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GUIDELINES

Second opinion system for sudden cardiac death cases in forensic practice

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Abstract

Sudden cardiac death (SCD) represents a considerable percentage of cardiovascular deaths worldwide. The most frequent pathological substrate of SCD is atherosclerotic coronary artery disease (CAD). The other, less common, pathologies which can cause SCD include cardiomyopathies, congenital diseases (including abnormal anatomy), and arrhythmias such as channelopathies, many of which are genetically determined. Autopsies of SCD victims are generally performed by forensic pathologists. In some cases, a third person responsibility could be invoked. While CAD diagnosis at post-mortem examination is not a major challenge for the forensic pathologist, the other rarer diseases may be. In such instances, referral of the hearts to specialized centers with recognized expertise is recommended, and this is particularly important in cases of SCDs of young people. Moreover, in order to avoid the frequent overdiagnosis of a pathological heart, an expert opinion should be sought for even in the presence of a morphologically normal heart. In cases where retention of the heart is not feasible, it is essential to provide an extensive photographic documentation, with the indication of the sampling sites for histological examination. However, some practical aspects, as the criteria for case selection in routine forensic practice are missing. In this paper, we present the recommendations for heart retention for a second expert opinion and the alternative of documentation and sampling for cases where retention is not possible.

Keywords Sudden cardiac death · Heart retention · Cardiovascular pathology · Forensic pathology · Autopsy

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Introduction

Cardiovascular diseases cause approximately 17 million deaths per year worldwide and sudden cardiac death (SCD) represents about 25% of these cases [1]. Sudden death (SD) is often the first clinical manifestation of an underlying cardiovascular disease in previously asymptomatic, "healthy" subjects [1, 2]. Atherosclerotic coronary artery disease (CAD) is recognized as the most frequent cause of sudden death in the general population [3, 4], while cardiomyopathies and channelopathies are often involved in a younger population [5, 6]. According to the literature, concerning the general US population, approximately 80% of SCD cases are attributed to CAD [7, 8]: 10–15% to cardiomyopathies with a pathomorphological substrate, and the remaining 5–10% is due either to congenital abnormal cardiac anatomy or to arrhythmias without any structural changes, including many genetically determined arrhythmias, such as channelopathies [3, 9].

According to the European and Swiss recommendations set in the field of forensic and clinical pathology, an autopsy

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should be carried out in every SCD case of a young adult, taking into account the real possibility of an underlying genetic cause [2, 8, 10, 11]. More precisely, an autopsy should be mandatory in all cases under 40 years of age, it should be considered in individuals between 40 and 65 years of age and can

65 years of age [4, 11]. However, in a highly varying degree of presumed SCDs, ranging between 3 and 53%, autopsy results are negative, despite comprehensive and detailed macro-anatomical and histological investigation, with negative toxicological analyses [12]. Such cases are classified as sudden arrhythmic death syndrome (SADS) [13, 14].

Referral of the hearts to specialized centers with recognized expertise, particularly in cases of sudden cardiac deaths of young people, is recommended by the Association for European Cardiovascular Pathology as well as the UK Royal College of Pathologists [15–17]. Where an underlying cardiomyopathy is suspected, referral is essential [16]. Nonetheless, also in the presence of a morphologically normal heart, an expert opinion by a dedicated cardiovascular pathologist should be sought. In fact, it has been demonstrated that a morphologically normal heart is often under- or misdiagnosed by the general or the forensic pathologist, with a frequent overdiagnosis of cardiomyopathy [15]. In cases where retention of the heart is not possible, it is crucial to ensure extensive photographic documentation, indicating where samples for histological examination were harvested [2]. In a consensus paper about training in cardiovascular pathology, three levels of pathological cardiovascular expertise were proposed. However, in many countries, including Switzerland, the training in cardiovascular pathology for forensic practitioners is limited. This also explains why referral of the heart to a center of expertise is crucial [2, 18–20].

In Switzerland, as in many European countries, most autopsies of SCD and SADS victims are performed in forensic institutes. The precise data as regards the autopsy rate and the utility of feedback of results are missing in daily practice in Switzerland [21]. While CAD does not usually represent a diagnostic challenge for the forensic pathologist, other (less common) structural cardiac diseases, including cardiomyopathies, congenital malformations, and (subtle) anatomical anomalies, require an expert cardiac pathologist opinion, taking also into account the limited average training in forensic pathology [2, 8, 22].

