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Research

Etiology and Pathogenesis of Sudden Cardiac Death

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Abstract

Background and definitions*:* This article contributes to the current state of knowledge in etiology and pathogenesis of sudden cardiac death (SCD). SCD is a well - defined disease entity which recently approved international guidelines address (cardiac death within 1 hour).

Etiology: The condition of coronary arteries contributes to common causes of SCD. Stenotic coronary artery sclerosis (80%) has been reported in most cases. In non-coronary causes (15%), cardiomyopathies (CMP) are frequently found, and alcoholic CMP dominates the CMP cohort. Genetically related causes are comparatively rare (5%).

Pathogenesis: In pathogenesis, only the consecutives of coronary ischemia have been extensively studied, in contrast to non-coronary causes. Herein, only some (mostly infectious) forms of myocarditis have been investigated in detail

The pathogenesis of different causes of SCD is less well studied. These include pathologic changes of adrenergic and cholinergic heart nerves, of intra- and extra-cardiac ganglia and of the conduction system. Morphological changes that clearly explain SCD are still difficult to reproducibly detect in clinical-pathologic and forensic autopsy diagnosis because these lesions might morphologically at first manifest after 1 hour or even later. This statement holds particularly true for detecting early ischemic heart muscle cell deaths being the most common cause of SCD.

Conclusions: The reported methods and special staining have proven to be less suitable for routine diagnostics. Attempts are now undergoing to solve the problem by the use

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of specific antibodies. They provide evidence of immunoreactivity of ischemic damaged cardiomyocytes which can be detected even after prolonged postmortem lay times.

Keywords: Sudden cardiac death, ischemia, early heart muscle damage, adrenergic cardiac nerves, autopsy.

Introduction

Prevention, diagnosis and therapy of sudden cardiac death (SCD) are still a challenge for surgical and clinical pathology and in particular for practicing physicians, cardiologists and so-called intensive care physicians, i.e. specialists in anesthetics and intensive care. A recently in the journal Cardio News published article analyzes two publications which were printed in the journal "Circulation" in 2018. Its deliberately lurid headline claims that the 'Sudden Cardiac Death' is in fact not a 'sudden cardiac' one [1]. The claim 'sudden cardiac death' would be wrong in its formulation. It is derived from one Californian study only, according to which a cardiac cause of suddenly deceased persons could not be detected in about 40% at autopsy. Therefore, one should better speak of 'sudden death'.

Coronary heart disease was only detected in 32% of cases, followed by cardiomyopathy (10%) and cardiac hypertrophy (8%). Including additional cardiac causes, sudden cardiac death was confirmed in 60% of autopsy cases, whereas 40% of sudden deaths did not display with cardiac causes.

The various causes of sudden death, in which, however, clearly outweigh cardiovascular diseases, are for long known to every pathologist and forensic physician and, therefore, offer nothing new. However, the doctor who completes the death certificate is well advised not to accept sudden death as the cause of death unless reliable medical history and medical examination findings are available, or appropriate medication indicates this heart disease.

The news in this study cited by Tseng et al. is the extremely high proportion of sudden deaths (13.5%) associated with an overdose of opiates. The authors explain the high proportion of drug-related deaths by "opioid epidemic" currently prevailing in the US. It should not be generalized.Clinical practice confirms the well - known experience that it is difficult to make the correct diagnosis of SCD in an acute emergency situation. Missing clinical history, previous findings and emergency related limited examinations increase the difficulty to differentiate the probable SCD from sudden death of another cause. In this respect, the cause of death stated on the death certificate is often incorrect.

It is the duty of the pathologist (or forensic pathologist) to determine the "true" cause of death, which defines the disease or circumstances that have led directly to the patient's (person's) death.

The described difficulties will probably not change in the foreseeable future. However, a synonymous use of the terms sudden death and sudden cardiac death should be

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avoided.
The problem described below concerns only the sudden cardiac death of the adult, and with respect to the type of death only deaths of natural cause. One might address the review of Bajanowski et al. who report in detail sudden deaths in children and forensic aspects in all age groups [2].

