

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Negative Autopsy in Infant and Juvenile Population: Role of Cardiac Arrhythmias

Georgia Sarquella-Brugada, Sergi Cesar,
Anna Fernandez-Falgueras,
Maria Dolores Zambrano, Anna Iglesias,
Josep Brugada, Ramon Brugada and
Oscar Campuzano

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.71042>

Abstract

Negative autopsy is a post-mortem examination in which a comprehensive analysis does not provide a cause of death. These include situation of death, anatomical and histological analysis, toxicology and microbiological study. A low part of autopsies remain without a conclusive cause of death, but all these cases are usually seen in young population, apparently healthy who died suddenly and unexpectedly. In these situations a cardiac arrhythmia is suspected as cause of death and genetic testing is recommended despite not regularly performed. Sudden death is a natural and unexpected decease that occurs in apparently healthy people, or whose disease was not severe enough to expect a fatal outcome. It can be due to several pathologies, usually of cardiac cause and called sudden cardiac death. In infants and young people, both long QT syndrome and catecholaminergic polymorphic ventricular tachycardia are main causes in negative autopsies. These genetic diseases lead to ventricular fibrillation, syncope and sudden cardiac death in a normal heart. Unfortunately, sudden cardiac death could be the first manifestation of the diseases, being early identification and prevention a crucial point in current medical practice. This chapter focuses on sudden death and negative autopsy in young population, mainly due to cardiac arrhythmias.

Keywords: sudden cardiac death, negative autopsy, arrhythmia, long QT syndrome, genetics

1. Introduction

An autopsy is a post-mortem examination of a deceased person in order to unravel the cause and time of death. In 5% of all cases, the autopsy may be classified as negative, concerning that no conclusive cause of death is identified after comprehensive analysis of all data recompiled. These data included gross and microscopically examination, and laboratory investigations [1]. Hence, unexplained death or "*mors sine materia*" is defined as "*the death that remains unsolved after a thorough autopsy, of an individual without previous cardiac history and who has been seen alive within the previous 12 hours of the death*" [2]. In these situations, cardiac death due to electric disorders without heart structural alterations could be considered the most common origin of the death [3]. Most part of these SD occurs in infants -sudden infant death syndrome (SIDS)-, and young population [4]. The two main disease associated with cardiac arrhythmias are long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). Both arrhythmias are of genetic origin and characterized with typical parameters in the electrocardiogram (ECG). For this reason, preventive medicine recommends to perform an ECG in all infants and young population (at least one ECG before 14 years old) in order to identify ECG alterations and, if positive, adopt preventive therapeutic measures to avoid a malignant arrhythmia. Unfortunately, the first manifestation of one cardiac arrhythmia may be the SCD, without previous symptoms.

Genetic analysis in post-mortem patients (also called molecular autopsy) may identify the genetic alteration responsible for an arrhythmogenic cardiac disease [5]. Current guidelines recommend performing the molecular autopsy in all these cases as a part of the comprehensive medico-legal investigation in SCD cases [6] but post-mortem genetic testing of the proband was reported in a low percentage of SCD cases with no structural alterations patients [7–9], mainly because forensic centers do not have the economic resources to perform genetic testing or do not collect samples due to currently legal restrictions involved with the sampling and storage of DNA [10]. Use of next generation sequencing technology (NGS) allows a comprehensive genetic analysis of all genes associated with SCD and cardiac arrhythmias, in a reduced time and in a cost-effective way, solving the economic problem. Due to genetic origin, family members could be also affected by the disease and at risk of SCD, despite asymptomatic. Therefore, both clinical and genetic analysis should be performed in all relatives, and interviewing family members may reveal helpful information not discovered in the initial research. It has been recommended that all relatives of unexplained SD victims undergo evaluation by a multidisciplinary team of cardiologists, forensic pathologists and geneticists [7] because of the investigation of an unexplained SD is extremely complicated in the families of the victims, mainly when the victim is a child (SIDS) [11, 12].

