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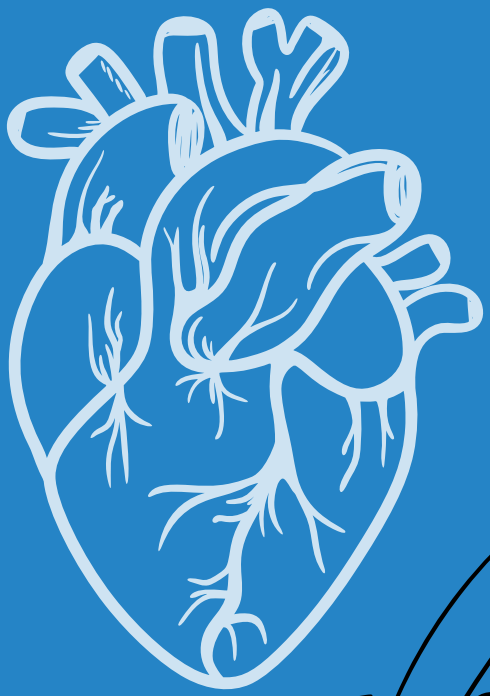
2nd International Meeting SUDDEN CARDIAC DEATH in the Balkan Area

BOOK OF ABSTRACTS



Macedonian Society for Forensic Medicine

Македонско Здружение за Судска Медицина

Contents

Welcome Note

Dear Colleagues and Friends,

It is my great pleasure and honor, on behalf of the Macedonian Association for Forensic Medicine, to welcome you to the **2nd International Meeting on Sudden Cardiac Death in the Balkan Area**, held here in Skopje.

Sudden cardiac death remains one of the most pressing challenges in medicine — not only because of its impact on patients and families, but also because of its complexity that demands a truly multidisciplinary approach. The phenomenon touches upon cardiology, pathology, genetics, emergency medicine, and forensic sciences. It is precisely at the crossroads of these fields that progress can be made, and it is through dialogue and cooperation that we can better understand the causes, mechanisms, and strategies for prevention.

The Balkan region, with its diversity and shared history, offers a unique context for such collaboration. By bringing together distinguished experts, researchers, clinicians, and forensic specialists from across the Balkans and beyond, this meeting provides a rare opportunity to exchange knowledge, compare experiences, and build bridges for future joint initiatives. It is our hope that these discussions will lead not only to scientific enrichment, but also to practical improvements in clinical practice, public health policies, and forensic investigations.

This meeting also carries a symbolic meaning — it reflects the commitment of our Association and our colleagues to stand at the forefront of scientific progress, to remain open to cooperation, and to contribute to a safer and healthier society. Each lecture, each abstract, and each conversation you will encounter here is part of a larger mission: saving lives, supporting families, and advancing the profession.

I warmly thank all contributors, speakers, and participants who made this meeting possible, as well as our partners and supporters who recognized its importance. I invite you to take an active role in the sessions, to challenge ideas, to share your own insights, and to strengthen professional bonds that will outlast this gathering.

May this meeting inspire new perspectives, collaborations, and solutions. I wish you productive sessions, meaningful exchanges, and a pleasant stay in Skopje.

With sincere regards,

Prof. Dr. Zlatko Jakjovski
President, Macedonian Society for Forensic Medicine
Organizer, 2nd International Meeting on Sudden Cardiac Death in the Balkan Area

ABSTRACTS

SUDDEN CARDIAC DEATH: ESTABLISHING A NATIONAL PATHOLOGICAL, GENETIC AND CARDIOLOGICAL SCREENING PROGRAMME IN UK

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Sudden unexpected death (SUD) with a cardiac cause, sudden cardiac death (SCD), is a major global health problem, with an estimated incidence varying from 1.3 to 159 per 100,000 persons per annum. In older populations, SCD is associated with age degenerative causes such as coronary artery disease. In younger populations, inherited cardiac conditions (ICCs), including cardiomyopathies, inherited arrhythmia syndromes, and aortopathies, are the predominant causes We have established a national referral pathway for cardiac examination of cases of SCD in UK. We have published on our large database of 7000 cases indicating that Sudden arrhythmic death syndrome in which the heart is morphologically normal (SADS) and cardiomyopathies predominate in UK. We have also indicated that genetic testing of probands and their relatives as well as clinical cariological screening is essential in these SCD cases SCD can be the first presentation of a previously undiagnosed Inherited cardiac condition (ICC) in a family; therefore, establishing a diagnosis permits identification of other family members who may be at risk. The optimal pathway requires three main components for the comprehensive personalised medical management of families: 1. initial autopsy examination with specialist cardiac pathology and toxicological studies; 2. post-mortem genetic testing if an ICC is suspected or the cause is unexplained, known as the sudden arrhythmic death syndrome (SADS); and 3. familial genetic and clinical evaluation guided by the results of post-mortem genetic testing. Patient pathways capable of providing the appropriate evaluation of these families are highly variable across England, as well as internationally[i], and require close working between the legal /coronial service (governed by the Ministry of Justice) and the NHS/National Health Service . To address the variation in access to ICC services and ensure optimal delivery of care**, the NHS and Coronial Sudden Unexpected Death (NHS-C-SUD) programme was established to enhance and standardise the patient pathway for families following a SCD in individuals aged 1-60 years. The programme focused upon improving the referral pathway between coronial and ICC services to ensure timely post-mortem genetic testing followed by appropriate genetic and clinical evaluation of family members. The unique nature of this programme was the prospective use of integrated forensic /coronial, genomic and cardiac services in an optimised pathway to identify and manage population risk of SCD. We performed an analysis of this programme, focusing on the genetic and clinical outcomes of decedents and their family members referred to the novel ICC pathway.** There are several indicators that the programme enabled effective identification and evaluation of family members at risk of SCD. Of the 107 decedent cases initially referred by HM Coroner, 89 (83%) completed post-mortem genetic testing, thereby enabling appropriate cascade predictive genomic testing of their families. This high rate of decedent post-mortem genetic testing was

due to newly implemented processes for the retention of sufficient tissue, consenting of next of kin, and coordination between the coronial service, genetic hubs, and the ICC clinic. 17% of tested decedent cases were identified as having a P or LP variant associated with an ICC. This is consistent with published estimates from selected SCD cohorts, indicating that the programme population is representative of that likely to be encountered in usual clinical practice

THE ROLE OF SUBSTANCE ABUSE IN SUDDEN CARDIAC DEATH

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Substance abuse is increasingly recognized as a major contributor to sudden cardiac death (SCD), particularly in younger populations without pre-existing cardiovascular disease.

