A, B, C antigens in normal human organs. Transplantation 38:287–292
Daar AS, Fuggle SV, Fabre JW, Ting A, Morris PJ (1984b) The detailed distribution of MHC class II antigens in normal human organs. Transplantation 38:293–298
Dada MA, Lazarus NG, Kharsany ABM, Sturm AW (2000) Sudden death caused by myocardial tuberculosis. Am J Forensic Med Pathol 21:385–388
Dalal P, Fujisic K, Hupart P, Schweizer P (1994) Arrhythmogenic right ventricular dysplasia: a review. Cardiology 85:361–369
Davies JM, Pomerance A, Lamb D (1975) Techniques in examination and anatomy of the heart. In: Pomerance A, Davies MJ (eds) The pathology of the heart. Blackwell, Oxford
de Lourdes Higuchi M, Guitierrez PS, Demarchi Aiello V, Palomino S, Bocchi E, Kalil J, Bellotti G, Pileggi F (1993) Immunohistochemical characterization of infiltrating cells in human chronic Chagas myocarditis: comparison with myocardial rejection process. Virch Arch A Pathol Anat 423:157–160
D'Errico S, Neri M, Nieddu A, Mazzeo E, Riezzo I, Turillazi E, Fineschi V (2011) Cardiac ß$_1$-adrenoceptor expression in two stress-induced cardiomyopathy-related deaths. Forensic Sci Int 207:e8-e11
Dermengiu D, Ceausu M, Rusu MC, Dermengiu S, Curca GC, Hostiuc S (2010a) Sudden death with borderline hypertrophic cardiomyopathy and multiple coronary anomalies. Case report and literature review. Rom J Legal Med 18:3–12
Dermengiu D, Vovolis I, Hostiuc S, Curca GC, Rusu MC, Luca L (2010b) Morphological features in myocardial bridging. Rom J Legal Med 18:163–170
Dermengiu D, Curcă GC, Sărbu N, Hostiuc S, Ceauşu M (2010c) Sudden cardiac death in non-atherosclerotic and non-inflammatory intimal cellular proliferations. A case report. Rom J Legal Med 18:183–188
Dettmeyer R, Kandolf R (2009) Cardiomyopathies – misdiagnosed as sudden infant death syndrome (SIDS). Forensic Sci Int 194:e21–e24
Dettmeyer R, Madea B (2002) Myokarditis durch Enteroviren in Griechenland – und bei uns? Leserbrief zum Beitrag aus Dtsch Med Wochenschr 127:1364 (2002). Dtsch Med Wochenschr 27:2467–2468
Dettmeyer R, Madea B (2003) Commentary to the letter of Arya SC and Agarval N to our report "Fatal parvovirus B19 myocarditis in an 8-year-old boy", J Forensic Sci 2003; 48:183–186 – authors response. J Forensic Sci 48:1205
Dettmeyer R, Madea B (2004) Sudden, unexpected death related to viral myocarditis. A survey of histological, immunohistochemical, and molecular pathological methods for the postmortem diagnosis. In: Tsokos M (ed) Forensic pathology reviews, vol 2. Humana Press, Totowa, pp 169–186
Dettmeyer R, Haag C, Madea B (2002a) Leserbrief zum Beitrag "Plötzlicher Tod einer 12-jährigen mit klinisch inapparenter Myokarditis unter psychischer und physischer Belastung". Rechtsmedizin 12:229–232 (2002). Rechtsmedizin 12:395–396
Dettmeyer R, Reith K, Madea B (2002b) Alcoholic cardiomyopathy versus chronic myocarditis – immunohistological investigations with LCA, CD3, CD68 and tenascin. Forensic Sci Int 126:57–62
Dettmeyer R, Kandolf R, Baasner A, Banaschak S, Eis-Hübinger AM, Madea B (2003) Fatal parvovirus B19 myocarditis in an 8-year-old boy. J Forensic Sci 48:183–186
Dettmeyer R, Padosch SA, Baasner A, Madea B (2004a) PCR-based diagnosis of adenovirus and Epstein-Barr virus in paraffin-embedded heart tissue. In: Doutremépuich C, Morling N (eds.) Progress in Forensic Genetics 10. Proceedings of the 20th International ISFG Congress, Arcachon, 9.-13. September 2003, France. Int Congr Ser 1261:605–607
Dettmeyer R, Schmidt P, Kandolf R, Madea B (2004b) Evolution of dilated cardiomyopathy (DCM) from idiopathic hypertrophic cardiomyopathy (IHCM) vs. inflammatory dilated cardiomyopathy (DCMi): a rare case of sudden death in an 8-year-old boy. Pathol Res Pract 200:411–415
Dettmeyer R, Stiel M, Madea B (2006a) Heat shock protein 60 (cHSP60) as a marker for chronic infection with Chlamydia pneumoniae in atherosclerosis – investigation of atherosclerotic coronary arteries by immunocytochemistry. Forensic Sci Med Pathol 2:173–178
Dettmeyer R, Strehler M, Winkelmann S, Madea B (2006b) Myokarditis. Rechtsmedizin 16:138–142
Dettmeyer R, Padosch SA, Madea B (2006c) Lethal enterovirus-induced myocarditis and pancreatitis in a 4-month-old boy. Forensic Sci Int 156:51–54
Dettmeyer R, Müller J, Poster S, Madea B (2006d) PCR-based diagnosis of cytomegaloviruses in paraffin-embedded heart tissue in cases of suspected sudden infant death syndrome (SIDS). In: Progress in Forensic Genetics11. Proceedings of the 21st international