In cases where heart retention is advised, the problem of consent may arise, especially in non-forensic cases. It is important to keep in mind that the heart represents a very emotive organ for the public. This fact in itself may already represent an obstacle for its retention. For instance, the "Alder Hey" organ scandal at the Royal Liverpool Children's Hospital, UK, attracted public attention in the 1990s [23]. According to the result of the public inquiry in this affair, many parents did not give "proper consent" for the removal, examination, and subsequent retention of organs of their children, and consequently, there was a significant reduction in the consent to clinical autopsies and an even greater reluctance to grant permission for organ retention. The negative impact of this on the progress of medical sciences is readily obvious.

In this paper, we propose recommendations for heart retention for a second expert opinion and the alternative of documentation and sampling for cases where retention of the organ is not possible.

Swiss legal aspects of heart retention in forensic and clinical practice

According to the Swiss Criminal Procedure Code (2007), the retention and conservation of the body or parts of the body is possible during forensic investigations ordered by a district attorney for unnatural deaths, and the consent of the next-of kin is not required. One of the most important duties of forensic expertise is to establish the cause of death. In challenging cases where specialist knowledge is required, the forensic expert should therefore seek a second expert opinion (for example for heart and/or brain examination) to this end. This can be the case not only for evident, unnatural causes of death, but also for cases where a third person involvement or medical responsibility could be questioned, even in natural deaths.

In clinical autopsy practice, the consent of the next-of kin is necessary to perform the autopsy and to retain organs. For research purposes and for teaching, the retention of the heart and sampling should follow a different legal and ethical framework [24, 25].

Limitations for retrieving and retaining the entire heart include legal, social, and economic issues, as well as local and cantonal differences and heterogeneity in interest and expertise in cardiovascular pathology. The major pro and cons are presented in Table 1.

Based on the literature and on the observed needs in daily practice, the working group SCD of the Swiss society of legal medicine (SSLM) established the criteria to select cases, which are presented in Table 2.

In some situations, when it is impossible to retain the whole heart, the alternative solution remains the appropriate documentation and sampling. The minimal-standard recommendations concerning heart examination were established by the working group SCD of the SSLM in 2014 [26]. For cases of presumed SCD, in forensic as well as in clinical autopsy cases, a more detailed examination of the heart is essential in order to determine the underlying pathology and precise cause of death. Our present recommendations are based on the AECVP guidelines by Basso et al. from 2017 [2].

Table 1 Pros and cons for whole heart retaining

Pro	Contra
1. Possibility for a second opinion by an expert regarding less common pathologies or pathologies of uncertain significance, thus enabling a more precise diagnosis	1. Longer case work-up due to the involvement of different experts
2. Improved diagnosis of cardiac pathologies will enable a more focused clinical investigation of family members	2. Potential disagreement by the next-of-kin for emotional reasons
	3. No guarantee for the commissioning of additional examinations by the district attorney if the manner of death is clear

Recommended documentation and sampling for SCD cases where retention is not possible

The suggested workflow for suspected SCD is

1. As suggested by Basso et al. [2], all autopsies in cases of sudden death and SCD should be performed in a structured and sequential manner. Detailed external examination of the body should precede any other invasive analysis. In particular, non-cardiac causes of sudden death should be ruled out. Examination and preparation of the heart should be done as published in the guidelines for autopsy investigation of sudden cardiac death [2]. Following the steps as detailed in this publication is not excessively laborious and if done routinely, not prohibitively complex.
2. If expertise is lacking to perform these steps, the heart may be analyzed macroscopically as detailed in the publication and should then be referred for expert cardiovascular pathology assessment. A close collaboration between the "local" pathology department and the institute of forensic medicine is of great importance in this setting.
3. If the whole heart cannot be retained, comprehensive photographic documentation of the heart from the anterior and posterior aspects and following macroscopic work up should be performed. Of particular importance: the site of sampling should be noted in the photographs to allow for optimal reconstruction.