At autopsy, pathologists may encounter both acute and chronic changes related to drug use, ranging from myocardial hypertrophy, interstitial fibrosis, and coronary artery pathology to acute findings such as contraction band necrosis and arrhythmogenic structural alterations.

The contribution of substances such as cocaine, amphetamines, opioids, and novel psychoactive drugs is well documented in forensic and cardiology literature. Toxicological analyses play a pivotal role in these cases, not only confirming the presence of substances but also correlating blood, urine, and tissue concentrations with the morphological findings.

The forensic challenge lies in distinguishing deaths primarily due to substance toxicity from those where drugs act as a trigger for fatal arrhythmia in structurally vulnerable hearts.

Comprehensive postmortem investigation—integrating gross and histological examination with advanced toxicology—remains essential for accurate diagnosis. Recognition of these patterns has both medico-legal and public health implications, underscoring the importance of systematic documentation and reporting in forensic practice.

Keywords: *sudden cardiac death, substance abuse, forensic pathology, autopsy, toxicology*

SAVING LIVES AND LOWERING COSTS: THE FINANCIAL CASE FOR EARLY SCREENING IN SUDDEN CARDIAC DEATH

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Sudden Cardiac Death (SCD) remains one of the leading causes of mortality worldwide, often striking without warning in otherwise healthy individuals. Despite advances in emergency response and medical technologies, survival rates remain low once SCD occurs. This paper presents a compelling financial and public health case for implementing early screening programs to identify individuals at risk of SCD, particularly among youth and young adults. By analyzing current healthcare expenditures, incidence rates, and cost-benefit data and international models, we demonstrate that early screening—through proper clinical examination's, electrocardiograms (ECGs), genetic testing, postmortem forensic analyzes (autopsy, histopathology, biochemical and toxicological analyzes) risk stratification—can significantly reduce both mortality and long-term healthcare costs. Preventive interventions, including lifestyle modifications, medical monitoring, genetic testing, building genetic related SCD population studies, and implantable devices, are shown to be far more cost-effective than emergency care and post-event treatment. The findings support policy shifts toward mandatory or subsidized screening initiatives, particularly in high-risk populations such as athletes and those with a family history of cardiac conditions. Early detection not only saves lives but also presents a sustainable economic strategy in the long-term management of cardiovascular health.

Key words: Sudden Cardiac Death, Diagnosis, Prevention, Education, Financial benefit

AUTOPHAGY AND INFARCTED HEART: A SYSTEMATIC REVIEW OF CIRCULATING BIOMARKERS AND PRELIMINARY RESULTS OF AN IMMUNOHISTOCHEMISTRY EXPERIMENT WITH ANTI-LC3-II ANTIBODY

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Introduction

Cardiovascular diseases are the leading cause of mortality worldwide, with ischemic heart disease being the most prevalent form. In the previous years, multiple trials have been conducted to understand the role of autophagy - a fundamental cellular process for maintaining cellular homeostasis - in the pathogenesis of cardiovascular diseases, particularly in cardiac ischemia and infarction. The aim of this study is to identify potential autophagy biomarkers that can be applied in forensic pathology through the immunohistochemical analysis of ischemic and infarcted hearts.

Materials and Methods

This study is a systematic review based on several studies collected from the PubMed database, including research conducted on both human and animal models. The search terms used were “myocardial ischemia”, “myocardial infarction”, “autophagy” and “biomarker”. Our study proceeded with an experimental phase in which 10 cases of subjects who died from ischemic heart disease and 10 control cases of subjects who died from other causes were retrieved. All subjects were selected from a database containing all deaths recorded and analyzed between 2021 to 2025 at the Institute of Forensic Medicine of the University of Trieste. For each case, a left ventricular tissue sample was selected from specimens stored at our Institute to perform immunohistochemical analysis, using the most promising autophagy marker identified through the systematic review.

Results

The review included 14 studies, in which 13 distinct autophagy-related biomarkers were identified and selected as promising candidate markers. Among these, LC3-II emerged as the most significant biomarker directly involved in the autophagy process in heart tissue after an infarction. This antibody was therefore selected to perform immunohistochemical analysis on the 20 collected samples, to assess cardiomyocytes positivity. In the ischemic heart disease group, the most relevant LC3-II positivity was observed in subjects who had died from subacute ischemic heart disease, while controls and subject died suddenly after ischemic insult were mostly negative.

Discussion

In this study, the significant role of LC3-II in cardiomyocytes autophagy was further confirmed by comparing hematoxylin-eosin-stained heart tissue samples from individuals who died of subacute ischemic heart disease. In these cases, the presence and extent of leukocyte infiltration were found to be proportional to LC3-II positivity observed in the corresponding immunohistochemical samples. These findings suggest a potential link between inflammatory response and autophagic activity in ischemic myocardial tissue. However, further comprehensive research is needed to validate LC3-II as a reliable autophagy biomarker, with the aim of improving diagnostic protocols in the forensic pathology assessment of ischemic heart disease.

SUDDEN CARDIAC DEATH IN A MORPHOLOGICALLY NORMAL HEART

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Introduction: Sudden cardiac death (SCD) is a devastating clinical event, often attributed to structural heart disease such as coronary artery disease, cardiomyopathies, or valvular abnormalities. However, a significant subset of patients who experience SCD present with morphologically normal hearts upon autopsy or imaging, posing diagnostic and preventive challenges. This entity, sometimes referred to as "autopsy-negative sudden unexplained death" (SUD), is increasingly recognized as a manifestation of primary electrical diseases or inherited arrhythmia syndromes.

Mechanisms and Syndromes: The underlying mechanisms predominantly involve disturbances in cardiac ion channel function, resulting in life-threatening ventricular arrhythmias without overt structural abnormalities. Well-described syndromes include long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), and early repolarization syndrome. In addition, subclinical genetic mutations affecting desmosomal or cytoskeletal proteins may predispose individuals to arrhythmias before structural changes become evident. Environmental and pharmacological triggers, electrolyte imbalances, and autonomic influences can further unmask arrhythmic vulnerability.

Diagnosis and Management: Clinical identification remains challenging due to the absence of gross morphological markers. Diagnosis relies on a comprehensive evaluation, including detailed family history, electrocardiographic features, genetic testing, and in some cases provocative testing with sodium-channel or adrenergic blockers. The recognition of heritable arrhythmia syndromes has crucial implications for family screening and preventive strategies.