ISFG congress, 13–16 Sept 2005, Portugal. Int Congr Ser 1288:771–773
DiMaio VJM, Dana SE (2007) Handbook of forensic pathology. CRC Taylor & Francis, Boca Raton
Doerr W (1959) Histopathologie des Reizbildungs- und Reizleitungssystems des Herzens. Verh Dtsch Ges Inn Med 65:459–495
Doerr W (1969) Normale und pathologische Anatomie des reizbildenden und erregungsleitenden Gewebes. Verh Dtsch Ges Herz Kreislaufforsch 35:1–36
Doerr W (1975) Morphologische Äquivalente bei Rhythmusstörungen des Herzens. Verh Dtsch Ges Inn Med 81:36–69
Doerr W (1980) Sekundenherztod. Beitr Gerichtl Med 39:1–25
Drescher JZP, Verhagen W, Flik J, Milbradt H (1987) Recent influenza virus A infections in forensic cases of sudden unexplained death. Arch Virol 92:63–76
Drory TY, Hiss Y (1991) Sudden unexpected death in persons less than 40 years of age. Am J Cardiol 68:1388–1392
Druyts-Voets E, van Renterghem L, Gerniers S (1993) Epidemiology. Coxsackie B virus epidemiology and neonatal infection in Belgium. J Infect 27:311–316
Eber B, Kilzer K, Luha O, Schumacher M, Fruhwald FM, Gasser R, Klein W (1991) Coronary artery anomalies in adulthood. Wien Med Wochenschr 141:406–411
Edston E, Perskvist N (2009) Histiocytoid cardiomyopathy and ventricular non-compaction in a case of sudden death in a female infant. Int J Legal Med 123:47–53
Edston E, Grontoft L, Johnsson J (2002) TUNEL: a useful screening method in sudden cardiac death. Int J Legal Med 116:22–26
Edwards WD, Holmes DR Jr, Reeder GS (1982) Diagnosis of active lymphocytic myocarditis by endomyocardial biopsy. Quantitative criteria for light microscopy. Mayo Clin Proc 57:419–425
Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kühl U, Maisch B, McKenna WJ, Montserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A (2008) Classification of the cardiomyopathies; a position statement from the European Society of Cardiology Working Group on myocardial and pericardial diseases. Eur Heart J 29:270–277
Enders G, Dotsch J, Bauer J et al (1998) Life-threatening parvovirus B19-associated myocarditis and cardiac transplantation as possible therapy: two case reports. Clin Infect Dis 26:355–358
Engberding S, Bender F (1984) Identification of a rare congenital anomaly of the myocardium by two dimensional echocardiography: persistence of isolated myocardial sinusoids. Am J Cardiol 53:1733–1734
Fairley CK, Ryan M, Wall PG, Weinberg J (1996) The organisms reported to cause infective myocarditis and pericarditis in England and Wales. J Infect 32:223–225
Fechner GG, Sivaloganathan S (1987) Demonstration of myocardial infarction in putrefying bodies. J Clin Pathol 40:922–929
Feldmann AM, McNamara D (2000) Myocarditis. N Engl J Med 343:1388–1398
Ferrans VJ, McAllister HA, Haese WH (1976) Infantile cardiomyopathy with histiocytoid change in cardiac muscle cells. Report of six patients. Circulation 53:708–719
Ferreira AG, Trotter SE, König B, Décourt LV, Fox K, Olsen EG (1991) Myocardial bridges: morphological and functional aspects. Br Heart J 66:364–367
Figulla HR (2004) Transformation of myocarditis and inflammatory cardiomyopathy to idiopathic dilated cardiomyopathy: facts and fiction. Med Microbiol Immunol 193:61–64
Fineschi V, Pomara C (2004) A forensic pathological approach to sudden cardiac death. In: Tsokos M (ed) Forensic pathology reviews, vol 5. Humana, Totawa, pp 139–168
Fineschi V, Neri M, Riezzo I, Turillazzi E (2004) Sudden cardiac death due to hypersensitivity myocarditis during clozapine treatment. Int J Legal Med 118:307–309
Fineschi V, Baroldi G, Silver MA (2006) Pathology of the heart and sudden death in forensic medicine. CRC Press, Boca Raton
Fineschi V, Michalodimitrakis M, D'Errico S, Neri M, Pomara C, Turillazzi E (2010) Insight into stress-induced cardiomyopathy and sudden cardiac death due to stress. A forensic cardio-pathologist point of view. Forensic Sci Int 194:1–8
Finsterer J (2008) Histiocytoid cardiomyopathy: a mitochondrial disorder. Clin Cardiol 31:225–227
Finsterer J, Stöllberger C (2009) Is mitochondrial disease the common cause of histocytoid cardiomyopathy and non-compaction? Int J Legal Med 123:507–508
Finsterer J, Stöllberger C, Karner J, Keller H, Feichtinger F (2007) Left ventricular hypertrabeculation (noncompaction) with prominent calcifications in a patient with mannose-binding lectin deficiency and unclassified myopathy. Cardiovasc Pathol 16:310–312
Fischbein MC, Kulber D, Stancl M, Edwalds G (1986) Distribution of fibrinogen and albumin in normal, ischaemic, and necrotic myocardium during the evolution of myocardial infarction: an immunohistochemical study. Cardiovasc Res 20:36–41
Fragkouli K, Mitselou A, Boumba V, Michalis L, Vougiouklakis T (2011) An autopsy case of necrotizing eosinophilic myocarditis causing left ventricular wall rupture. Forensic Sci Med Pathol 7:350–354
Fraser WJ, Haffejee Z, Cooper K (1995) Rheumatic Aschoff nodules revisited: an immunohistological reappraisal of the cellular component. Histopathology 27:457–461
Frenzel H, Schwartzkopff B, Reinecke P, Kamino K, Lösse B (1987) Evidence for muscle fiber hyperplasia in the septum of patients with hypertrophic obstructive cardiomyopathy (HOCM). Quantitative examination of endomyocardial biopsies (EMCB) and myectomy specimens. Z Kardiol 76(suppl 3):14–19
Friman G, Fohlman J (1993) The epidemiology of viral heart disease. Scand J Infect Dis 88(suppl):7–10

Friman G, Wesslen L, Fohlman J, Karjalainen J, Rolf C (1995) The epidemiology of infectious myocarditis, lymphocytic myocarditis and dilated cardiomyopathy. Eur Heart J 16(suppl O):36–41

Gaaloul I, Riabi S, Harrath R, Evans M, Huber S, Aouni M (2011) Coxsackie B3 myocarditis in a case of sudden unexpected death in young athlete: histopathological, immunohistochemical and molecularpathological for diagnosis. Forensic Sci Int 208:e10–e14

Gdynia G, Schnitzler P, Brunner E, Kandolf R, Bläker H, Daum E, Schnabel P, Schirmacher P, Roth W (2011) Sudden death of an immunocompetent young adult caused by novel (swine origin) influenza A/H1N1-associated myocarditis. Virchows Arch 458:371–376

Ginellinová A, Farkaš D, Farkašová Iannaccone S, Vyhnálkova V (2016) Sudden unexpected death due to severe pulmonary and cardiac sarcoidosis. Forensic Sci Med Pathol 12:319–323

Grady KL, Costanzo-Nordin MR (1989) Myocarditis: review of a clinical enigma. Heart Lung 18:347–354

Greve G, Rotevath S, Svendby K, Grong K (1990) Early morphologic changes in cat heart muscles cells after acute coronary artery occlusion. Am J Pathol 136:273–283

Hagemeier L, Madea B (2009) Ursprungsanomalie der rechten Koronararterie und Roemhild-Syndrom – Ursache eines plötzlichen Todes. Rechtsmedizin 19:30–33

Hagemeier L, Mohr C, Schyma C et al (2010) Diagnose der arrythmogenen rechtsventrikulären Kardiomyopathie. Histomorphometrisches Verfahren zum postmortalen Nachweis. Rechtsmedizin 20:13–18

Hamilton RA, Sullivan L, Wolf BC (2007) Sudden cardiac death due to giant cell inflammatory processes. J Forensic Sci 52:943–948

Handlos P, Gruszka T, Staňková M, Marecová K, Joukal M (2017) Biventricular noncompaction cardiomyopathy with malignant arrhythmia as a cause of sudden death. Forensic Sci Med Pathol 13. https://doi.org/10.1007/s12024-017-9889-y

Hansen PR (2007) Takotsubo cardiomyopathy: an underrecognized myocardial syndrome. Eur J Intern Med 18:561–565

Hansen SH, Rossen K (1999) Evaluation of cardiac troponin I immunoreaction in autopsy hearts: a possible marker of early myocardial infarction. Forensic Sci Int 99:189–196

Hauck AJ, Kearney DL, Edwards W (1989) Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. Mayo Clin Proc 64:1235–1245

Hayes MA, Russell RG, Babiuk LA (1979) Sudden death in young dogs with myocarditis caused by parvovirus. J Am Vet Med Assoc 174:1197–1203

Hebert MM, Yu C, Towbin JA, Rogers BB (1995) Fatal Epstein-Barr virus myocarditis in a child with repetitive myocarditis. Pediatr Pathol Lab Med 15:805–812

Hermido-Prieto M, Montserrat L, Castro-Beiras A, Laredo R, Soler R, Peteiro J, Rodriguez E, Bouzasa B, Alvarez N, Muniz J et al (2004) Familial dilated cardiomyopathy and isolated left ventricular noncompaction associated with lamin A/C gene mutations. Am J Cardiol 94:50–54

Herzum M, Maisch B (1988) Humoral and cellular immune response in human myocarditis and dilated cardiomyopathy. Pathol Immunopathol Res 7:240–250

Holczabek W (1970) Über das histologische Bild der ischämischen Schädigung des Herzfleisches bei Anwendung der Weinsteinsäure-Kresylechtviolett-Einschlußfärbung. Beitr Gerichtl Med 27:275

Holczabek W (1973) Nachweis von Isoprotenerol-bedingten Herzmuskelschäden an der Ratte mittels der Weinsteinsäure-Kresylechtviolett-Einschlußfärbung. Beitr Gerichtl Med 30:175

Hort W (1965) Ventrikeldilatation und Muskelfaserdehnung als früheste morphologische Befunde beim Herzinfarkt. Virchows Arch 339:72

Hort W (ed) (2000) Pathologische Anatomie des Herzens und seiner Hüllen II. Pathologie des Endokard, der Kranzarterien und des Myokard. Springer, Berlin

Hu BJ, Chen YC, Zhu JZ (2002) Study on the specificity of fibronectin for post-mortem diagnosis of early myocardial infarction. Med Sci Law 42:195–199

Huber SA, Gauntt CJ, Sakkinen P (1999) Enteroviruses and myocarditis: viral pathogenesis through replication, cytokine induction, and immunopathogenicity. Adv Virus Res 51:35

Huckenbeck W, Papadomanolakis A (2005) Right and left ventricular arrythmogenic dysplasia. Pathological features and medicolegal significance. In: Tsokos M (ed) Forensic pathology reviews, vol 3. Humana Press, Totowa, pp 253–165