Standard/minimal sampling of the heart in cases of presumed SCD

Primary cardiac pathologies, in particular cardiomyopathies, often show a predilection for certain sites, e.g., "triangle of dysplasia" involving the right ventricular (RV) outflow tract, the RV inflow tract, and the RV apex, especially in early stages or subtle manifestations of the disease. Nonetheless, some changes characteristic for a pathology, such as "cardiomyocyte disarray" in hypertrophic obstructive cardiomyopathy, may be found in the posterior aspect of the septum without any evidence of disease. Therefore, particularly in the absence of a focal lesion, samples for histopathological analysis (performed using standard hematoxylin and eosin staining, eventually complemented by a trichrome or pentachrome staining—as Masson or Movat, respectively), should be taken in a standardized way to ensure accurate diagnosis. In such cases, immunohistochemistry (antibodies anti-fibronectin and C5b-9, among the most commonly used in forensic centers) can also be useful.

Samples mapped to images from the transversally sectioned heart should be taken as follows (Fig. 1):

- Left ventricle: anterior, lateral, posterior
- Interventricular septum: anterior, posterior
- Free wall of the right ventricle: anterior, lateral, posterior
- Right ventricular outflow tract

Table 2 Cases for which heart retention for a second opinion is recommended by the working group SCD of the SSLM

Autopsy findings	Age
Morphologically normal heart and unexplained cause of death (including also low level of suspicion of drug intoxication)	≤ 40 years
CAD as the cause of death	≤ 40 years
Diagnosis or suspicion of cardiomyopathy	≤ 40 years
Global hypertrophy of the heart [50], without other pathological findings	≤ 40 years
Aortic dissection	≤ 40 years
Cases with potential involvement of a third person (medical liability, cardiac surgery, death after a battle, police intervention, etc.), with probable/possible cardiovascular cause of death	No limit