Conclusion: SCD in morphologically normal hearts represents a clinically and genetically heterogeneous group of disorders. Improved recognition of these syndromes, coupled with advances in molecular diagnostics and family-based care, offers the potential to reduce mortality and improve long-term outcomes in affected individuals.

WHEN THE HEART CAN'T TAKE THE GAME: FORENSIC INSIGHTS INTO STRESS-TRIGGERED SUDDEN CARDIAC DEATH

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Emotional stress is a well-established trigger for acute cardiovascular events and sudden cardiac death (SCD) in vulnerable individuals.
It is well known that deaths can occur in sports venues. While most attention is usually focused on athletes, it is crucial to highlight that fans themselves may also be at risk. Major sporting events, characterized by intense emotional involvement, have been associated with increased cardiovascular mortality—the so-called "World Cup effect". For passionate fans, the combination of psychological stress with unhealthy lifestyle behaviors during matches (smoking, alcohol consumption, overeating) can significantly amplify cardiovascular vulnerability.
SCD commonly results from the interplay between pre-existing cardiac conditions and acute external triggers such as emotional stress. From a forensic perspective, investigations should extend beyond pathological findings to include situational circumstances. Recognition of preceding warning symptoms (e.g., chest or back pain) remains essential, as timely medical evaluation continues to be the most effective preventive strategy.
In this context, we present two fatal cases of male football fans in their fifties, both with underlying cardiac pathology (coronary artery disease, cardiac hypertrophy, hypertension), who were watching a match in a stadium in Athens, where the stress of the match acted as the precipitating factor. We have performed the postmortem examination at the Department of Forensic Medicine of Athens University, and we discuss our findings.
These incidents highlight that sudden cardiac death during sporting events is not confined to athletes but also threatens emotionally engaged fans. Awareness that both athletes and spectators may be susceptible to stress-related cardiovascular events is fundamental for the prevention of sudden cardiac death. Finally, ensuring the availability of automated external defibrillators (AEDs) and trained personnel in stadiums represents a critical intervention to improve survival in cases of sudden cardiac arrest during sporting events.

MOLECULAR AUTOPSY IN CROATIA – CURRENT STATE OF SAMPLING AND DNA ANALYSIS IN CASES OF SUDDEN CARDIAC DEATH

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Recognizing the significance of genetic testing in cases of deaths attributed to sudden cardiac death (SCD), the Institute of Forensic Medicine and Criminalistics in Zagreb has been working towards integrating this diagnostic method into autopsy procedures in the past few years.
Therefore, we have established a collaboration with the Institute for Personalized Medicine, Clinical Hospital Center Zagreb that will do massively parallel sequencing. DNA from the samples collected during the autopsy was isolated in our DNA laboratory and the first genetic tests have been successfully conducted. The first practical task was to define the best sample for collection, storage and extraction. The amount of DNA necessary for applied sequencing method was minimum of 30 ng of good quality DNA. For validation purposes we have decided to collect the whole blood, spleen tissue and blood stain on FTA card.
DNA was extracted from all samples using Forensic DNA Extraction Kit and Blood Extraction Kit and the BioMagPure12 instrument (Biosan). This is fast, simple and reliable DNA extraction method *that applies ready-to-use extraction magnetic bead-based kit for high-quality genomic DNA extraction from fresh or frozen whole blood, tissues, FFPE and forensic samples as well.* Quantification of DNA was done using RealTime PCR and Quantifiler Trio DNA Quantification Kit (Applied Biosystems). Selected samples were quantified in parallel with Qubit and Nanodrop (Thermo Fisher Scientific) and results were concordant. Good quality DNA was obtained for all tested samples and gained concentration were satisfied. FTA cards are the most convenient way of collecting, transporting, processing and storing samples for DNA extraction because they could be kept at room temperature for a long period of time and DNA is stable and of good quality, but generally the quantity of DNA is significantly higher in a tissue sample and the sample of whole blood as well. Whole exome sequencing was performed using TruSight One panel on Next 550 (Illumina), but we might consider some slight changes in the future.
Furthermore, we made a network with hospitals and forensic institutes across Croatia that will collect samples from individuals who have died from SCD and send them to our facility for genetic analysis. The main goal is to create Croatian national registry of SCD.

ALGORITHMIC FORENSICS: MACHINE LEARNING APPLICATIONS IN MEDICOLEGAL DEATH INVESTIGATION AND RESEARCH

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As is the case with other fields of medicine, Artificial Intelligence (AI) and Machine Learning (ML) are considered to be promising tools in forensic medicine and pathology regarding objectivization, automation, improvement in the decision-making process, and overall diagnostics: ideally, it should assist forensic experts by standardizing accuracy, eliminating subjective bias and improving evidence-based decisions and conclusions. This can be achieved by modeling the algorithms mainly from data such as tabular-organized numerical and categorical variables or images (radiology imaging, macroscopic photography, and histopathological slides). So, the main advantage of developing a reliable and effective AI model would be to consistently and accurately detect non-obvious associations in complex and heterogeneous data or to eliminate bias in relatively subjective diagnostic methods, for example, interpreting the routine histopathology findings (e.g., objective image analysis versus subjective grading scores). AI-based research in forensic medicine to date has mainly focused on the identification of individuals (e.g., estimation of the chronological age and/or sex from imaging data or anthropometric measurements), postmortem interval estimation, “reconstructing” various injury mechanisms, most notably mechanical trauma (for example, in pedestrians), as well as injury classification and bruise dating. Additionally, the medicolegal evaluation of sudden cardiac death, which is a significant aspect of forensic pathology, would benefit from the AI-based diagnostic improvements as part of the broader multidisciplinary approach to this prevalent and significant issue in medicine. Starting from the gross autopsy evaluation of heart and coronary vessels to microscopy, and over to data from multi-omics research, this is a field that would benefit from validated and generalized ML models. However, the present issue with ML models and AI-based research in forensic medicine remains the representativeness and validation, but also the explainability and interpretability of models, which essentially leaves AI-based methods in the field of research, for now.