Hudson REB (1960) The human pacemaker and its pathology. Br Heart J 22:153–167

Hudson REB (1963) The human conducting-system and its examination. J Clin Pathol 16:492–499

Hufnagel G, Maisch B (1991) Expression of MHC class I and II antigens and the IL-2 receptor in rejection, myocarditis and dilated cardiomyopathy. Eur Heart J 12(suppl D):137–140

Ichida F, Tsubata S, Bowles KR, Haneda N, Uese K, Miyawaki T, Dreyer WJ, Messina J, Li H, Bowles NE et al (2001) Novel gene mutations in patients with left ventricular noncompaction or Barth syndrome. Circulation 103:1256–1263

Iino M, Kimura T, Abiru H, Kaszynski RH, Yuan QH, Tsuruyama T, Tamaki K (2007) Unexpected sudden death resulting from anomalous origin of the right coronary artery from the left sinus of Valsalva: a case report involving identical twins. Legal Med 9:25–29

Indorato F, Akashi YJ, Rossitto C, Raffino C, Bartoloni G (2015) Takotsubo cardiomyopathy associated with rupture of the left ventricular apex: assessment of histopathological features of a fatal case and literature review. Forensic Sci Med Pathol 11:577–583

Indorato F, Bartolini G (2016) Post-mortem Takotsubo cardiomyopathy diagnosis: the challenge is open! Forensic Sci Med Pathol 12:227–228

Ishikawa T, Zhu BL, Li DR, Zhao D, Maeda H (2005) Epstein-Barr virus myocarditis as a cause of sudden death: two autopsy cases. Int J Legal Med 119:231–235

Ishiyama I, Kamiya M, Rose M, Komuro E, Takatsu A (1982) Fulminant deletion of myoglobin from myocardial fibers in state of acute cardiac failure including sudden cardiac arrest. Lancet 2:1468–1469

Jääskeläinen AJ (1968) Enzymhistochemischer Nachweis des frischen Myokardinfarkts bei Fällen von vermutetem gewaltsamem Tod. Dtsch Z Gerichtl Med 64:1–8

James TN, Marshall TK (1976) Multifocal stenosis due to fibromuscular dysplasia of the sinus node artery. Circulation 53:736–742

Janík M, Hejna P (2017) Necrotizing eosinophilic myocarditis. Forensic Sci Med Pathol 13:255–258

Janssen W (1968) Zur Arteriosklerose der Coronararterien jugendlicher Menschen. Morphologische und forensische Bedeutung. Dsch Zschr Gerichtl Med 62:39–50

Janssen W (1975) Todesfälle im Rahmen emotionaler Belastung. Beitr Gerichtl Med 33:97–102

Janssen W (1977) Forensische histologie. Schmidt-Römhild, Lübeck

Janssen W (1984) Forensic histopathology. Springer, Berlin, pp 187–190

Jenni R, Wyss CA, Eochslin EN, Kaufmann PA (2002) Isolated ventricular noncompaction is associated with coronary microcirculatory dysfunction. J Am Coll Cardiol 39:450–454

Jiang WX, Gao C, Sun J, Bunai Y (2009) Sudden cardiac death caused by a primary intimal sarcoma of the left coronary artery. Int J Legal Med 123:503–506

Jin O, Sole M, Butany JW, Chia WK, McLaughlin PR, Liu P et al (1990) Detection of enterovirus RNA in myocardial biopsies from patients with myocarditis and cardiomyopathy using gene amplification by polymerase chain reaction. Circulation 82:8–16

Joswig BC, Warren SE, Vieweg WV, Hagan AD (1978) Transmural myocardial infarction in the absence of coronary arterial luminal narrowing in a young man with single coronary arterial anomaly. Catheter Cardiovasc Diagn 4:297–304

Kammal AL, Püschel K, Tsokos M (2015) Takotsubo cardiomyopathy. Pathomorphological and medicolegal aspects of a rare syndrome. Rechtsmedizin 25:474–480

Kandolf R (1995) Molekulare Pathogenese der Enterovirusmyokarditits. Viruspersistenz und chronische Entzündung. Internist 36:430–438

Kandolf R, Ameis D, Kirschner P, Canu A, Hofschneider PH (1987) In situ detection of enteroviral genomes in myocardial cells by nucleic acid hybridization: an approach to the diagnosis of viral heart disease. Proc Natl Acad Sci U S A 84:6272–6276

Kandolf R, Klingel K, Zell R, Canu A, Fortmuller U, Hohenadl C et al (1993) Molecular mechanisms in the pathogenesis of enteroviral heart disease: acute and persistent infections. Clin Immunol Immunopathol 68:153–158

Karch SB (2009) Karch's pathology of drug abuse, 4th edn. CRC Press, Boca Raton, p 101

Karch SB, Billingham ME (1986) Myocardial contraction band revisited. Hum Pathol 17:9–13

Karch SB (2011) The unique histology of methamphetamine cardiomyopathy: a case report. Forensic Sci Int 212:e1–e4

Karjalainen J, Heikkila J (1999) Incidence of three presentations of acute myocarditis in young men in military service. A 20-year experience. Eur Heart J 20:1120–1125

Karjalainen J, Nieminen M, Heikkila J (1980) Influenza A1 myocarditis in conscripts. Acta Med Scand 207:27–30

Kauferstein S, Kiehne N, Neumann T, Pitschner HF, Bratzke H (2009) Cardiac gene defects can cause sudden cardiac death in young people. Dtsch Arztebl Int 106:41–47

Kauferstein S, Kiehne N, Peigneur S, Tytgat J, Bratzke H (2013) Cardiac channelopathy causing sudden death as revealed by molecular autopsy. Int J Legal Med 127:145–151

Kawai C (1999) From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death. Circulation 99:1091–1100

Kawai C, Matsumori A, Fujiwara H (1987) Myocarditis and dilated cardiomyopathy. Annu Rev Med 38:221–239

Kawano H, Okada R, Kawano Y, Sueyoshi N, Shirai T (1994) Apoptosis in acute and chronic myocarditis. Jpn Heart J 35:745–750

Kenton AB, Sanchez X, Coveler KJ, Kavar KA, Jiminez S, Ichida F, Murphy RT, Elliott PM, McKenna W, Bowles NE et al (2004) Isolated left ventricular noncompaction is rarely caused by mutations in G4.5, alpha-dystrobrevin and FK Binding Protein-12. Mol Genet Metab 82:162–166

Kiryakova T, Nikolov D, Alexandrov A (2016) Sudden death due to asymptomatic myocarditis – a forensic case report. Rom J Leg Med 24:281–283

Kittulwatte ID, Kim PJH, Pollanen MS (2010) Sudden death related myocarditis: a study of 56 cases. Forensic Sci Med Pathol 6:13–19

Klages U, Gerken F (1972) Eine Methode zur Objektivierung fraglicher entzündlicher Zellvermehrung im Interstitium des Herzmuskels. Beitr Z Gerichtl Med 14:429

Klein RM, Vester EG, Perings C, Strauer BE (1995) Arrhythmien bei Myokarditis. Internist 36:458–468

Klein RM, Vester EG, Brehm MU et al (2000) Entzündung des Myokards als Arrhythmietrigger. Z Kardiol 89(suppl 3):24–35

Klingel K, Kandolf R (2009) Virale Myokarditis im Kindesalter. Stellenwert der modernen kardiopathologischen Diagnostik. Rechtsmedizin 18:349–358

Klingel K, Albrecht M, Canu A, Hofschneider PH, Kandolf R (1992a) Molekulare Pathogenese der Myokarditis: Viruspersistenz und chronische Herzmuskelentzündung. Verh Dtsch Ges Pathol 76:394

Klingel K, Hohenadl C, Canu A et al (1992b) Ongoing enterovirus-induced myocarditis is associated with

persistent heart muscle infection: quantitative analysis of virus replication, tissue damage and inflammation. Proc Natl Acad Sci U S A 89:314–318

Klingel K, Selinka HC, Huber M, Sauer M, Leube M, Kandolf R (2000) Molecular pathology and structural features of enteroviral replication. Towards understanding the pathogenesis of viral heart disease. Heart 25:216–220