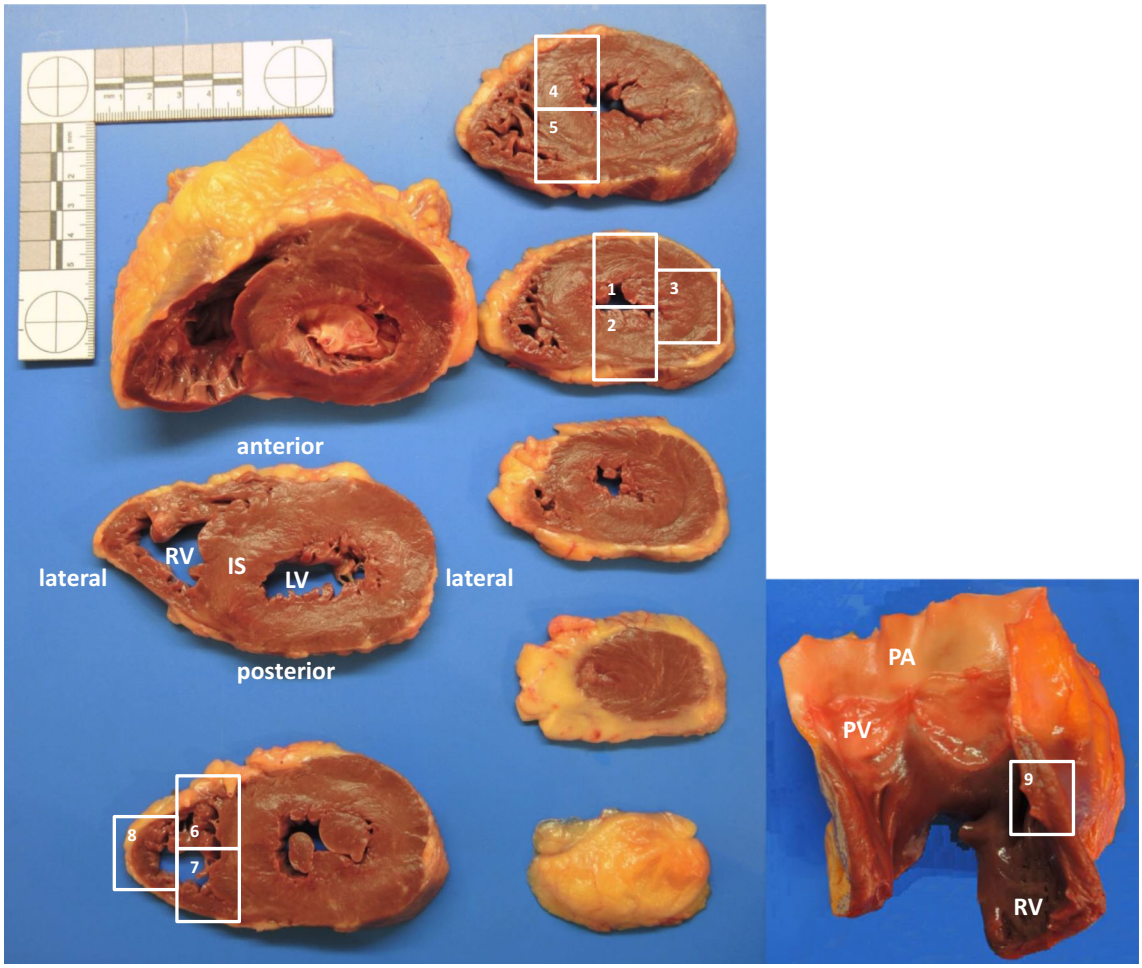

Fig. 1 Photographic documentation and sampling sites. a Photographic documentation of the transversally sectioned heart with sampling sites. b View of the pulmonary valve, with sampling site of the right ventricular outflow tract. LV (left ventricle): anterior (1), posterior (2), lateral (3). IS (interventricular septum): anterior (4), posterior (5). FWRV (free wall of the right ventricle): anterior (6), posterior (7), lateral (8). Right ventricular outflow tract: (9) PV: pulmonary valve. PA: pulmonary artery

Sampling of the conduction system (AV node) can be tedious. Moreover, histological examination of the conduction system is rarely conclusive or, at best, difficult to interpret, even for the experienced and dedicated cardiovascular pathologist. Only in exceptional cases, the cause of death could be established by examination of the conduction system [27]. Therefore, we recommend this sampling only in cases where a structural problem of the conduction system is suspected or the clinical history or electrocardiogram tracing (where available) suggests a possible conduction anomaly. The sampling of the AV node and of the bundle of His is shown in Fig. 2.

If retention of the whole heart is problematic for any reasons (in particular the requirement to return "all" tissues back to the deceased, in some instances), but essential for a correct diagnosis, pathologically less relevant parts of the heart (usually aspects of the atria or atrial appendage) can be returned to the deceased, without considerable risk of missing a diagnosis.

Standard/minimal sampling of the large vessels, in particular aorta

Primary pathologies of the aorta or large associated arteries may be relevant to SCD, mainly in the form of ruptured aneurysms or acute dissections. In a large proportion of cases, a macroscopic evaluation, in particular in medico-legal autopsies, may be sufficient to render a correct diagnosis [28]. In the light of the fact that a relevant amount of deaths will arise in the setting of atherosclerotic or hypertensive vasculopathy, histological work-up may not necessarily contribute in a relevant manner to the final diagnosis. Nevertheless, it is recommended that a minimum of six pieces of aorta are submitted in two cassettes, in the absence of worrisome features, as suggested by previously published consensus reports on processing of aortic samples [29, 30]. The term "worrisome" may be interpreted differently, depending on the viewpoint of the examining person. Worrisome features may include intimal changes such as "wrinkling/tree-barking", which are

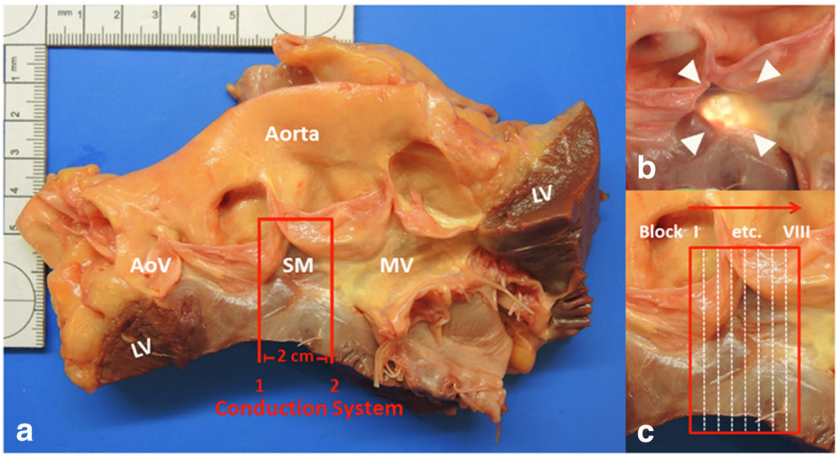

Fig. 2 Sampling and embedment of the conduction system. a Removal of the conduction system by two parallel cuts, one at the septum membranaceum (1) and the other one at the attachment of the mitral valve (2). b The septum membranaceum (white arrowheads) when held against the light. c Embedment of the conduction system by cutting it into 2-mm wide slices from the aortic valve to mitral valve. AoV: aortic valve. MV: mitral valve. LV: left ventricle. SM: septum membranaceum