Keywords: Forensic Medicine; Forensic Pathology; Artificial Intelligence; Machine Learning; Autopsy;

THE SCIENCE BEHIND THE TECHNOLOGY – DECODING SUDDEN DEATH: THE GENETIC ARCHITECTURE OF CARDIAC VULNERABILITY

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Abstract:
Sudden cardiac death (SCD) remains a leading cause of mortality worldwide, often striking individuals without prior symptoms. Advances in genomics and molecular cardiology have revealed that underlying genetic predispositions play a crucial role in determining cardiac vulnerability. This seminar will explore the complex genetic architecture that underlies SCD, integrating insights from genome-wide association studies (GWAS), familial linkage analyses, and next-generation sequencing approaches. We will discuss the identification of monogenic disorders such as long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and hypertrophic cardiomyopathy, which highlight the direct impact of single-gene mutations on arrhythmogenic risk. Beyond monogenic conditions, we will examine polygenic contributions, epigenetic modifications, and gene-environment interactions that modulate susceptibility in seemingly healthy individuals. Special attention will be given to emerging biomarkers, including rare genetic variants and regulatory non-coding elements, that may refine risk stratification. Technological advances, such as CRISPR-based modeling and induced pluripotent stem cell-derived cardiomyocytes, have enabled functional validation of genetic findings and provided novel platforms for personalized therapeutic strategies. Furthermore, integration of genomics with wearable devices, artificial intelligence, and big data analytics is paving the way toward predictive cardiology, where high-risk individuals may be identified before the onset of catastrophic events. This lecture aims to provide a comprehensive understanding of how genetic determinants interact with environmental and physiological factors to influence cardiac vulnerability, translating cutting-edge research into clinical practice. Attendees will gain insights into current diagnostic strategies, risk prediction tools, and potential therapeutic avenues to mitigate SCD risk.

Keywords: Sudden cardiac death, cardiac vulnerability, genetics, monogenic disorders, polygenic risk, arrhythmia, genome-wide association studies, precision cardiology, risk stratification, functional genomics

TOXICOLOGICAL PROFILE OF SUDDEN CARDIAC DEATH CASES

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Several drugs increase the risk of sudden cardiac death (SCD), especially drugs of abuse, which use may accelerate coronary disease or stimulate arrhythmias. Therefore, the aim of our study was to investigate the toxicological profile of SCD cases. Data evaluation included cardiac related death cases autopsied at the Institute of forensic medicine, criminology and medical deontology, Medical Faculty, UKIM, Skopje in the past 12 years. Only 29 cases, of which 38% female and 62% male (average age 32.38 years), met the criteria to be included in this study. These were cases that underwent sequencing with the Ion Torrent GeneStudio™ S5 platform on a set of selected genes for cardiomyopathies and arrhythmias and full toxicological screening. Positive toxicology findings were observed in 34% of SCD cases. Alcohol was present in 10.34% of the cases, with blood alcohol concentration not exceeding 0.5 g/L. Opiates, methadone, THC or cocaine were identified in 13.79% of all cases. Most prevalent group of medicines detected were benzodiazepines (17.24%), corresponding with literature data. However, in our study only small number of SCD cases are related with positive post-mortem toxicology findings compared with previously published data on similar topics. The underlying cause of this occurrence is probably the divergence in the case selection. Nonetheless, toxicological analyses are essential in omission death of toxic origin. Furthermore, their importance is emphasized due to determination of substances which may have potential to act as triggering factors of the SCD.

Key words: cardiac death, toxicology, arrhythmia, alcohol, drugs of abuse.

PATHOMORPHOLOGICAL CHANGES IN THE CARDIAC CONDUCTION SYSTEM IN DUCHENNE MUSCULAR DYSTROPHY: ANALYSIS OF A CASE OF SUDDEN DEATH IN A 7-YEAR-OLD BOY

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Background: In cases of sudden death of children and young individuals, postmortem examination of the cardiac conduction system is crucial for determining thanatogenesis and the causes of death.

The aim of this work is a pathomorphological analysis of a case concerning the sudden death of a 7-year-old boy with Duchenne muscular dystrophy, which delineated the primary changes in the cardiac conduction system.

Materials and methods. A forensic medical examination of the corpse of a boy aged 7 years and 11 months was conducted in the forensic medical department of the State Medical Service "Main Bureau of the Ministry of Health of Ukraine" following the standard method for examining the deceased. The histological examination included staining with hematoxylin and eosin and additional histochemical methods: Masson's trichrome staining and Gomori's silver impregnation.

Results. Duchenne muscular dystrophy was diagnosed at age 2 through genetic testing. The child died during dental procedures involving the inhalation anesthetic "Sevoran," a 1% solution of "Propofol," and 2 ml (40 mg) of Ditilin solution.

During the forensic examination of the boy's body, it was found that the muscles of the arms and thighs were somewhat atrophied, while the muscles of the lower legs were well-defined and "athletic." The heart had the shape of a flattened cone, a flabby consistency, and was enlarged (weight 131 g) with moderate ventricular chamber dilatation. The thickness of the walls of the left and right ventricles and the interventricular septum was within normal limits. The myocardium, upon sectioning, appeared light brown, flaccid, and dull.

According to the results of toxicological research, metabolites of the drug "Sevoran" were detected, along with traces of "Propofol" at 2 μg/g blood.

Histological examination of the lower legs, thighs, and the diaphragm muscles reveals intramuscular fibrosis, stromal edema, and alternating rounded hypertrophied muscle fibers alongside single thinned and atrophied fibers. In the myocardial tissue, diffuse interstitial and perivascular fibrosis, medial hyperplasia of the intramural coronary arteries, diffuse stromal edema, and pronounced endocardial fibrosis were observed. Elements of the cardiac conduction system were seen as focally fibrotic embryonic cardiomyocytes surrounded by proliferating reticular fibers. In the area of the sinoatrial node, foci of atrophied cardiomyocytes were identified.

Conclusion. The detected changes in the heart of the deceased boy can be classified as dilated cardiomyopathy in Duchenne muscular dystrophy. Acute heart failure caused the child's death. The detected changes in the conduction system of the heart, in particular dystrophic changes and fibrosis of embryonic cardiomyocytes with compensatory proliferation of reticular fibers, probably led to the child's sudden cardiac death.