Several studies proved that the majority of sudden deaths in adults are related to cardiovascular diseases (CVD) in so-called industrialized countries. They are primarily of cardiac origin. In Germany, about 65,000 sudden cardiac deaths per year are estimated. About 20% of all deaths are induced by coronary heart disease (CHD) [3]. According to Zheng et al. [4] 60% of all cardiac deaths occur suddenly and unexpected.

Studies on risk stratification have shown that 45-50% of those who died suddenly did not previously present with heart disease [5-7].

On the other hand, these data demonstrate that cardiac diseases are involved in at least 50 % of the cases and that a cardiac attack or disease should not be unexpected in SCD, especially if cardiovascular risk factors are known. However, it is still difficult to identify high-risk patients and to perform preventive strategies. Thus, strategies and implementation of early risk detection are still indicated.

Goal

The current knowledge state of etiology and pathogenesis of sudden cardiac death (SCD) is presented in this review. In addition, we want to weight the individual causes according to their frequency and significance, to describe the relevant pathological - anatomical findings and to compare the difficulties, symptoms and examination results of cardiologic intensive care with the results of macroscopic and microscopic cardiac examinations. We will reconcile histological diagnosis and thus verify or concretely prove the clinical diagnosis of sudden cardiac death (SCD). These include the recognition of the underlying disease, which has led, directly or indirectly, to sudden cardiac death and to the description of the causal relationships of the reliably detected diseases.

Definitions

The term sudden cardiac death (SCD) is not clearly and in detail defined. In particular the definition of the term "sudden" is missing. Certainly, the patient's survival time can be used as a criterion. However, the onset of acute symptoms is not or not exactly known in many cases. The survival time between onset of the disease and the patient's death remains often an estimate. A longer survival time or the so-called reflective second heart death is a rare special form of SCD.

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The sudden cardiac death has been defined by the WHO in 1985 as a pathological cardiac event that induces death within one hour [8]. The same definition is included in the current guidelines of the American Heart Association 2006 [9] and the European Society of Cardiology 2015 [10]. This results in the challenge for the pathologist to search for an adequate morphological correlate. In practice, prolonged cardiac survival is also often indicated for sudden clinical cardiac death. Additional diagnoses consistent with SCD are or may be used too; for example acute coronary insufficiency, acute cardiac decompensate, or sudden heart failure, cardiac arrest, or asystole.

It is crucial for correct diagnosis and classification of SCD according to the ICD-10 that the entity SCD is the direct cause of death, in contrast to the mentioned clinical synonyms. Therefore, SCD should be distinguished from detectable acute myocardial infarction, decompensated hypertensive heart disease or primary, acutely decompensated heart failure. On the other hand, a number of cardiomyopathies might be the cause of SCD.

In conclusion, the international guidelines apply to define SCD in detail. However, the guidelines do frequently not meet the practice of general practitioners, cardiologists, intensive care physicians or pathologists. As a result, the concept of SCD is interpreted and applied differently. Several analogous or synonymous terms of cardiac disease and inadequate diagnoses are in use in clinical, pathological and forensic practice. These include acute heart failure, cardiac arrest, asystolia, acute coronary insufficiency, acute coronary syndrome, acute cardiac insufficiency etc., and complicate both the autopsy diagnosis and the comparability of studies on pathogenesis and prevention of sudden death caused by cardiac failure.

Etiology

The most common causative factors of SCD are well known today. As a rule, defined morphological findings explaining cardiac death can also be obtained for these cases. The rarer causes can either be detected only with greater technical efforts or even not at all. In principle, three major causes can be distinguished from the etiological point of view: coronary artery causes, non - vascular cardiac causes and genetic cardiac causes [10].