suggestive of aortitis/vasculitis in the context of a clinical autopsy and will be of general medical interest. However, in the case of a medico-legal autopsy with aortic aneurysm rupture or dissection, confirmation of inflammatory aortic disease may not be of immediate relevance. In these cases, as also in clinical pathology, the duty in particular is to discern if gross features or histopathological alterations are suggestive of a syndromic/hereditary vasculopathy, which may be relevant to the next-of-kin. Common settings suggestive of a possible underlying genetic condition—in addition to possible phenotypic peculiarities such as marfanoid habitus in Marfan's disease or bifid uvula in Loeys-Dietz syndrome—include aortic aneurysms or dissections in a macroscopically apparently normal aorta. This is particularly relevant in younger individuals (< 40 or, better, < 50 years of age) and should be actively looked out for. Also, anulo-aortic ectasia (with or without additional aortic alterations) or extreme tortuosity of the aorta should lead to high suspicion of possible underlying genetic disease and prompt extensive sampling. Ideally, the aorta and large branches should be harvested completely and be kept until completion of histological work-up. Structural alterations may be focal, and therefore, sampling may include 12 or more blocks. If retention of the whole aorta is not possible, extensive sampling (aortic annulus, ascending aorta, aortic arch, descending aorta, and abdominal aorta) should be done, as indicated in Fig. 3, with photographic documentation of where material was taken.

Discussion

According to European recommendations, in cases of sudden unexplained death, the preservation of the whole heart and its examination by a tertiary referral center are recommended to allow an accurate re-examination and to achieve the correct pathological diagnosis. In forensic practice, post-mortem diagnosis of some rare pathologies (as cardiomyopathies) might be challenging and requires good experience in cardiovascular pathology, which could be missing considering the average forensic training. In this paper, we propose practical recommendations for forensic pathologists on how to select cases for referral and to proceed if the retaining of the heart is not possible.

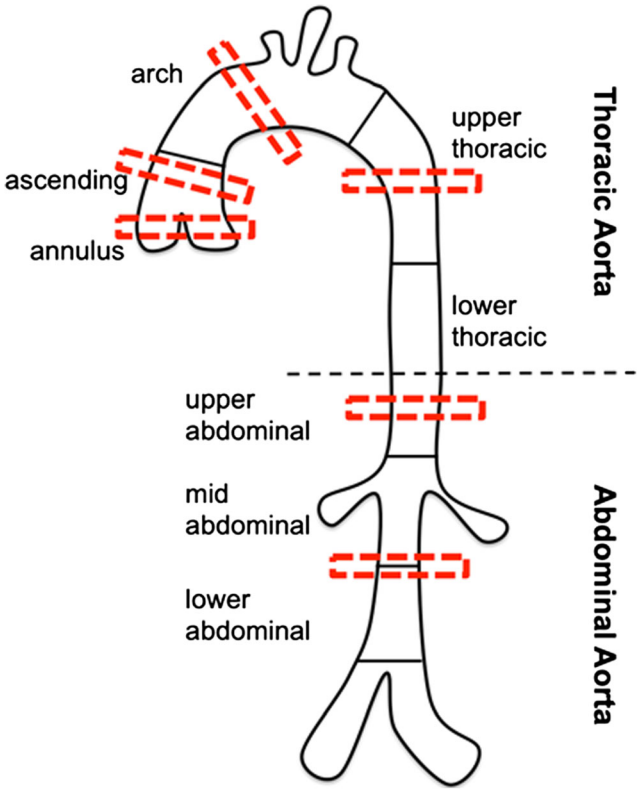

Fig. 3 Schematic representation of the thoracic and abdominal aorta sampling. In cases of aortic pathology (including in particular annulo-aortic ectasia, aortic aneurysms, or aortic dissection) extensive sampling of the aorta and its main branches may be necessary to determine the underlying pathology. In the absence of an obvious structural anomaly (e.g., aneurysm), the aorta should be sampled at various thoracic and abdominal levels (depicted as red rectangles). It is recommended that roughly two blocks per site, each with 2–3 transmural strips of the aortic wall are sampled. In cases with relevant atherosclerotic lesions, blocks with and without plaques should be sampled