CHALLENGES IN REGIONAL GENETIC VARIANT REGISTERS FOR SUDDEN CARDIAC ARREST

Robert Janevski

Sudden cardiac arrest (SCA) accounts for a substantial proportion of global mortality, yet effective prevention remains limited by insufficient tools for identifying at-risk individuals. Regional genetic variant registers have emerged as a potential strategy to centralize genomic data, improve variant interpretation, and facilitate familial screening. However, their establishment is challenged by uneven geographic distribution, reliance on incomplete or inaccurate case-ascertainment methods, declining autopsy rates, and deficiencies in adjudication processes. Furthermore, only a minority of existing sudden cardiac death registries systematically collect genetic data or maintain long-term biobanks, restricting opportunities for robust genotype–phenotype correlation. Additional barriers include the significant infrastructural demands of integrating multisource data, the complexity of cross-jurisdictional ethical approvals, and the need for harmonized standards for variant classification. To overcome these limitations, the adoption of multisource surveillance systems, cross-system data reconciliation, systematic genetic data acquisition with biobanking, standardized reporting frameworks, and centralized governance is proposed. Such measures would enhance data completeness, ensure reliability of case classification, and facilitate secure and interoperable data sharing. Ultimately, well-structured genetic variant registers are essential to advance precision medicine in cardiology, enabling earlier diagnosis, targeted interventions, and improved outcomes for individuals and families at risk of sudden cardiac arrest.

CORONARY ORIGIN ABNORMALITIES AND MYOCARDIAL BRIDGING: A DIAGNOSTIC CHALLENGE?

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Coronary origin abnormalities (COA) represent a rare but clinically significant group of congenital cardiovascular anomalies, characterized by an abnormal origin or course of any of the three main epicardial coronary arteries (CAA). While some anomalies remain asymptomatic and are discovered incidentally, others are associated with serious outcomes, such as myocardial ischemia, arrhythmias, syncope, or sudden cardiac death (SCD), often as the first presentation.

Although rare, COA play an important role in SCD, especially in young individuals and athletes. They differ in their likelihood of causing SCD. An anomalous left coronary artery (LCA) arising from the pulmonary artery (ALCAPA) is a major cause of myocardial ischemia and infarction in children, with a high mortality rate in infancy if left untreated. Survival into adulthood is rare and depends on collateral circulation from the right coronary artery (RCA). The origin of the RCA from the pulmonary artery is less common but carries similar risks of SCD.

Unlike ALCAPA, most subtypes of anomalous aortic origin of a coronary artery (AAOCA) are benign, with the exception of an interarterial anomalous LCA (ALCA) arising from the right sinus of Valsalva, and an interarterial anomalous RCA (ARCA) arising from the left sinus, both of which can be associated with ischemic symptoms. This configuration increases the risk of SCD, especially during exertion.

A single CA is usually benign, typically following the course of the LAD or RCA, and may divide into two or three main branches after its origin.

"High take-off," defined as a coronary origin >2.5 mm (up to 10 mm, according to some literature) above the sinotubular junction, may be associated with SCD in some cases, although its clinical significance remains uncertain.

A myocardial bridge is a congenital variant in which a segment of a CA, most often the LAD, runs within the myocardium. Its role in SCD is still debated. Certain anatomical features, such as a deeper (>5 mm) and longer (2–3 cm) intramyocardial course, may lead to ischemia.

Keywords:
Coronary Arteries, Coronary Origin Anomalies, Congenital Malformation, Sudden Cardiac Death, Myocardial Bridging

EXERCISE-INDUCED VENTRICULAR TACHYCARDIA IN A YOUNG ATHLETE: DIAGNOSTIC CHALLENGES AND LONG-TERM MANAGEMENT WITHOUT ICD IMPLANTATION

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Sudden cardiac death and arrhythmia represent a major worldwide public health problem, accounting for 15–20 % of all deaths. Majority of cases are due to coronary heart diseases and 15% are contributed to underlying cardiomyopathies. We present you a clinical case of ventricular tachycardia in young athlete who is suspected to have non-compaction cardiomyopathy, and long term management options including ICD and new approaches as AI monitoring devices.

A 32-year-old male, an active athlete, experienced fainting, nausea and vomiting during 21km marathon. He had a brief loss of consciousness and visual disturbances. Initial ECG demonstrated ventricular tachycardia, which was pharmacologically converted to sinus rhythm. Due to elevated troponin I levels, coronary angiography was performed which demonstrated normal finding. The patient was referred to a tertiary care center for further evaluation. Upon admission, ECG revealed sinus rhythm with signs of LVH with a heart rate of 61 bpm. Holter monitoring over 94 and coronary stress test revealed no significant pathology. Echocardiography demonstrated interventricular septum thickness of 13mm, preserved left ventricular function with zones of hypokinesia, and marked trabeculation of both ventricles that raised suspicion for non-compacted cardiomyopathy. Implantation of an ICD was indicated but declined by the patient. He was started on beta-blocker therapy and scheduled for cardiac MRI. Long-term follow-up was advised, including continuous cardiac rhythm monitoring using artificial intelligence and smart devices.

Outcomes of out-of-hospital resuscitation for episodes of cardiac arrest are generally poor (about 3-10% survive in most studies), and those people who survive a first episode of a life-threatening ventricular arrhythmia are at high risk of further episodes. Mainstay of treatment of VT implantation of ICD, but our patient refused so different approach method is mandatory, and discussed further in our report.

Key words: Ventricular Tachycardia, Sudden Cardiac Death, ICD, Smart Device

LET'S REVIEW HOW TO PERFORM CPR AND SAVE A LIFE DURING CARDIAC ARREST

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Introduction Cardiac arrest is a life-threatening emergency in which the heart suddenly stops beating, leading to a cessation of blood flow to the brain and other vital organs. Immediate response with cardiopulmonary resuscitation (CPR) can significantly increase the chances of survival. However, even trained individuals may struggle to recall and correctly perform the necessary steps under pressure. Therefore, reinforcing the knowledge and skills related to CPR and the use of an automated external defibrillator (AED) is crucial for improving outcomes in emergency situations.

Purpose The purpose of this review is to reinforce essential CPR techniques by focusing on key steps: assessing a collapsed victim, performing effective chest compressions and rescue breaths, utilizing an AED correctly. This information aims to enhance the confidence and competence of responders in delivering high-quality CPR during cardiac emergencies.

Methods Firstly, very important point is to check the scene for safety and approach safely. Then the rescuer should check for response and if there is not, shout for help. Next step is opening the airway. Tilt the patient`s head back by pushing down on the forehead. Place the tips of your second and third fingers under the chin and pull up on the mandible. This lifts the tongue away from the posterior pharynx and improves airway patency. To check for breathing for 10 seconds place your ear near their mouth and nose to look at their chest, listen for breath sounds, and feel for breath on your cheek, Do this for no more than 10 second. Remember that agonal gasping is not normal breathing, and if the person is unresponsive and not breathing normally, you must call for emergency help and begin CPR immediately. To begin CPR, place the heel of your hand in the center of the person`s chest, on the lower half of the sternum. Stack your other hand on top, interlock your fingers, and ensure your shoulders are directly over your hands with straight arms before you start compressions pressing down 4-5 centimetres at a rate of 100-120 per minute. After 30 compressions, give 2 rescue breaths, pinch the nose, take a normal breath, place lips over mouth, blow until the chest rises, take about 1-2 seconds, allow chest to fall and repeat once again. You should continue performing CPR until there are obvious signs of life, until a healthcare professional arrives to take over, or an automated external defibrillator is brought. Turn the ARD on and apply the self-adhesive pads to the patient`s bare chest, following the voice prompts. The AED will analyze the heart rhythm and, if needed, instruct you to press the flashing button to deliver a shock. After a shock or analysis, you will be prompted to re-start chest compressions (CPR). Continue to follow the AED voice prompts and perform CPR until emergency medical services arrive.