1. Coronary causes

Considering the high incidence of coronary heart disease (chronic ischemic heart disease) associated complications such as SCD account for about 80% followed by non-coronary causes (15%) and genetic causes (5%). According to the study by Titus et al. [11] the proportion of coronary causes was as high as 95%. It should be noted that all individuals who died within 6 hours of the onset of symptoms were included in this

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group. Therefore, it can be assumed that this group also contains numerous cases in which already an acute myocardial infarction has been previously detected. Due to the stringent definition of the new international guidelines, the clinically and histologically detectable acute myocardial infarction and its acute complications (e.g. ventricular wall rupture, papillary muscle tear) should, strictly speaking, not to be included in this group, as well as all non - primary cardiac causes, such as acute cor pulmonale induced by an acute (fulminant) pulmonary thromboembolism, acutely decompensated chronic cor pulmonale or a malignant lesion of adjacent organs that invades the myocardium. The picture of coronary (ischemic) heart disease is well known, and does not need be described in details herein. Decisive are the number, the localization (proximal vs. distal) and the severity of the coronary stenoses, where a stenosis degree of >75% is considered haemodynamically effective. After implantation of one (or more) stents or after bypass operation, the status of the stents and bypasses is important because secondary stenoses and thromboses or arteriosclerotic and thrombotic vessel occlusions may be the cause of SCD. In all cases, risk factors such as hypertension, diabetes mellitus, lipid metabolism disorders, obesity, smoking, stress, family stress and others have to be considered at the time of diagnosis. The risk of sudden cardiac death increases by a factor of 2 to 4 in the presence of risk factors, or even by a factor of 6 to 10 in case of pre-existing, clinically relevant heart disease [12]. Patients with overt diabetes mellitus represent a high-risk group [13-14].Practice has shown that even a single, proximally localized, high-grade coronary stenosis in one of the main coronary artery branches (RIVA, RCX, RCA) can induce SCD if one or more risk factors are present. Both together release an acute hypoxia, especially in case of physical stress. Endangered are also people with complicated plaques as a result of rupture of the fibrous cap and thrombosis constricting or occluding the vessel lumen or unrecognized heart valve defects. Misperceptions of physical capacity can affect younger people, men more often than women. Other coronary causes of SCD including coronary artery embolism, coronary aneurysms and malformations, which are rare and do not play a significant role in pathologic-anatomical diagnostics. Occasionally, a dissection is seen in the basal aorta ascending with cardiac tamponade or thromboembolism obliterans of the coronary arteries. Fibromuscular dysplasia of the AV node artery [15] is another rare lesion. It requires special reprocessing of the heart, similar to those of pathological changes of the conduction system [16, 17].

2. Non-coronary causes

Non-coronary causes comprise frequent and rare cardiomyopathies, diseases of the valves, and infectious myocarditis of viral, bacterial and other pathogens, in particular fungi (Candida albicans, Aspergillus fumigatus, etc.) or protozoa (Toxoplasma gondii, Trypanosoma cruzi).

A broad variety of additional chronic diseases such as AIDS, drug or alcohol abuse, drug intoxication, or other noxious (immunosuppressive) conditions might be associated with

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myocarditis, and explain rare myocardial infections, for example myocardial tuberculosis.

Other forms of myocarditis are extremely rare, such as eosinophilic myocarditis or giant cell myocarditis, which we have seen only in one case.

The rheumatic myocarditis associated with typical granulomas, which was once more commonly seen as a complication of rheumatic fever, is also a very rare cause of SCD today.

Among the non-ischemic cardiomyopathies (CMP), dilated cardiomyopathy (DCMP) is the most common type. The alcohol-induced CMP has been in focus of morphological and pathophysiological studies and the subject of epidemiological studies for decades. It is outnumbered only by investigations on virus influence [18].

Alcohol abuse has for a long time been considered the most common cause of dilated CMP in Europe. Difficulties in the evaluation result from the fact that the clinical presentation and history of alcohol abuse is often superimposed by coexisting stenotic coronary sclerosis and other risk factors, especially hypertension, smoking and metabolic disorders such as the often predominant obesity.

In some sudden cardiac deaths cases, the probable cause cannot be distinguished from a different one, for example after stent implantation or bypass surgery. The obtained DCMP can also be interpreted as coronary heart disease even without evidence of myocardial scars, or as hypertensive heart disease in case of significant left ventricular wall hypertrophy.

By contrast, alcoholic-only DCMP is usually not associated (except in heavy smokers) with stenotic coronary sclerosis or significant cardiac hypertrophy, in lieu thereof with characteristic changes in the intra- and extra- cardiac autonomic nervous system, as discussed in the pathogenesis section more in detail.