Klingel K, Sauer M, Bock CT, Szalay G, Schnorr JJ, Kandolf R (2004) Molecular pathology of inflammatory cardiomyopathy. Med Microbiol Immunol 193:101–107

Klump WM, Bergmann I, Muller BC, Ameis D, Kandolf R (1990) Complete nucleotide sequence of infectious Coxsackievirus B3 cDNA: two initial 5′ uridine residues are regained during plus-strand RNA syntheses. J Virol 64:1573–1583

Knieriem HJ, Mecking D, Seipel L (1979) Pathomorphologie des Sinusknotens beim Sinusknotensyndrom und anderen Herzrhythmusstörungen. Pathologie 1:233

Knight B (1967) Early myocardial infarction: practical methods for its postmortem demonstration. J Forensic Med 14:101–107

Korb G, Knorr G (1962) Vergleichende licht- und fluoreszenzmikroskopische Untersuchungen frischer Herzmuskelschäden beim Menschen. Virchows Arch 335:159

Kurosu A, Kuroyanagi K, Yamauchi S, Omura K, Saito K (2016) Sudden death caused by anomalous origin on the coronary artery during exercise. J Forensic Sci 61:548–550

Kühl U, Daun B, Seeberg B, Schultheiss HP, Strauer BE (1992) Dilatative kardiomyopathie – eine chronische myokarditits? Herz 17:97–106

Kühl U, Noutsias M, Seeberg B, Schannwell M, Welp LB, Schultheiss HP (1994) Chronic inflammation in the myocardium of patients with clinically suspected dilated cardiomyopathy. J Card Fail 1:13–25

Kühl U, Noutsias M, Seeberg B, Schultheiß HP (1996) Immunohistochemical analysis of the chronic inflammatory process in dilated cardiomyopathy. Heart 75:295–300

Kühl U, Pauschinger M, Schultheiss HP (1997) Neue konzepte zur diagnostik der entzündlichen herzmuskelerkrankung. Dtsch Med Wochenschr 122:690–698

Kühl U, Pauschinger M, Bock T, Klingel K, Schwimmbeck CPL, Seeberg B, Krautwurm L, Poller W, Schultheiss HP, Kandolf R (2003) Parvovirus B19 infection mimicking acute myocardial infarction. Circulation 108:945–950

Kytö V, Vuorinen T, Saukko P, Lautenschlager I, Lignitz E, Saraste A, Voipio-Pulkki LM (2005) Cytomegalovirus infection of the heart is common in patients with fatal myocarditis. Clin Infect Dis 40:683–688

Lang C, Sauter M, Szalay G, Racchi G, Grassi G, Rainaldi G, Mercantanti A, Lang F, Kandolf R, Klingel K (2008) Connective tissue growth factor: a crucial cytokine-mediating cardiac fibrosis in ongoing enterovirus myocarditis. J Mol Med 86:49–60

Langlois NE (2009) Sudden adult death. Forensic Sci Med Pathol 5:210–232

Lau RCH (1983) Coxsackie B virus infections in New Zealand patients with cardiac and non-cardiac diseases. J Med Virol 11:131–137

Lau G (1994) Acute fulminant fatal coxsackie B virus infection: a report of two cases. Ann Acad Med 23:917–920

Lauer B, Schulze K, Kühl U, Pauschinger M, Schwimmbeck PL, Strauer BE, Schultheiss HP (1998) Biphasischer Verlauf der linksventrikulären Funktion bei einer 22 jährigen Patientin mit akuter Myokarditis. Dtsch Med Wochenschr 123:74–80

Lazaros GA, Stefanaki KS, Panayiotides IG, Tzardi MN, Vlachonikolis IG, Kanavaros PE, Delides GS (1998) Nuclear morphometry of the myocardial cells as a diagnostic tool in cases of sudden death due to coronary thrombosis. Forensic Sci Int 96:173–180

Leadbetter S, Wawman HM, Jasani B (1989) Immunocytochemical diagnosis of early myocardial ischaemic/hypoxic damage. Forensic Sci Int 40:171–180

Leadbetter S, Wawman HM, Jasani B (1990) Further evaluation of immunocytochemical staining in the diagnosis of early myocardial ischaemic/hypoxic damage. Forensic Sci Int 45:135–141

Lenègre J, Chevalier H (1951) Note technique préliminaire concernant l'étude histologique de la cloison du cœur. Arch Mal Coeur 44:512–524

Lentini S, Klingel K, Skowasch R, Kandolf R, Bauriedel G (2001) Epstein-Barr virus assoziierte perikarditis. Dtsch Med Wochenshr 126:1043–1046

Leone A (2014) Relation between coronary lesions and cigarette smoking of subjects deceased from acute myocardial infarction. A histopathological study. J Cardiobiol 2:1–5

Lev M, Kinave SG, Pick A (1970) The pathogenesis of atrioventricular block in coronary disease. Circulation 42:409–426

Lev M, Nordenberg A, Carvalho AG, Bharati S, Rosen K, Varghese JP, Bauernfeind RA (1979) The anatomic substrate for the sick sinus syndrome in adolescence. Circulation 59(suppl II):437

Li Y, Bourlet T, Andreoletti L, Mosnier JF, Peng T, Yang Y, Archard LC, Pozzetto B, Zhang H (2000) Enteroviral capsid protein is present in myocardial tissues from some patients with myocarditis or dilated cardiomyopathy. Circulation 101:231–234

Lie JT (1968) Detection of early myocardial infarction by the acid fuchsin staining technic. Am J Clin Pathol 50:317–319

Lie JT, Holley KE, Kampa WR, Titus IL (1971) New histochemical method for morphologic diagnosis of early stages of myocardial ischemia. Mayo Clin Proc 46:319–327

Lim A, Langlois N (2016) Non-compaction cardiomyopathy. Forensic Sci Med Pathol 12:104–107

Lin YT, Chen CH, Ding PY (1998) Evolution of dilated cardiomyopathy from hypertrophic obstructive cardiomyopathy in a child. J Formos Med Assoc 97:416–419

Linder J, Cassling RS, Rogler WC, Wilson JE, Markin RS, Sears TD, McManus BM (1985) Immunohistochemical characterization of lymphocytes in uninflamed ventricular myocardium. Arch Pathol Lab Med 109:917–920

Lipsett J, Cohle SD, Berry PJ, Russell G, Byard RW (1994) Anomalous coronary arteries: a multicenter pediatric autopsy study. Pediatr Pathol 14:287–300

Liu PP, Mason JW (2001) Advances in the understanding of myocarditis. Circulation 104:1076–1082

Lobo FV, Ha H, Butany J et al (1992) Right ventricular dysplasia: morphological findings in 13 cases. Can J Cardiol 8:261–268

Löffler W (1936) Endocarditis parietalis fibroplastica mit Bluteosinophilie. Ein eigenartiges Krankheitsbild. Schweiz Med Wochenschr 66:817

Lozinski GM, Davis GG, Krous HF, Billman GF, Shimizu H, Burns JC (1994) Adenovirus myocarditis: retrospective diagnosis by gene amplification from formalin-fixed, paraffin-embedded tissues. Hum Pathol 25:831–834

Madea B, Dettmeyer R (1998) Sudden death in cases with anomalous origin of the left coronary artery. Forensic Sci Int 96:91–100

Maisch B (1994) Myokarditis. Internist 35:91–93

Maisch B, Schönian U, Crombach M, Wendl I, Bethge C, Herzum M et al (1993) Cytomegalovirus associated inflammatory heart muscle disease. Scand J Infect Dis Suppl 88:135–148

Maisch B, Schönian U, Herzum M, Hufnagel G (1995) Immunserologische und immunhistologische Untersuchungen bei Myokarditis und Perikarditis. Internist 36:448–457

Maisch B, Portig I, Ristic A, Hufnagel G, Pankuweit S (2000) Definition of inflammatory cardiomyopathy (myocarditis): on the way to consensus. Herz 25:200–209

Mall G (1995) Morphologie der myokarditis. Internist 36:426–429

Mallory GK, White PD, Salcedo Salgar J (1939) The speed of healing of myocardial infarction. A study of the pathologic anatomy in seventy-two cases. Am Heart J 18:647

Maron BJ (2002) Hypertrophic cardiomyopathy: a systemic review. JAMA 287:1308–1320