Conclusions Effective cardiopulmonary resuscitation (CPR) is essential in improving survival outcomes during cardiac arrest. Proper assessment of the scene and victim, accurate performing of chest compressions and rescue breaths, and the correct use of an automated external defibrillator (AED) are all critical components of high-quality CPR. By understanding and practicing these steps, the chances of saving a life until professional medical help arrives can significantly increase.

CARDIAC DEATH IN THE BALKAN AREA

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Update on Myocarditis Diagnostic Criteria

An international panel of cardiovascular pathologists representing the Society for Cardiovascular Pathology (SCVP) and the Association for European Cardiovascular Pathology (AECVP) developed a new classification system of lymphocytic myocarditis, which was completed at a final meeting in the Seaport area of Boston in 2025. Lymphocytic myocarditis, characterized by lymphocyte-predominant myocardial inflammation with associated myocyte injury, is a term based on histopathological criteria dating back several decades when detected during endomyocardial biopsy. To date however, non-biopsy specimens such as surgical resections and autopsy samples have not been included in other published myocarditis criteria including so-called Dallas Criteria established in 1987 which were proposed for the histopathologic diagnosis of lymphocytic myocarditis on endomyocardial biopsy specimens (1). The new draft criteria were presented at a meeting of the SCVP in 2024 in Baltimore and then reworked. The Seaport Criteria were finalized at a SCVP meeting in March 2025 at the Seaport in Boston and published recently (2). A companion paper on the criteria for biopsy specimens was also published (3, 4).

The objective of this presentation will be to familiarize (forensic) pathologists with the Seaport diagnostic criteria for autopsy practice for which a minimum of six full-thickness sections of ventricular myocardium should be evaluated histologically. Lymphocytic myocarditis is defined as myocardial lymphocyte-predominate inflammation with myocyte injury that is not explained by another cause (e.g., ischemia, trauma, foreign body, amyloid, etc.). In addition to the diagnosis, extent should also be described as focal, multifocal or diffuse. Focal is to be used when a single focus of lymphocytic myocarditis is identified that does not involve ≥50% of the area of myocardium on the examined tissue section. Multifocal is to be used when two or more non-contiguous foci are identified (on a single tissue section or across multiple tissue sections), but the areas collectively involve <50% area of the examined tissue section. Diffuse is to be used when ≥50% of the area of a single tissue section is involved by active lymphocytic myocarditis. Discussions of myocyte injury, lymphocytic inflammation of uncertain significance (LIUS), and the use of immunohistochemistry and molecular studies will also be discussed during this presentation.

It is important to note that the histopathological diagnosis of myocarditis using these criteria does not correspond to determining the cause of death (5, 6) as each case must be evaluated in the context of the scene investigation and macroscopical and laboratory findings.

GENETIC CAUSES OF CARDIOMYOPATHIES: EXPERIENCE OF THE CLINICAL INSTITUTE OF GENOMIC MEDICINE, LJUBLJANA

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Advances in molecular technology have improved our understanding of the hereditary causes of cardiomyopathies. We investigated the molecular pathology of cardiomyopathies in patients, who underwent genetic testing at the Clinical Institute of Genomic Medicine, UMC Ljubljana, Slovenia, using next-generation sequencing techniques. We investigated: (1) the proportion of probands for whom a molecular cause was identified by exome sequencing; (2) the proportion of variants for which the classification changed significantly over time; (3) the yield of genome sequencing in individuals with previously negative exome results; and (4) the presence of founder variants. The study included a total of 567 individuals. A molecular diagnosis was established for 28.8% (145 out of 503) of probands who underwent whole exome sequencing (WES). The classification of eight variants (2.6%) changed clinically significantly, affecting the management of 24 (4.2%) individuals. Whole genome sequencing (WGS) was performed on 25 probands, establishing a diagnosis in one (4%) proband. Four recurrently identified variants (FHOD3:c.1646+2T>C, DSP:c.3793G>T, TTN:c.12478del, and MYBPC3:c.913_914del) are likely founder variants. This study is the first to describe the molecular pathology of cardiomyopathies in the Slovenian population. The results facilitate comparison of molecular pathology with other global populations, enabling more accurate classification of variants, improved diagnostic yield of genetic testing and, consequently, better management of patients with hereditary cardiomyopathies.

OBESITY CARDIOMYOPATHY IN SUDDEN CARDIAC DEATH: A DISTINCT ENTITY? A COMPARATIVE STUDY.

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Background

Obesity cardiomyopathy (OCM) can be associated with sudden cardiac death (SCD) but its pathologic features are not well described.

Objective

The objective of this study is to characterise the clinical and pathological features of OCM associated with SCD.

Methods

This was a retrospective case control autopsy study. OCM was identified by an increased heart weight (>550g in males; >450g in females) in individuals with obesity (BMI≥30) in the absence of other causes. Cases of OCM with SCD were compared to sex and age matched SCD controls with obesity or with normal weight (18.5≥BMI≤24.9) and morphologically normal hearts. Autopsy measures included: heart weight, atrial dimensions, ventricular wall thickness and epicardial adipose tissue.

Results

Of 6457 SCD cases, 53 cases of OCM were identified and matched to 106 controls with obesity and 106 normal weight controls. The mean age at death of individuals with OCM was 42±12 with a male predominance (n=34, 64%). Males died younger than females (40±13 vs 45±10, p=0.036). BMI was increased in OCM cases compared to controls with obesity (42±8 vs 35±5). The average heart weight was 598±93g in OCM. There were increases in right and left ventricular wall thickness (all $p<0.05$) in OCM cases compared to controls. Right ventricular epicardial fat was increased in OCM compared to normal weight controls only. Left ventricular fibrosis was identified in 7 (13%) cases.