2. Inherited arrhythmias

Nowadays, nearly 85% of all SD are of cardiac origin (SCD) being responsible for around 30–200/100.000 yearly [13]. In population major 50 years old, around 80% of SCD cases are

consequence of coronary disease [14], but in the younger population (less than 35 years) the cause is mainly due to inherited arrhythmias of genetic origin [15]. This last collection of diseases can be classified into two main groups [16]:

2.1. Cardiomyopathies

Arrhythmia is induced by structural abnormalities. These anatomical modifications are caused by alterations in genes encoding three types of proteins: sarcomeric which mainly cause hypertrophic cardiomyopathy (HCM); cytoskeletal, which mainly cause dilated cardiomyopathy (DCM), and desmosomal alterations, which mainly cause arrhythmogenic cardiomyopathy (ACM) [17]. These diseases imply a structural alteration of the heart, usually identified during an autopsy examination. In early stages of the disease, the alteration may be only identified using microscopic analysis but not at gross level. Curiously, both in SIDS and young people died suddenly, recent studies identified genetic alteration associated with any of these diseases but without any cardiac alteration, neither macroscopic nor microscopic. It could be explained because of the first structural alterations induced by the disease occurs at ultramicroscopic level (identified using only electronic microscopic). The electrical disturbance prior to malignant arrhythmia could be induced by these ultra-structural alterations. Hence, negative autopsy of infant and young population carrying alterations in genes encoding cardiomyopathies should not be discarding without a comprehensive analysis [18].

2.2. Channelopathies

Arrhythmogenic substrate is found in the electrical properties of the heart because genetic alterations occur in genes encoding for ion channels, their subunits or associated proteins playing a key role in the function of the channel. Ion channel diseases are not accompanied by structural cardiac defects and their first manifestation is a malignant arrhythmia or even SCD [19]. Cardiac channelopathies may be clinically identified only by the presence of some characteristic ECG abnormalities [20]. However, incomplete penetrance and variable expressivity in inherited arrhythmogenic disorders imply that the distinctive ECG patterns that characterize these disorders may be masked. When a SD occurs in a healthy young individual with no previous symptoms of any disease, arrhythmia is suspected as explanation of the disease but only identification of a genetic alteration may help us to identify the cause of the arrhythmia, and therefore, the cause of the death. Nowadays, hundreds of pathogenic variants have been identified in more than 40 genes, affecting sodium, potassium or calcium ion currents and depending on which ion channel is affected, different syndromes will be present [21]. Nevertheless, the same syndrome may show a certain degree of overlap if different types of channel can be affected. However, knowledge is not limited to the familial form, as it opens up new hypotheses as to how the gene interacts with the environment, drugs, and damaged muscle, and how arrhythmias arise in acquired or non-inherited forms [22]. This group includes LQTS, CPVT but also Brugada syndrome (BrS), and short QT syndrome (SQTS), among others [23]. In this chapter we will focus mainly in these diseases because of negative autopsy implies no cardiac abnormalities identified during post-mortem examination.

3. Long QT syndrome

This lethal entity is characterized for a prolongation of the QT interval (QTc>460 ms women and >450 ms men). The clinical presentation can be variable, ranging from asymptomatic patients to syncope and even SCD, mainly due to ventricular tachyarrhythmias (*torsade de pointes*) in the setting of a structurally normal heart. The spectrum of ECG abnormalities inducing electrical instability includes notched or biphasic T waves and T wave alternant. The prevalence is estimated in 1 of 2500 individuals [24, 25] being one of the leading causes of SCD among infants and young population. In recent years, massive ECG screening in young population has been performed with success of lowering rates of SD among infants and athletes [26]. In all patients, beta-blocker administration at high doses is highly recommended because it decreases the risk of SCD although do not provide full protection. The dose is adjusted according to the medical tolerance to these drugs (www.torsades.org). Implantable cardioverter-defibrillator (ICD) implantation is mandatory for those patients having had an aborted SCD and for those at risk of fatal arrhythmias [27]. LQTS can be acquired (associated with drugs and electrolyte imbalance such as hypokalemia, hypocalcaemia and hypomagnesaemia) or congenital (associated with pathogenic alterations in ion channels and/or associated proteins). Currently, more than 1000 genetic alterations have been identified in 20 genes (*AKAP9*, *ANK2*, *CACNA1C*, *CALM1*, *CALM2*, *CALM3*, *CAV3*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNJ5*, *KCNQ1*, *RYR2*, *SCN1B*, *SCN4B*, *SCN5A*, *SNTA1*, *TRDN* and *TRPM4*). All these genes together are responsible for 80–85% of all LQT cases [28] (**Figure 1**). Major genes associated with LQTS are *KCNQ1* –type 1- (30–35%), *KCNH2* –type 2- (25–30%) and *SCN5A* type 3- (5–10%) which are responsible for 65–75% of all LQTS cases [29]. A negative autopsy of a young case died suddenly (usually during exercise but also at rest) (**Figure 2**) could be caused by this arrhythmogenic entity.