Maron BJ, Bonow RO, Cannon RO, Leon MB, Epstein SE (1997) Hypertrophic cardiomyopathy: interrelations of clinical manifestations, pathophysiology, and therapy: parts 1 and 2. N Engl J Med 316:780–789. 844–852

Maron BJ, Towbin JA, Thiene G, Antzelevith C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB (2006) Contemporary definitions and classifications of the cardiomyopathies: an American heart association scientific statement from the council on clinical cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working group; and council on epidemiology and prevention. Circulation 113:1807–1816

Marsman RFJ, Bezzina CR, Freiberg F, Verkerk AO, Adriaens ME, Podliesna S, Chen C, Purfürst B, Spallek B, Koopmann TT, Baczko I, dos Remedios CG, George AL, Bishopric NH, Lodder EM, de Bakker JMT, Fischer R, Coronel R, Wilde AAM, Gotthardt M, Remme CA (2014) Coxsackie and adenovirus receptor is a modifier of cardiac conduction and arrhythmia vulnerability in the setting of myocardial ischemia. J Am Coll Cardiol 63:549–559

Martin AB, Webber S, Fricker FJ, Jaffe R, Demmler G, Kearney D et al (1994) Acute myocarditis: rapid diagnosis by PCR in children. Circulation 90:330–339

Martinez S, Miranda E, Kim P, Pollanen MS (2013) Giant cell myocarditis associated with amoxicillin hypersensitivity. Forensic Sci Med Pathol 9:403–406

Martino TA, Liu P, Sole MJ (1994) Viral infection and the pathogenesis of dilated cardiomyopathy. Circ Res 74:182–188

Martino TA, Liui P, Petric M, Sole MJ (1995) Enteroviral myocarditis and dilated cardiomyopathy: a review of clinical and experimental studies. In: Rothbard HA (ed) Human enterovirus infections. American Society for Microbiology, Washington DC, pp 291–350

Matejic D, Schönfeld C, Tsokos M (2010) Plötzlicher Tod bei akuter idiopathischer Riesenzellmyokarditis. Rechtsmedizin 20:275–277

Mayer F, Pröpper S, Ritz-Timme S (2014) Dityrosine, a protein product of oxidative stress, as a possible marker of acute myocardial infarctions. Int J Legal Med 128:787–794

Mayer F, Falk M, Huhn R, Behmenburg F, Ritz-Timme S (2016) Dityrosine as a marker of acute myocardial infarction? Experiments with the isolated Langendorff heart. Int J Legal Med 130:1053–1060

McCaffrey FM, Braden DS, Strong WB (1991) Sudden cardiac death in young athletes. Am J Dis Child 145:177–183

McConnell SE, Collins KA (1998) Sudden unexpected death from an anomalous hypoplastic left coronary artery. J Forensic Sci 43:708–711

McConnell MV, Ganz P, Selwyn AP, Li W, Edelmann RR, Manning WJ (1995) Identification of anomalous coronary arteries and their anatomic course by magnetic resonance coronary angiography. Circulation 92:3158–3162

McKenna WJ, Thiene G, Nava A et al (1994) Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Br Heart J 71:215–218

McVie JG (1970) Postmortem detection of inapparent myocardial infarction. J Clin Pathol 23:203–209

Metze K, Meves R, Moreira PRS (1993) Seasonal variation in rheumatic heart disease – letter to the editor. Int J Cardiol 38:01–102

Michaud K, Romain N, Taroni F, Horisberger B, Mangin P (2002) Evaluation of a simplified method of the conduction system analysis in 110 forensic cases. Forensic Sci Int 130:13–24

Michaud K, Mangin P, Elger BS (2011) Genetic analysis of sudden cardiac death victims: a survey of

current forensic autopsy practices. Int J Legal Med 125:359–366
Mihatsch MJ (1988) Die morphologie des myokardinfarkts. Schweiz Med Wochenschr 118:1688–1691
Milei J, Bortman G, Fernandez-Alonso G, Grancelli H, Beigelman R (1990) Immunohistochemical staining of lymphocytes for the reliable diagnosis of myocarditis in endomyocardial biopsies. Cardiology 77:77–85
Miller R, Ward C, Amsterdam E (1973) Focal mononucleosis myocarditis simulating myocardial infarction. Chest 63:102–105
Möhlenkamp S, Wort W, Ge J, Erbel R (2002) Update on myocardial bridging. Circulation 106:2616–2622
Mondello C, Cardia L, Ventura-Spagnolo E (2017) Immunohistochemical detection of early myocardial infarction: a systematic review. Int J Leg Med 131:411–421
Moral GL, Rubio-Calduch EM, Broto-Escapa P, Caballero-Requero E, Calico-Bosch I, Bertran-Sangues JM (1993) Enteroviral infections in children: clinical and epidemiological findings in 530 patients (1984–1991). An Esp Pediatr 39:521–527
Mounts AW, Amr S, Jamshidi R, Graves C, Dwyer D, Guarner J et al (2001) A cluster of fulminant myocarditis cases in children, Baltimore, Maryland, 1997. Pediatr Cardiol 22:34–39
Muir P (1993) Enteroviruses and heart disease. Br J Biomed Sci 50:258–271
Mund MT, Hailemariam S, Gathomas G (2002) Die arrhythmogene rechtsventrikuläre Kardiomyopathie als Ursache des plötzlichen Herztodes. Rechtsmedizin 12:371–374
Munkholm J, Andersen CB, Ottesen GL (2015) Plakkoglobin: a diagnostic marker of arrhythmogenic right ventricular cardiomyopathy in forensic pathology? Forensic Sci Med Pathol 11:47–52
Murry CE, Jerome KR, Reichenbach DD (2001) Fatal parvovirus myocarditis in an 5-year-old girl. Hum Pathol 32:342–345
Murty OP (2008) Giant cell myocarditis with cardiac tamponade. Am J Forensic Med Pathol 29:245–248
Narula J, Haider N, Virmani R, DiSalvo TG, Kolodgie FD, Hajjar RJ et al (1996) Apoptosis in myocytes in end-stage heart failure. N Engl J Med 335:1182–1189
Nielsen TS, Nyengaard JR, Møller J, Banner J, Nielsen LP, Baandrup UT (2014a) Quantitative diagnosis of lymphocytic myocarditis in forensic medicine. Forensic Sci Int 238:9–15
Nielsen TS, Hansen J, Nielsen LP, Baandrup UT, Banner J (2014b) The presence of enterovirus, adenovirus, and parvovirus B19 in myocardial tissue samples from autopsies: an evaluation of their frequencies in deceased individuals with myocarditis and in non-inflamed control hearts. Forensic Sci Med Pathol 10:433–350
Nishida N, Ikeda N, Kudo K, Tsuji A, Kiyoshima A (2002) Forensic significance of conduction system abnormalities as a precise cause of accidental death. Int J Legal Med 116:344–349
Noutsias M, Seeberg B, Schultheiss HP, Kühl U (1999) Expression of cell adhesion molecules in dilated cardiomyopathy. Evidence for endothelial activation in inflammatory cardiomyopathy. Circulation 99:2124–2131
Noutsias M, Fechner H, de Jonge H, Wand X, Dekkers D, Houtsmuller AB, Pauschinger M, Bergelson JM, Warraich R, Yacoub M et al (2001) Human coxsackie-adenoviruses receptor is colocalized with integrins alpha(v)beta(3) and alpha(v)beta(5) on the cardiomyocyte sarcolemma and upregulated in dilated cardiomyopathy: implications for cardiotropic viral infections. Circulation 104:275–280
Noutsias M, Pauschinger M, Kühl U, Schultheiss HP (2002) Myokarditis und dilatative Kardiomyopathie. Neue Wege in Diagnostik und Therapie. Münch Med Wochenschr 144:36–40
Oechslin EN, Attenhofer JCH, Rojas JR, Kaufmann PA, Jenni R (2000) Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol 36:493–500
Oehmichen M, Pedal I, Hofmann P (1990a) Diagnostic significance of myofibrillar degeneration of cardiocytes in forensic pathology. Forensic Sci Int 48:163–173
Oehmichen M, Pedal I, Hohmann P (1990b) Myofibrilläre degeneration der herzmuskulatur: diagnostische wertigkeit am ausgesuchten forensisch-pathologischen fallmaterial. Beitr Gerichtl Med 48:245–249
Ogbuihi S (1989) On the forensic significance of sinuatrial node lesions in sudden death. Z Rechtsmed 102:315–322
Ogbuihi S, Fechner G, Brinkmann B (1993) Sudden death due to cardiac sarcoidosis in a case of suspected homicide. Int J Legal Med 106:99–102
Oka K, Oohira K, Yatabe Y, Tanaka T, Kurano K, Kosugi R, Murata M, Hakozaki H, Nishikawa T, Tsutsumi Y (2005) Fulminant myocarditis demonstrating uncommon morphology – a report of two cases. Virchows Arch 446:259–264
Okada R, Kawai S (1983) Histopathology of the conduction system in sudden cardiac death. Jpn Circ J 47:573–580
Orth T, Herr W, Spahn T et al (1997) Human parvovirus B19 infection associated with severe acute perimyocarditis in an 34-year-old man [letter]. Eur Heart J 18:524–525
Osuna E, Perez Carceles MD, Jakobson SW, Luna A (1990) Biochemical and morphological markers in the post mortem diagnosis of ischemic heart distress. Acta Med Leg Soc 40:275–283
Oyer CE, Ongeapin EH, Ni J, Bowles NE, Towbin JA (2000) Fatal intrauterine adenoviral endomyocarditis with aortic and pulmonary valve stenosis: diagnosis by polymerase chain reaction. Hum Pathol 31:1433–1435
Pampín JB, Aranzazu García Rivero S, Cepeda JLO, Vázquez Boquete A, Forteza Vila J, Fonseca RH (2006) Immunohistochemical expression of HIF-1-alpha in response to early myocardial ischemia. J Forensic Sci 51:120–124