Other rare cardiomyopathies, such as arrhythmogenic right ventricular CMP, cannot be resolved without analysis of clinical findings or the patient's history. An example applies to Takotsubo-CMP (Stress CMP, Broken Heart Syndrome), which can induce lethal ventricular arrhythmias [19] and disorders of the arousal and conduction system.

3. Genetic causes

This group includes hypertrophic (obstructive or non-obstructive) cardiomyopathy (HCM), which is pathologically-anatomically rarely diagnosed. It distinguishes between obstructive and non-obstructive forms. The HCM is a multiplicity of gene mutations (>1500) and a conditional hereditary and thus congenital disease, which exhibits only small histological changes (cellular disarray of myocytes, fibrosis). SCD associated heart

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diseases of genetic origin and without detectable morphological explanation include primary arrhythmia syndromes or the so-called ion channel diseases. The most common of these frequently autosomal dominant inherited diseases encompass the long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome, which is associated with life-threatening tachyarrhythmias.

The molecular genetic verification of the underlying mutations of these diseases is technically complex and not always diagnostically relevant. Molecular genetic investigations, however, are of particular importance in forensic medicine, as sudden deaths without autopsy-related morphological findings contribute to 30% of SCD in young people [20].

Pathogenesis

Acute myocardial infarction has not been discussed in the etiology chapters or in the formal and causal pathogenesis of SCD for several reasons. First, one might argue that the process of formal development and onset of SCD are well-known and, in addition, are confirmed by a large number of studies and publications. It is generally accepted that the morphological manifestation of an acute infarction requires at least 6-8 hours, depending on various factors. Only after this time it can be reproducibly confirmed histologically by the HE stains.

Thus, myocardial infarction does not correspond to the definition of SCD, which has to occur within one hour after onset of symptoms. The onset of an infarction can often not be defined precisely. Usually a time interval of 1-2 hours has to be calculated in routine diagnostics. Therefore, and according to the frequency of suggested causes the main task is to detect alterations in the coronary vascular walls and the resulting ischemic damage of the myocardium as well as to specifically inspect the heart muscle cells.

1. Coronary arteries and myocardium

A coronary SCD can be diagnosed with reasonable certainty if a severe stenosis or occlusive atherosclerosis can be detected. In this case a three-vessel disease is not mandatory to explain SCD, and an isolated high-grade stenosis, for example in the main trunk of the left coronary arteries is sufficient. In addition to acute obturating thrombosis which induces absolute ischemia, critical stenoses of> 75% might evoke a so - called relative ischemia. It may affect the supply zone or even the whole myocardium.

Malignant arrhythmias, followed by ventricular fibrillation and asystole are the common consecutives [21]. Although ischemia is by far the most common pathogen that results via electrical instability in SCD, it is only one of multiple factors. The percentage of SCD in the ischemia cohort varies from 60% [22] to 95% [11].

If the ischemic attack is survived, the relative ischemia induces either already macroscopically detectable or only histologically demonstrable disseminated

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myocardial scars. Occasionally an infarction scar (>10 mm in diameter) or a chronic cardiac wall aneurysm already may exist. The focally increased collagenous connective tissue lesions should be distinguished from interstitial fibrosis because small disseminated myocardial scars presuppose focal myocardial cell deaths.

These lesions occur in SCD and also in different diseases which are primarily not associated with cardiac cell necrosis. They arise in the majority of cases in several distinct events within a period of multiple years. The necrotic heart muscle cell subsets (mostly group necrosis in clusters) are initially replaced by a cellular and vascularized granulation tissue, and progress in non-cellular, collagenous fibrous scars.

If death occurs within one hour, it is not possible to clearly identify myocardial cell necroses or early cardiac cell deaths by common HE stains or by special stains (e.g. according to Mallory, Selye, Lie, Arnold, etc.). The visible cell changes can only be interpreted irreversible cell damage. Loss of transverse streaks, the appearance of contraction bands as well as karyolysis, cytolysis and a so-called lax myocardial decay are microscopically interpreted the first signs of ischemic myocardial damage. In a later stage a wavy arrangement of the cardiac muscle fibers (wavy fibers) appears as a result of cell damage [23].