Although some pathologies could be diagnosed by forensic pathologist, some diagnostic issues are particularly challenging. For myocardial diseases, the border between physiological and pathological changes is sometimes poorly defined and some changes are considered within the range of normal or classified as secondary changes (e.g., exercise-induced changes or secondary to resuscitative maneuvers). The most problematic reported findings are fatty infiltration of the right ventricular wall, exercise-induced left ventricular hypertrophy (athlete's heart), focal myocardial disarray without hypertrophy, scattered inflammatory foci with or without small foci of fibrosis and circumferential and subendocardial myocardial ischemia with or without hemorrhage, after resuscitative maneuvers [2, 31]. These conditions are illustrated in Table 3. Some autopsy findings such as ventricular hypertrophy, myocardial fatty infiltrations, myocardial fibrosis, minor coronary artery disease, and pathologies of the conduction system have uncertain significance and might be explained by primary arrhythmogenic syndromes [2, 14, 15, 31–34]. Isolated left ventricular hypertrophy is present in a considerable proportion of SCDs and its significance remains unclear [15]. In a UK study, it was reported that general pathologists without sufficient experience are likely to overestimate the significance of autopsy findings and to attribute deaths to cardiomyopathy at the expense of diagnosis of a morphologically normal heart [15]. All these situations are considered as criteria for selection for a second opinion examination.

In forensic practice of autopsy of SCD, atherosclerotic CAD, complicated or not by an acute thrombosis, represents the most frequent diagnosis. In our recommendations, we propose to select cases of SCD related to CAD of young victims for a second opinion. In fact, sudden coronary death is not always atherosclerotic and some pathologies can be misdiagnosed. CAD with an acute occlusive thrombosis does not represent a diagnostic challenge for the forensic pathologist in most of situations, but in some cases, an eroded plaque can be missed [35–37]. Premature coronary artery disease observed in young people may be associated with a channelopathy in some cases. In some borderline cases with advanced CAD, an associated cardiomyopathy was reported [38–40]. It should be also underlined that different degrees of certainty exist in defining the cause-effect relationship between the cardiovascular findings and the sudden death event and are classified as certain, highly probable, or uncertain (Table 4). The diagnosis with certainty of a sudden coronary death, either acquired or congenital, and of myocardial infarction allows to rule out genetically transmissible diseases and to spare useless, costly, and stressful investigations for family members [38, 41]. Therefore, this diagnosis has to be validated by an experienced pathologist.

In Table 2, we included SD cases with low drug blood levels. In our opinion, cardiac pathology should be carefully searched for also in drug-related SCD. In psychiatric patients, QT-acting drugs might play a role [32, 42–45]. In a recent

Table 3 The gray zone between normal and/or secondary changes and pathologic changes of the myocardium [2]

Changes in the range of normality or secondary changes	Pathologic changes	Comments
Fatty infiltration of the right ventricular wall	Arrhythmogenic CM	Massive fatty infiltration of the right ventricle, without any evidence of replacement-type fibrosis and myocyte degeneration, should not be considered a diagnostic finding of arrhythmogenic CM, especially in obese, elderly people and people with alcohol abuse
Exercise induced left ventricular hypertrophy (athlete's heart)	Hypertrophic CM	An enlarged left ventricular cavity with increased wall thicknesses up to 13–14 mm is present in more than one third of highly trained athletes. Detailed histology essential
Focal myocardial disarray without hypertrophy	Hypertrophic CM without hypertrophy	Macroscopic changes are not always present in hypertrophic cardiomyopathy. Isolated myocardial disarray confined to the antero-septal and postero-septal junctions should be considered physiologic. For a confident diagnosis, additional findings, such as interstitial and/or replacement fibrosis and abnormal intramyocardial blood vessels should be searched for
Scattered inflammatory foci with or without small foci of fibrosis	Focal myocarditis	In the absence of myocyte necrosis, small foci of inflammatory cells (even after immunohistochemistry), are not sufficient evidence of myocarditis. Scattered small foci of fibrosis are also insignificant. Both findings should prompt examination of additional blocks.
Circumferential, subendocardial myocardial ischemia ± hemorrhage after resuscitative maneuvers	Regional or circumferential, subendocardial myocardial ischemia without resuscitative maneuvers	Ischemic changes of the myocardium, particularly when subendocardial and diffuse require exclusion of prolonged resuscitative maneuvers

Danish study, pharmacotherapy was identified in 58% of SCD cases. After multivariable adjustment, there was a 2- and 3-fold increased risk of SADS compared with explained SCD in patients receiving brugadogenic drugs or > 1 QT-prolonging drug, respectively. Identification of high-risk patients is warranted to lower the burden of SCD [45]. In another Danish study, it was shown that more than half of all toxicologically investigated SCD victims had positive post-mortem toxicological findings and polypharmacy was displayed in a considerable proportion of cases suggesting that some compounds may play a proarrhythmogenic role [46].