Patel J, Sheppard MN (2011) Cystic tumour of the atrioventricular node: three cases of sudden death. Int J Legal Med 125:139–142

Pauschinger M, Meissner G, Preis S, Kühl U, Kandolf R, Schultheiss HP et al (1994) Detection of enteroviral RNA by polymerase chain reaction in patients with myocarditis and dilated cardiomyopathy. JACC 1994:880

Pauschinger M, Kühl U, Dörner A, Schieferecke K, Petschauer S, Rauch U, Schwimmbeck PL, Kandolf R, Schultheiss HP (1998) Nachweis enteroviraler RNA in endomyokardialen Biopsien bei inflammatorischer Kardiomyopathie und idiopathischer dilatativer Kardiomyopathie. Z Kardiol 87:443–452

Pedal I (1976) Ursprungsanomalie einer Koronararterie. Dtsch Med Wochenschr 101:1601–1604

Pedal I, Oehmichen M (1990) Myofibrilläre Degeneration der Herzmuskulatur: Histologisches Bild und pathophysiologische Bedeutung. Beitr Gerichtl Med 48:237–244

Pedal I, Teufel M (1993) Plötzlicher Herztod im Kindesalter durch eine Ursprungsanomalie der Koronararterie. Dtsch Med Wochenschr 118:861–866

Pedersen PK (1980) Poor results in attempting to demonstrate the cause of death by examination of the conduction system of the heart in cases of sudden death. Forensic Sci Int 16:281–282

Philipps CA, Aronson MD, Tomkow J, Philipps ME (1980) Enteroviruses in Vermont, 1969–1978: an important cause of illness throughout the year. J Infect Dis 141:162–164

Philips M, Robiniwitz M, Higgins JR, Boran KJ, Reed T, Virmani R (1986) Sudden cardiac death in air force recruits. JAMA 256:2696–2699

Pichotka J (1942) Tierexperimentelle Untersuchungen zur pathologischen Histologie des akuten Höhentodes. Beitr Pathol Anat 197:117

Piercecchi-Marti MD, Lepidi H, Leonetti G, Vire O, Cianfarani F, Pellissier JF (2001) Immunostaining by complement C9: a tool for early diagnosis of myocardial infarction and application in forensic medicine. J Forensic Sci 46:328–334

Piercecchi-Marti MD, Mohamed H, Chau C, Liprandi A, Fredouille C (2003) Congenital atrioventricular block: histological aspects. Forensic Sci Int 136:12–15

Prasad A, Lerman A, Rihal CS (2008) Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 155:408–417

Priemer F, Keil W, Kandolf R (1999) Hydrocution in a case of Coxsackie virus infection. Int J Legal Med 112:368–371

Pusta CT, Mihalache G, Buhas C, Pop O (2015) A rare case of cardiac fibroma in a dead truck driver. Rom J Leg Med 23:247–250

Rahlf G (1980) Intramyocardial microarteriopathy. Virch Arch A Path Anat Histol 388:289–311

Raza-Ahmad A (1994) Fibrinogen: a diagnostic marker for early ischemia. Biotech Histochem 69:268–272

Rentea I, Voinea OC, Hostiuc S, Iancu CB, Petre N, Ceausu M (2016) Usefulness of angiotensin type 2 receptor in establishing the histological age of myocardial infarction. Rom J Leg Med 24:100–105

Rérolle C, Faisant M, Lefrancq T, Saint-Martin P (2016) Sudden death due to undiagnosed rheumatic heart disease in a child. J Forensic Sci 61:848–850

Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, Olsen E, Thiene G, Goodwin J, Gyarfas I, Martin I, Nordet P (1996) Report on the 1995 world health organization/international society and federation of cardiology task force on the definition and classification of cardiomyopathies. Circulation 93:841–842

Riedel J, Neudorf U, Schmaltz AA (1997) Rasche Progredienz einer hypertrophen Kardiomyopathie in eine dilatative Form – Ungewöhnlicher Verlauf bei einem jugendlichen Patienten. Eine Fallbeschreibung. Z Kardiol 88:427–432

Riezzo I, Ventura F, D'Errico S, Neri M, Turillazzi E, Fineschi V (2009) Arrhythmogenesis and diagnosis of cardiac sarcoidosis. An immunohistochemical study in a sudden cardiac death. Forensic Sci Int 183:e1–e5

Riße M, Weiler G (1985) Die koronare Muskelbrücke und ihre Beziehungen zu lokaler Koronarsklerose, regionaler Myokardischämie und Koronarspasmus. Eine morphometrische Studie. Z Kardiol 74:700–705

Riße M, Verhoff MA, Dettmeyer R (2008) Kardiale sarkoidose. Rechtsmedizin 18:267–268

Roberts WC (1986) Major anomalies of coronary arterial origin seen in adulthood. Am Heart J 111:941–963

Roberts WC, Shirami J (1992) The four subtypes of anomalous origin of the left main coronary artery from the right aortic sinus (or from the right coronary artery). Am J Cardiol 70:119–123

Rodríguez-Calvo MS, Brion M, Alleque C, Concheiro L, Carracedo A (2008) Molecular genetics of sudden cardiac death. Forensic Sci Int 182:1–12

Rohayem J, Dinger J, Fischer R et al (2001) Fatal myocarditis associated with acute parvovirus B19 and human herpesvirus 6 coinfection. J Clin Microbiol 39:4585–4587

Roynard JL, Cattan S, Artigou JY (1994) Anomalous course of the left anterior descending coronary artery between the aorta and pulmonary trunk: a rare cause of myocardial ischaemia at rest. Br Heart J 72:397–399

Ruszkiewicz AR, Vernon-Roberts E (1993) Sudden death in an infant due to histiocytoid cardiomyopathy. A light-microscopic, ultrastructural and immunohistochemical study. Am J Forensic Med Pathol 16:74–80

Sabatasso S, Mangin P, Fracasso T, Moretti M, Docquier M, Djonov V (2016) Early markers for myocardial ischemia and sudden cardiac death. Int J Legal Med 130:1265–1280

Sahai VB (1976) The post-mortem detection of early myocardial infarction by a simple fluorescent method. Med Sci Law 16:17–20