The reported results of special stains were either not reproducible in comparative studies, did only occur at longer manifestation times (after several hours) or were obtained in animal experiments only [24].

In human SCD, however, the manifestation time is often not known. In addition, the time of microscopic examination and the postmortem autolysis are limiting factors in the assessment of myocardial cell changes. In this respect, the known microscopic methods for ACD diagnosis are of little help. Elaborate cell counts and measurements are biased. These attempts including the special stains require great experience and are not suitable for routine diagnostics.

Different techniques, such as fluorescence microscopy could detect disseminated myocardial necroses in 642 autopsy cases with suspected myocardial infarction already 2 hours after the infarction and a lying time of 7 days at maximum [25]. Corresponding reports of other authors and animal experiments confirmed the findings already after a post infarction time of 60 min [25, 26, 27]. None of these techniques could be introduced in routine practice because of the considerable methodological effort and the inability to preserve the sections (Table 1).

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Detection techniques of morphologic changes in myocardial ischemia

Method	Evidence	Benefit	Disadvantage
HE staining	5-8 h post mortem	routine procedure, golden standard	no evidence of early ischemic cell damage
TTC/NBT	2-3 h	quick performance, low costs	application in unfixed tissue
Fluorescence microscopy	1-2 h	evidence of ischemic cell damage possible	stained sections cannot be archived
HBSP staining (Lie)	30 min – 3 h	evidence of ischemic cell damage possible	early evidence mainly in experimental studies, different staining quality
Modified LFB staining (Arnold)	<5 h	evidence of contraction bands	non-specific for ischemic cell damage, poor reproducibility
Immunohistochemistry (by using complement antibodies, e.g. C9c)	40 min s	specific evidence of ischemic cell lesions, automated standardized method, internal control proved	special equipment required
Electron microscopy	20 min	evidence of ultra-structural cell damage	special equipment required, after 3 h no distinction between ischemic and autolytic changes possible

Table 1 Comparison of different methods to provide evidence of early ischemic damage of heart muscle cells.

2. Cardiac nerves and conduction system

The innervation of the heart by adrenergic and cholinergic nerves undergoes certain stages in ontogenesis and postnatal development, termed pre- and postmediator stages. The nervous invasion phase begins after the age of 40 years. It increases after the age of 60 years, and is most likely causally associated with the increased occurrence of unexpected sudden deaths at these ages [28].

Retinal fluorescence microscopy studies have shown that the adrenergic nerve plexus is significantly reduced in cardiac wall sections of patients with sudden death [29] as shown in Fig 1.

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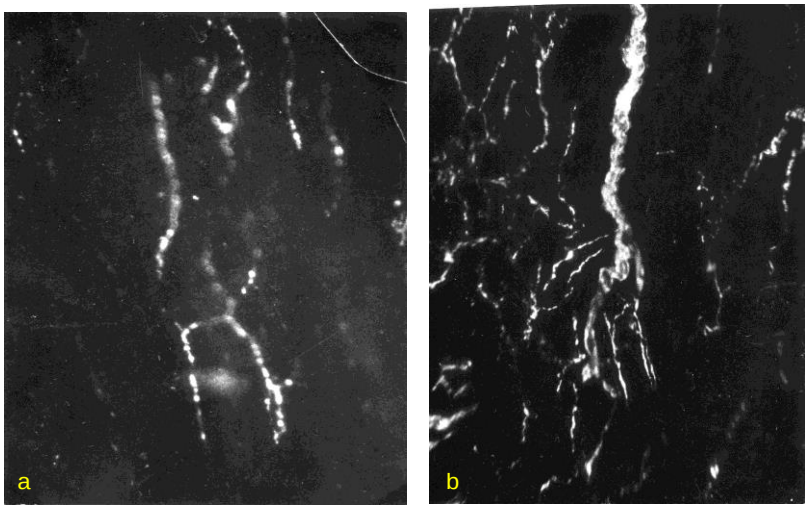

Figure 1: Male, 52 Years: Lost of adrenergic nerves in alcoholic cardiomyopathy (a) in comparison with a 25 Year old male control person (b)

These findings correlate with biochemically determinations of the catecholamine concentration, which have revealed a loss of norepinephrine in the cardiac muscle tissue. In cases of SCD, the ratio of norepinephrine to epinephrine drops from normal 10-20% to less than 1%.