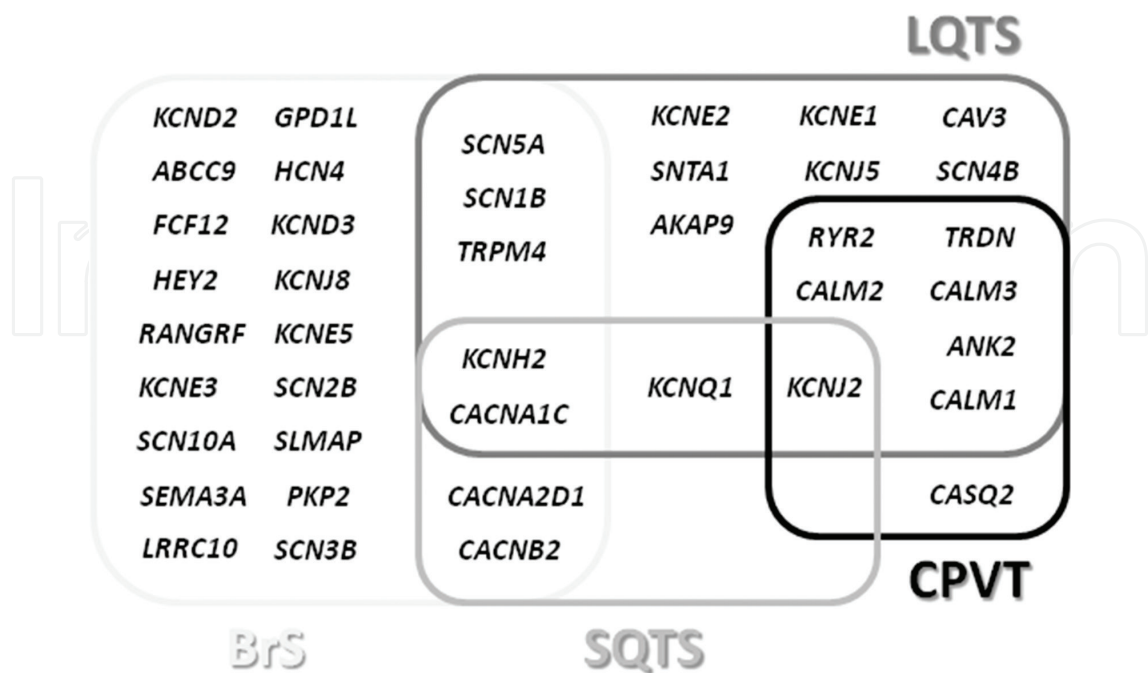


Figure 1. All genes associated with cardiac channelopathies. LQTS, long QT syndrome. BrS, Brugada syndrome. SQTs, short QT syndrome. CPVT, catecholaminergic polymorphic ventricular tachycardia.