Conclusions

OCM may be a specific pathological entity associated with sudden cardiac death. It is most commonly seen in young males with increased BMI.

RECOMMENDATIONS FOR SCREENING IN ATHLETES FOR ASSESSMENT OF CARDIOVASCULARC RISK AND SUDDEN CARDIAC DEATH

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Introduction:The latest evidence demonstrates that electrocardiogram (ECG) screening in young athletes increases the detection of conditions associated with sudden cardiac death (SCD) compared to history and physical examination alone, but the impact on overall SCD incidence and cost-effectiveness remains debated, especially between United States and European guidelines.The American Heart Association and American College of Cardiology recommend preparticipation screening with physical examination , reserving ECG for select cases with suspicious findings, citing concerns about false positives, downstream costs, and limited evidence for mortality reduction in large-scale US populations Meta-analyses and real-world studies confirm that ECG screening is significantly more sensitive for detecting SCD-associated conditions (odds ratio for detection with ECG vs physical examination alone: 5–60), but also increases false positives, leading to unnecessary secondary testing and potential psychological or financial harm.Cost analyses in US collegiate athletes show that adding ECG improves cost per diagnosis (from $312,407 to $61,712 per case detected), but the absolute event rate of SCD remains extremely low, and no mortality benefit has been conclusively demonstrated in US cohorts. In contrast, the European Society of Cardiology recommends universal ECG screening for competitive athletes under 35, based on Italian data showing a reduction in SCD incidence after implementation of mandatory ECG-based screening.However, these results may not generalize to other populations due to differences in disease prevalence, healthcare infrastructure, and resource allocation. In summary, ECG screening is more effective than physical examination alone for detecting SCD risk conditions in young athletes, but its cost-benefit and impact on SCD rates remain uncertain in the US context. The American Heart Association and American College of Cardiology do not recommend universal ECG screening, while the European Society of Cardiology supports it for all competitive athletes under 35.

DAILY LIFE TRIGGERS OF SUDDEN CARDIAC DEATH

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Sudden cardiac death (SCD) refers to an unexpected death from a cardiovascular cause and, in at least 25% of cases, SCD is the first symptomatic cardiac event. By accounting for approximately 50% of cardiovascular and 20% of all natural deaths, SCD is a major public health problem. While SCD in persons under the age of 35 is predominantly caused by structural cardiac disease, often with an underlying genetic basis, SCD in older adults is mostly a consequence of coronary artery disease.

Similar to acute myocardial infarction, the occurrence of SCD is occasionally associated with certain triggers exposure to daily life activities and circumstances such as physical exertion, psycho-emotional life events, or psychoactive substances intake.

Ranking of the identified triggers reveals a risk increase from highest to lowest for physical exertion, recent cocaine use, episodic alcohol consumption, recent amphetamine use, coffee consumption, psycho-emotional stress, influenza infection, and recent cannabis use. Another concern is the contribution of minor injuries in causing sudden cardiac death. Many times, in Courts we are called upon to explain the relation of a fight in causing SCD of one of the persons involved.

Since such events are potentially preventable, this information is of the utmost importance for patients having any uncertainty about their cardiac disease. In those patients, an attempt to avoid daily life triggers may significantly reduce the risk of SCD until appropriate treatment is performed. Finally, ensuring the availability of automated external defibrillators (AEDs) and trained personnel in public areas (for instance in stadiums) represents a critical intervention to improve survival in cases of sudden cardiac arrest.

STRESS RELATED CARDIOMYOPATHY

Tomaž Zupanc

Background
Stress cardiomyopathy, or Takotsubo syndrome, is an acute and reversible form of heart failure that accounts for 1–2% of patients presenting with suspected acute coronary syndrome. It is characterized by transient left ventricular systolic dysfunction and distinctive wall motion abnormalities, most often in postmenopausal women (>90% of cases).

Methods
We reviewed current literature on epidemiology, pathophysiology, and clinical outcomes of stress cardiomyopathy, with particular attention to data emerging during the COVID-19 pandemic.

Results
Excessive sympathetic activation and catecholamine surges are central to the pathogenesis, driving microvascular dysfunction, oxidative stress, and cytokine-mediated injury. During the COVID-19 pandemic, observational studies demonstrated a two- to four-fold increase in incidence, implicating systemic inflammation, cytokine storm, and psychosocial stressors. Chronic stress and hypothalamic–pituitary–adrenal axis dysregulation further heighten vulnerability. Clinically, patients often mimic acute myocardial infarction with chest pain, ECG changes, and biomarker elevation, necessitating coronary angiography to exclude obstructive disease. Although most recover, adverse events occur in 20–25% of cases, with in-hospital mortality rates of 4–5%. Complications include arrhythmias, cardiogenic shock, left ventricular thrombus, and long-term recurrence in 5–10% of patients.

Conclusion
Stress cardiomyopathy is not a benign condition, despite its reversible nature. Its rising incidence during the COVID-19 era underscores the need to integrate clinical vigilance with mechanistic research. Future priorities include elucidating molecular pathways linking neurohormonal activation to myocardial dysfunction, refining biomarkers for risk stratification, and developing strategies to reduce recurrence and improve outcomes.

THE MANAGEMENT OF SUDDEN CARDIAC DEATH IN SERBIA: A GENETICIST`S PERSPECTIVE

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Sudden cardiac death (SCD) is a leading cause of mortality worldwide. In young individuals, SCD most often results from inherited channelopathies or cardiomyopathies. The genetic basis of SCD can range from monogenic forms, typically caused by rare variants with large effect sizes and Mendelian inheritance, to complex forms, where common variants with smaller effect sizes may influence disease penetrance and expressivity by modifying the impact of rare variants, or interact with non-genetic risk factors in the absence of a major genetic defect.

Assessment and management of families affected by SCD largely depend on the age of the deceased and the results of a comprehensive autopsy. This includes macroscopic and microscopic cardiac examination as well as the exclusion of non-cardiac causes such as intoxication or systemic disease. In cases with negative autopsy findings, or those suggesting cardiomyopathy—particularly in the young—a molecular autopsy should be pursued to identify potential genetic causes.

Simultaneously, first-degree relatives of the deceased should undergo clinical and electrophysiological evaluation. These assessments can help narrow the pool of candidate genes and increase the likelihood of reaching a definitive diagnosis. Identification of a pathogenic variant not only enables disease-specific treatment and surveillance for affected relatives but also allows unaffected family members to be released from unnecessary monitoring.