Sandritter W, Thomas C (eds) (1977) Histopathologie. F.K. Schattauer, Stuttgart

Santer R (2004) Metabolische kardiomyopathien. Monatsschr Kinderheilkd 152:639–648
Sasse-Klaassen S, Gerull B, Oechslin E, Jenni R, Thierfelder L (2003) Isolated noncompaction of the left ventricular myocardium in the adult is an autosomal dominant disorder in the majority of patients. Am J Med Genet A 119:162–167
Sasse-Klaassen S, Probst S, Gerull B, Oechslin E, Nurnberg P, Heuser A, Jenni R, Hennies HC, Thierfelder L (2004) Novel gene locus for autosomal dominant left ventricular noncompaction maps to chromosome 11p15. Circulation 109:2720–2723
Sato T, Nishio H, Suzuki K (2015) Identification of arrhythmogenic right ventricular cardiomyopathy-causing gene mutations in young sudden unexpected death autopsy cases. J Forensic Sci 60:457–461
Saukko P, Knight B (1989) Evaluation of eosin-fluorescence in the diagnosis of sudden cardiac death. Forensic Sci Int 40:285–290
Schäfer H, Mathey D, Hugo F, Bhakdi S (1986) Deposition of the terminal C5b-9 complement complex in infarcted areas of human myocardium. J Immunol 137:1945–1949
Schaper J, Lorenz-Meyer S, Suzuku K (1999) The role of apoptosis in dilated cardiomyopathy. Herz 24:219–224
Schnitt SJ, Ciano PS, Schoen FJ (1987) Quantitation of lymphocytes in endomyocardial biopsies: use and limitations of antibodies to leukocyte common antigen. Hum Pathol 18:796–800
Schultheiß HP (1993) Die dilatative Kardiomyopathie – eine chronische Myokarditis? Neue Aspekte zur Diagnostik und Therapie. Z Kardiol 82(suppl 4):25–33
Schwartz DA, Finkelstein SD, Lumb GD (1988) Fat embolism to the cardiac conduction system associated with sudden death. Hum Pathol 19:116–119
Schwartz ML, Cox GF, Lin AE, Korson MS, Perez-Atayde A, Lacro RV, Lishultz SE (1996) Clinical approach to genetic cardiomyopathy in children. Circulation 94:2021–2038
Schwartzkopff B, Klein RM, Strauer BE (1995) Diagnostik und therapie der myokarditis. Internist 36:469–483
Schwartzkopff B, Klein RM, Strauer BE (1998) Evidence of endothelial dysfunction of epicardial coronary arteries in patients with immunohistochemically proven myocarditis. Am Heart J 136:389–397
Seidman CD, McKenna WJ, Watkins HC, Seidman JG (1992) Molecular genetic approaches to diagnosis and management of hypertrophic cardiomyopathy. In: Braunwald E (ed) Heart disease. A textbook of cardiovascular medicine. W.B. Saunders Co, New York, pp 77–83
Seko Y, Tsuchimochi H, Nakamura T, Okumura K, Naito S, Imatako K (1990) Expression of major histocompatibility complex class I antigen in murine ventricular myocytes infected with Coxsackievirus B3. Circ Res 67:360–367
Shanes JG, Ghali J, Billingham ME, Ferrans VJ, Fenoglio JJ, Edwards WD, Tsai CC, Saffitz JE, Isner J, Furner S (1987) Interobserver variability in the pathologic interpretation of endomyocardial biopsy results. Circulation 75:401–405
Shekhonin BV, Guriev SB, Irgashev SB, Koteliansky VE (1990) Immunofluorescent identification of fibronectin and fibrinogen/fibrin in experimental myocardial infarction. J Mol Cell Cardiol 22:533–541
Sigrist T, Germann U (1998) Morphological alterations in the conducting system for the diagnosis of sudden cardiac death. Rechtsmedizin 8:69–72
Smith ET, Davis G (1997) Sudden cardiac death associated with hypoplasia of the coronary arteries and conduction system alteration. Am J Forensic Med Pathol 18:189–193
Song Y, Yao Q, Luo B, Zhu J, Liang S (1991) A simplified method for examining the human cardiac conduction system. Chin. J Forensic Med 6:92–93
Song Y, Zhu J, Laaksonen H, Saukko P (1997) A modified method for examining the cardiac conduction system. Forensic Sci Int 86:135–138
Song Y, Yao Q, Zhu J, Bin L, Shangyon L (1999) Age-related variation in the interstitial tissues of the cardiac conduction system; an autopsy study of 230 Han Chinese. Forensic Sci Int 104:133–142
Song Y, Laaksonen H, Saukko P, Toivonen S, Zhu J (2001) Histopathological findings of cardiac conduction system of 150 Finns. Forensic Sci Int 119:310–317
Srettabunjong S (2016) Myocardial bridging of coronary arteries: sudden unexpected deaths in a 24-year-old man. Rom. J Leg Med 24:83–86
Stahl J, Couper RTL, Byard RW (1997) Oncocytic cardiomyopathy: a rare cause of early childhood death associated with fitting. Med Sci Law 37:84–87
Steenbergen C, Kolbeck PC, Wolfe JA, Anthony RM, Sanfilippo FP, Jennings RB (1986) Detection of lymphocytes in endomyocardium using immunohistochemical techniques. Relevance to evaluation of endomyocardial biopsies in suspected cases of lymphocytic myocarditis. J Appl Cardiol 1:63–73
Steenbergen C, Hill ML, Jennings RB (1987) Cytoskeletal damage during myocardial ischemia: changes in vinculin immunofluorescence staining during total in vitro ischemia in canine heart. Circ Res 60:478–486
Stöllberger C, Sporn R, Skala K, Schneider B, Finsterer J (2010) Assault-induced Takotsubo cardiomyopathy associated with persisting anterograde amnesia and myopathy. Int J Legal Med 124:467–470
Strauer B, Kandolf R, Mall G, Maisch B, Mertens T, Figulla HR et al (2001) Myokarditis – kardiomyopathie. Update 2001. Med Klin 96:608–625
Suarez-Mier MP, Aguilera B (1998) Histopathology of the conduction system in sudden infant death. Forensic Sci Int 93:143–154
Suarez-Mier MP, Fernandez-Simón L, Gawallo C (1995) Pathologic changes of the cardiac conduction tissue in sudden cardiac death. Am J Forensic Med Pathol 16:193–202
Sunnassee A, Shaohua Z, Liang R, Liang L (2011) Unexpected death of a young woman: is myocardial bridging significant? A case report and review of the literature. Forensic Sci Med Pathol 7:42–46

Takahashi S, Kanetake J, Moriya T, Funayama M (2008) Sudden infant death from dilated cardiomyopathy with endocardial fibroelastosis. Legal Med 10:277–280

Takeichi S, Nakajima Y, Yukawa N, Saito T, Seto Y, Huang XL, Kusakabe T, Jin ZB, Hasegawa I, Nakano T, Saniabadi R, Adachi M, Ohara N, Wang T, Nakajima K (2001) Association of plasma triglyceride-rich lipoprotein remnants with "Pokkuri disease". Legal Med 3:84–94

Tamura A, Kusachi S, Nogami K, Yamanishi A, Kajikawa Y, Hirohata S, Tsuji T (1996) Tenascin expression in endomyocardial biopsy specimens in patients with dilated cardiomyopathy: distribution along margin of fibrotic lesions. Heart 75:291–294

Tansey DK, Aly Z, Sheppard MN (2005) Fat in the right ventricle of the normal heart. Histopathology 46:98–104

Tatrai E, Bedi K, Kovalszky I, Hartyanszky I, Laszik A, Acsady G, Sotonyi P, Hubay M (2011) No mutation but high mRNA expression of Coxsackie-Adenovirus receptor was observed in both dilated and ischemic cardiomyopathy. Forensic Sci Int 212:47–50

Tausch D (1974) Experimentelle Untersuchungen über den histologischen Nachweis frischer ischämischer Herzmuskelschädigungen mit der Methode nach Lie und Mitarb. Beitr Gerichtl Med 32:274–278

Taylor AJ, Rogan KM, Virman R (1992) Sudden cardiac death associated with isolated congenital coronary anomalies. J Am Coll Cardiol 20:640–647

Thiene G, Bruneval P, Veinot J, Leone O (2013) Diagnostic use of the endomyocardial biopsy: a consensus statement. Virchows Arch 463:1–5

Thierauf A, Dettmeyer R, Wollersen H, Madea B (2007) Aplastic right coronary artery and left coronary artery with a separate origin of the circumflex branch in a 31-year-old man. Forensic Sci Int 173:178–181

Thomsen H, Held H (1995) Immunohistochemical detection of C5b-9 (m) in myocardium: an aid in distinguishing infarction-induced ischemic heart muscle necrosis from other forms of lethal myocardial injury. Forensic Sci Int 71:87–95