Microscopically, the authors described an extreme heterogeneity of the adrenergic plexus density in different sections of the myocardium, resulting in a mosaic-like distribution pattern [30]. Additional structural, mainly degenerative changes affect the myocardial and extramyocardial (cervicothoracal) ganglion cells and receptors. These lesions and the associated transmitter loss are considered to be the morphological correlate of fatal arrhythmias [31].

The pathogenesis of SCD related to alcoholic CMP is of particular importance in the context. Alcoholic CMP was underestimated in terms of their frequency and clinical significance for a long time. Alcoholic CMP patients or individuals commonly present with characteristic myocardial alterations without stenosing coronary sclerosis.

The morphological findings are consistent with an apparently toxically induced herd-shaped chronic progressive destruction of the predominantly adrenergic nerve plexus in the myocardium. It can be visualized by fluorescence microscopy on frozen sections using the Falck method. The lesion provokes a damage of the motor end plate and subsequently electromechanical decoupling. The end stage results in electrical instability as well as ventricular fibrillation and asystole [29, 30, 33-35].

The described lesions have in common a pathogenic mechanism that induces electrical instability of the myocardium. Additional changes were described at the ultrastructural level [35]. At light microscopy, HE sections commonly display with intramural perivascular fibrosis and lipomatosis.

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Less common are pathological changes of the conduction system (HCS), which might occur with nonspecific fibrosis and lipomatosis. They account to 10-15% of SCD. Stenotic lesions may occur at the AV and sinus node arteries [23]. The detection of relevant changes in the HCS requires a special, time-consuming preparation technique [17], which has probably prevented its application in routine diagnostics.

These investigations of the above-described changes also apply to the morphology of the autonomic heart nerves. The lesions are relatively common and have been referred to as cardio-neuropathies (CNP) which have been extensively investigated by James [33].

Similar to CMP, primary, inside the heart localized CNPs have to be distinguished from secondary CNPs which are located in the cardiac nerves and associated with generalized neuropathy [36].

The findings of the autonomic nervous system in SCD have been confirmed by numerous studies. Many of them were published in three major US-USSR Joint Symposia on Sudden Cardiac Death in 1977, 1979, and 1982 [24].

We refer also to two previous publications which discus the significant findings of the SCD pathogenesis with particular reference to the changes of the autonomic nervous system and cardiac nerves [31, 32]. Herein we addressed the problem of the ‘one hour period’ of sudden death too, and how to accurately define in the period of symptom onset and death.

Conclusions

Unfortunately, clinico-pathological and forensic autopsy diagnoses have not significantly contributed to knowledge of causes and evidence of SCD in the past 30 years, with the exception that rare genetic-related sudden deaths can be differentiated more in detail by molecular pathology and molecular genetic examinations. Therefore, autopsy findings, which are supposed to confirm or suggest a SCD with significant probability, often fall short of expectations. The unambiguous detection of early morphological changes in cardiomyocytes, cardiac nerves and neurons of the conduction system or of other cardiac structures still remains a challenge in postmortem diagnostics. The detailed macroscopic and histological examination using conventional HE stains will continue to be standard, especially for cases with coronary causes.

Experience collected by years of continuous in autopsy diagnostics is of the great importance too. Special examination techniques are helpful in cases that cannot be clarified in detail. Herein, the application of new specific markers is promising to clearly detect certain otherwise hard to identify lesions, such as early myocardial cell deaths or apoptosis, even after prolonged periods between death and autopsy performance.

Recently, an autopsy study on 128 cardiac deaths confirmed the appropriate routine application of this technique in our institution. The study specifically demonstrated that

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the immunohistochemical application of specific markers (C9c antibody) is a highly specific, easy to apply and to standardize technique in routine autopsies. It offers the opportunity to meet the limiting conditions of routine pathological and forensic autopsy diagnostics and advanced technical performance.

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