The precise diagnosis of aortic dissection in young patients is important as it is frequently genetically determined. The forensic or clinical pathologist should follow the recent recommendations for the investigation of these cases [2, 28–30, 47].

The responsibility of the pathologist (either forensic or clinical) is enormous, because a wrong or misleading postmortem diagnosis may entail potentially catastrophic medical and/or penal/juridical consequences [2, 28]. For instance, some sudden cardiac arrests related to police interventions could be explained by channelopathies/cardiomyopathies [48, 49]. Moreover, many causes of sudden arrhythmic death have a genetic basis and can affect the next-of-kin of the deceased: in such cases, the correct diagnosis is of paramount importance, as it might prevent another unnecessary premature death of the next of kin.

Table 4 Certainty of diagnosis of cardiovascular substrates of SCD at postmortem [2]

	Certain	Highly probable	Uncertain
Coronary artery disease (native coronary arteries/stent/grafts/-cardiac allograft)	Myocardial infarction, acute (any cause) Acute coronary occlusion (atherothrombosis, arteritis, dissection or embolism, cardiac allograft vasculopathy) Coronary ostia mechanical obstruction (aortic or valve prosthesis, tumor, vegetation) Anomalous origin of the coronary artery from the pulmonary trunk	Chronic ischemic heart disease (ischemic scar, any cause) Atherosclerotic plaque with coronary luminal stenosis > 75% Anomalous origin of the LCA from the right sinus with interarterial course	Anomalous origin of the RCA from the left sinus with interarterial course Aortic sinus coronary artery anomalies without interarterial course High take-off from the tubular portion Anomalous LCx branch originating from the right sinus or coronary artery Anomalous LAD origin with course anterior to the pulmonary artery Coronary ostia plication Intramyocardial course of a coronary artery (myocardial bridge) Small vessel disease
Myocardial diseases	Acute diffuse myocarditis (any morphological type)	Hypertrophic CM Arrhythmogenic CM Dilated CM Idiopathic fibrosis (non ischemic LV scar) Multifocal myocarditis Sarcoidosis Storage diseases Amyloidosis	Focal myocarditis Idiopathic LV Hypertrophy Hypertensive heart disease Hypertrabeculation (non compacted) myocardium
Native/prosthetic valves diseases	Mitral valve papillary muscle or chordae tendineae rupture with mitral valve incompetence and pulmonary edema Thrombotic block or endocarditis vegetations on valve prosthesis Laceration/Dehiscence/leaflet escape of valve prosthesis with acute valve incompetence	Calcific aortic valve stenosis with LV hypertrophy and fibrosis Myxoid degeneration of the mitral valve with prolapse with atrial dilatation or LV myocardial fibrosis and intact chordae	Moderate aortic valve sclerosis without LV hypertrophy/mitral annular calcification Dystrophic calcification of the membranous septum (±mitral annulus/aortic valve) Aortic insufficiency (dilated aortic annulus) Myxoid degeneration of the mitral valve with prolapse without atrial dilatation or LV fibrosis and intact chordae
Conduction system diseases *		AV node cystic tumor Purkinje cell hamartoma Sarcoidosis of the AV conduction system Surgical stitches, perimembranous	Hemorrhage of the subaortic septum (iatrogenic, dissection, etc.) Fibrosis of RBB and LBB (Lenegre disease)

In conclusion, the progress made in the understanding of the genetic origin of some cardiac diseases resulting in SD requires a precise pathological diagnosis. Retention of the heart and the creation of a second opinion system will allow to improve the post-mortem diagnosis and enable a more focused clinical approach for family members. Cardiovascular pathologies might also explain some SD involving a third person responsibility, which is regularly questioned in forensic practice.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This is a recommendation paper: neither human participants nor animals were involved.

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