Thomsen H, Schulz A, Bhakdi S (1990) Immunohistochemische C5b-9-Komplement-Komplex-Darstellung in Frühstadien der Herzmuskelnekrosen am Paraffinschnitt. Z Rechtsmed 103:199–206

Titus JL, Daugherty GW, Kirklin JW, Edwards JE (1963) Lesions of the atrio-ventricular conduction system after repair of ventricular septal defect. Relation to heart block. Circulation 28:82–88

Todd GL, Baroldi G, Pieper GM, Clayton F, Eliot RS (1985a) Experimental catecholamine-induced myocardial necrosis. I Morphology, quantification and regional distribution of acute contraction band lesions. J Mol Cell Cardiol 17:317–338

Todd GL, Baroldi G, Pieper GM, Clayton F, Eliot RS (1985b) Experimental catecholamine-induced myocardial necrosis. II Temporal development of isoproterenol-induced contraction band lesions correlated with ECG, hemodynamic and biochemical changes. J Mol Cell Cardiol 17:647–656

Tsung SH, Huang TY, Chang HH (1982) Sudden death in young athletes. Arch Pathol Lab Med 106:168–170

Tyson AA, Hackshaw BT, Kutcher MA (1989) Acute Epstein-Barr virus myocarditis simulating myocardial infarction with cardiogenic shock. South Med J 82:1184–1187

Vallance HD, Jeven G, Wallace DC, Brown MD (2004) A case of sporadic infantile histiocytoid cardiomyopathy caused by the A8344G (MERRF) mitochondrial DNA mutation. Pediatr Cardiol 25:538–540

Veinot JP, Johnston B (1998) Cardiac sarcoidosis – an occult cause of sudden death: a case report and literature review. J Forensic Sci 43:715–717

Veinot JP, Johnston B, Acharya V, Healey J (2002) The spectrum of intramyocardial small vessel disease associated with sudden death. J Forensic Sci 47:384–388

Ventéo L, Bourlet T, Renois F, Douche-Aourik F, Mosnier JF, Maison GL, Pluot M, Pozzetto B, Andreoletti L (2010) Enterovirus-related activation of the cardiomyocyte mitochondrial apoptotic pathway in patients with acute myocarditis. Eur Heart J 31:728–736

Ventura F, Landolfa MC, Leoncini A, Gentile R, Gaggero G, Bonsignore A, de Stefano F (2012) Sudden death due to primary atrial neoplasms: report of two cases and review of the literature. Forensic Sci Int 214:e30–e33

Voigt J (1976) Reflections on the value of histological examination of the cardiac conduction system in cases of natural unexpected death. Forensic Sci Int 8:29–31

Walthard B (1942) Die Koronarsklerose der Jugendlichen. Schweiz Med Wochenschr 72:1261

Weiler G, Knieriem HJ (1975) Beitrag zur Morphometrie der Coronarsklerose. Z Rechtsmed 75:241–254

Weiler G, Risse M (1981) Morphological examinations in cases of stenosing coronary sclerosis and their importance for evaluation of competing causes of death. Forensic Sci Int 18:131–139

Weiler G, Risse M (1994) New aspects concerning the morphology and significance of coronary muscle bridges. Cardiovasc Pathol 3:51–55

Wick MR, Siegal GP (1988) Antibodies to desmin in diagnostic pathology. In: Wick MR (ed) Monoclonal antibodies in diagnostic immunohistochemistry. Marcel Dekker, New York, pp 93–114

Wigle ED, Sasson Z, Henderson MA, Ruddy TD, Fulop J, Rakoski H, Williams WG (1985) Hypertrophic cardiomyopathy: the importance of the site and the extent of hypertrophy: a review. Prog Cardiovasc Dis 28:1–83

Wingenfeld L, Freislederer A, Schulze-Bahr E, Paul M, Bajanowski T (2010) Life-threatening hobbies in the youth? Two autoptic cases suggesting arrhythmogenic right ventricular cardiomyopathy. Forensic Sci Int 171:e1–e4

Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC (2005) Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 352:539–548

Wojnicz R, Nowalany-Kozielska E, Wodniecki J, Szczurek-Katanski K, Nożyński J, Zembala M, Rozek MM (1998) Immunohistological diagnosis of myocarditis – potential role of sarcolemmal induction of the MHC and ICAM-1 in the detection of autoimmune mediated myocyte injury. Eur Heart J 19:1564–1572

Woźniewicz B, Czarnowska E, Kubicka K, Ziólkowska L, Cielecka-Kuszyk J, Zaleska T (1998) Coexistence of arrhythmogenic right ventricular cardiomyopathy and chronic myocarditis in children. Ann Diagn Paediatr Pathol 2:13–17

Xiaohong Z, Xiaorui C, Jun H, Qisheng Q (2002) The contrast of immunohistochemical studies of myocardial fibrinogen and myoglobin in early myocardial ischemia in rats. Legal Med 4:47–51

Xu XH, Chen JG, Zhu JZ (2001) Primary study of vascular endothelial growth factor immunohistochemical staining in the diagnosis of early acute myocardial ischemia. Forensic Sci Int 118:11–14

Yamanaka O, Hobbs RE (1990) Coronary artery anomalies in 126,595 patients undergoing coronary angiography. Catheter Cardiovasc Diagn 21:28–40

Yazaki Y, Isobe M, Yamazaki S, Sekiguchi M, Usuda N (1998) Ultrastructural and immunohistochemical analysis of biopsy-proven chronic active myocarditis with numerous clusters of lymphocytes. Virchows Arch 433:161–166

Zack F, Rummel J, Büttner A (2011) Fibromuscular dysplasia and sudden cardiac death. Brief review. Rechtsmedizin 21:513–517

Zack F, Manhart J, Rentsch D, Büttner A (2014a) Rare cause of death due to treatment of schizophrenia and alcohol abuse. Rechtsmedizin 24:22–25

Zack F, Kutter G, Blaas V, Rodewald AK, Büttner A (2014b) Fibromuscular dysplasia of cardiac conduction system arteries in traumatic and non-natural sudden death victims aged 0 to 40 years: a histological analysis of 100 cases. Cardiovasc Pathol 23:12–16

Zack F, Rummel J, Wegener R (1996) Hochgradige Sinusknotenfibrose als Ursache eines plötzlichen Herztodes. Rechtsmedizin 6:133–136

Zack F, Wegener R (1994) Zur Problematik der Diagnose "rhythmogener Herztod" durch histologische Untersuchungen des Erregungsbildungs- und –leitungssystems. Rechtsmedizin 5:1–5

Zack F, Rodewald AK, Blaas V, Büttner A (2016) Histologic spectrum of the cardiac conducting tissue in non-natural deaths under 30 years of age: an analysis of 43 cases with special implications for sudden cardiac death. Int J Legal Med 130:173–178

Zell R, Klingel K, Bültmann B, Kandolf R (1995) Nachweis enteroviraler RNA aus Formalin-fixiertem Paraffin-eingebettetem Myokardgewebe durch nested RT-PCR. Verh Dtsch Ges Pathol 79:359

Zhang JM, Riddick L (1996) Cytoskeleton immunohistochemical study of early ischemic myocardium. Forensic Sci Int 80:229–238

Zhang M, Tavora F, Zhang Y, Ripple M, Fowler D, Li L, Zhao Z, Burke A (2013) The role of focal myocardial inflammation in sudden unexpected cardiac death and noncardiac deaths – a clinicopathological study. Int J Legal Med 127:131–138

Zhu BL, Tanaka S, Ishikawa T, Zhao D, Li DR, Michiue T, Quan L, Maeda H (2008) Forensic pathological investigation of myocardial hypoxia-induced factor-1a, erythropoietin and vascular endothelial growth factor in cardiac death. Legal Med 10:11–19

Zollinger U (1983) Die Chromotrop-Anilinblau-Färbung zur besseren Darstellung frischer Herzmuskelfaserschädigungen. Z Rechtsmed 90:269–275

Zugibe FT, Zugibe FT Jr, Costello JT, Breithaupt MK (1993) Hypoplastic coronary artery disease within the spectrum of sudden unexpected death in young and middle age adults. Am J Forensic Med Pathol 14:276–283