When no clear pathogenic variant is identified, attention should shift to polygenic contributions, incorporating common variants identified through GWAS into a polygenic risk score. If genetic testing reveals variants of uncertain significance (VUS), such findings should be considered uninformative. Families with VUS require continued follow-up, and reclassification of these variants should be pursued as new evidence emerges.

A CHALLENGING CASE REPORT OF FEMALE NEWBORN WITH D-TGA, DAP, PFO WITH CONSECUTIVE L-D SHANT AND TRIVIAL PULMONARY REGURGITATION

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Introduction: Dextro-transposition of the great arteries (D-TGA) represents, second most common cyanotic heart disease, accounting for 5-7% of all congenital heart defects, characterized by ventriculoarterial (VA) connection discordance, atrioventricular (AV) concordance, and a parallel relationship with D-TGA. As a result, the pulmonary and systemic circulations are separated [the morphological right ventricle (RV) is connected to the aorta and the morphological left ventricle (LV) is connected to the pulmonary artery].

Case Presentation: A one-day-old female baby was admit to the Department of Pediatric Cardiac Surgery at "Acibadem Sistina" Clinical Hospital in Skopje, via neonatologist with chief medical concerns of desaturation followed by cyanosis. An urgent indication for imaging diagnostics and laboratory exams were ordinated. CVC and NGT were insert by initial clinical exam. ECHO of the heart showed Situs solitus. The aorta arising from the right ventricle, pulmonary artery from left ventricle, basis of the great vessels are being Trans positioned, the rest of the coronary vascular system, without any pathologies and without pericardial effusion. Prior to surgical intervention an interventional catheterization was done – Rashkind method (balloon atrial septostomy). Later on, the arterial switch operation (ASO), also known as the Jatene procedure, was indicated as a surgical technique. The ASO involves switching the positions of the aorta and pulmonary artery and re-implanting the coronary arteries into the newly formed aorta.

Conclusion: The typical concomitant cardiac anomalies that may occur in patients with D-TGA include ventriculoseptal defects, (VSD's), Patent Ductus Arteriosus (PDA), left ventricular outflow tract obstruction (LVOTO), mitral and tricuspid valve abnormalities, and coronary artery variations. Cardiac surgical correction of the defect during infancy is the preferred treatment for D-TGA (especially in the first two weeks). Balloon atrial septostomy (BAS) is necessary prior to the surgical treatment, hence is indicated in patients with severe cyanosis and sPO_2 <60%.

Keywords: D-TGA, pFAP, L-D shant, female infant, cardiac surgery, pediatric surgery, catheterization, management

TITIN CARDIOMYOPATHY AND A RECURRENT *TTN* VARIANT IN THE I BAND: INSIGHTS FROM THE CLINICAL INSTITUTE FOR GENOMIC MEDICINE LJUBLJANA

Karin Writzl, Nina Vodnjov, Aleš Maver, Andraž Cerar, Borut Peterlin

TTN truncating variants (*TTN*tv) are the most frequent genetic cause of dilated cardiomyopathy (DCM), identified in ~15–20% of unselected DCM probands in large cohorts. Interpretation of *TTN*tv pathogenicity depends on their sarcomeric location and isoform expression: *TTN*tv in constitutively expressed A-band exons are classified as likely pathogenic/pathogenic (LP/P) (Morales et al., 2020), whereas variants outside this region are often considered variants of uncertain significance (VUS).

In Slovenia, genetic testing of 211 probands with DCM identified pathogenic or likely pathogenic variants in 27.1%. *TTN*tv accounted for 73.3% of genotype-positive probands, nearly twice the proportion reported in international cohorts (~30–40%). This excess was partly explained by a recurrent *TTN*:c.12478del, a frameshift variant in the proximal I-band (N2Bus). This variant was the most frequent, detected in 11.6% of *TTN*-positive probands. Phenotypic consistency, segregation analysis, and haplotype sharing supported its pathogenicity, and suggested a founder effect, providing strong evidence that I-band *TTN*tv can be classified as LP (Vodnjov et al., 2025).

Subsequent large family-based studies supported that *TTN*tv in I-band exons with high percent spliced-in (PSI) scores can be pathogenic and confer similar penetrance to A-band TTNtv (Johnson et al., 2025), further validating this interpretation.

The contribution of *TTN* variants to sudden cardiac death (SCD) remains poorly defined .The most recent countywide autopsy study reported *TTN* variants in ~15% of arrhythmic deaths, about 1.5-fold more frequent than in non-arrhythmic deaths. Most were missense, while rare *TTN*tv were identified in the Z-disk, I-band and M-band, but none in the A-band. Given that nearly all variants were classified as VUS, the clinical significance of *TTN* variants in SCD remains uncertain (Yee et al., JACC EP 2025).

THE ROLE OF IMAGING IN SUDDEN CARDIAC DEATH

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Introduction: Sudden cardiac death (SCD) - an unexpected natural death within ~1 hour of symptom onset - remains a leading cause of mortality, most commonly due to coronary artery disease and acute myocardial ischemia. Determining precise cause and mechanism is critical for clinical, forensic, and medico-legal contexts.

Objective: To summarize contemporary postmortem imaging (PMI) approaches for investigating SCD and highlight their diagnostic yield, limitations, and future directions.

Content: Conventional autopsy is the diagnostic gold standard but may miss focal or vascular lesions without extensive dissection. PMI complements autopsy with: postmortem CT (PMCT) for skeletal findings, gas, calcifications, hemothorax/hemopericardium, and aortic pathology; multiphase postmortem CT angiography (PMCTA) for coronary stenosis/occlusion and vascular leaks; (iii) postmortem MRI (PMMR) for superior soft-tissue contrast, myocardial edema/necrosis, and targeted histologic sampling; and (iv) targeted coronary catheter techniques and PMI-guided tissue/fluids/gas sampling. Case material illustrates combined PMCT/PMCTA detection of coronary lesions with concordant autopsy findings, and recognition of confounders such as resuscitation artifacts and postmortem changes. Key interpretive challenges include differentiating antemortem injury from postmortem artifact, dependency on postmortem interval, and requisite specialized training.

Conclusion: A multimodal PM imaging strategy - tailored to case needs and integrated with autopsy and histology - improves diagnostic accuracy in SCD investigations. Emerging photon-counting CT and AI-assisted analysis may further enhance coronary assessment and soft-tissue characterization, while cost-effective, targeted protocols broaden accessibility. Careful method selection and artifact awareness are essential to avoid diagnostic error and medico-legal pitfalls.

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