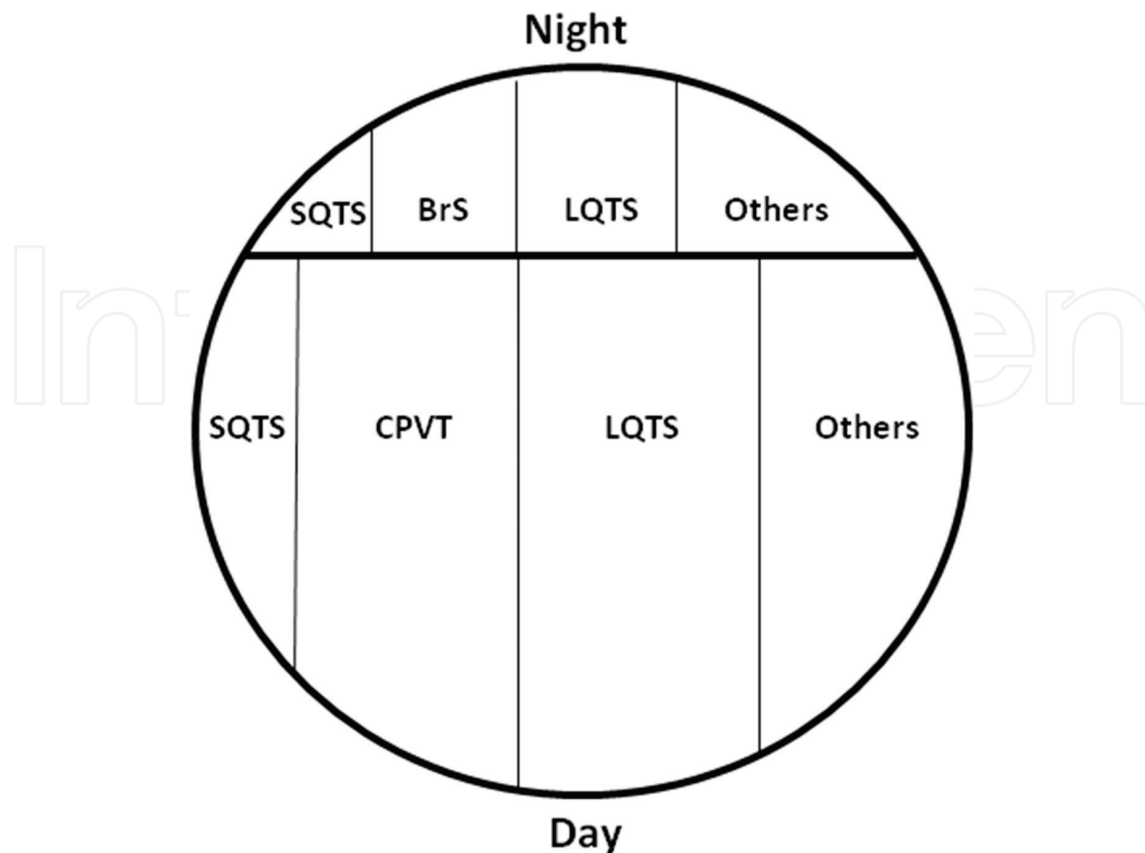


Figure 2. Distribution of arrhythmogenic diseases in negative autopsies. Most of deaths in young population before 16 years old occur during day. Adrenergic situations are the triggers of the arrhythmia during daily activities (exercise, emotion). The main diseases responsible for these sudden deaths are long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). A less proportion of deaths occur during night, meanly in infants before 2–3 years old. At rest, the main diseases associated with sudden death are LQTS and Brugada syndrome (BrS).

4. Catecholaminergic polymorphic ventricular tachycardia

This entity is an inherited disorder with a normal ECG at rest (occasionally with bradycardia, and U waves), and triggered exclusively by adrenergic stimulus (mainly exertion, extreme stress or emotion). It is characterized in the ECG by a 2-way polymorphic ventricular tachycardia in structural normal hearts [30]. It occurs mainly in children and adolescents and is increasingly recognized as a cause of unexplained SCD in young individuals, predominately in young males (30% by the age of 40 years) [31]. It was thought that the event happened in childhood (before age 10) with a high mortality rate [32]. Diagnosing CPVT can be difficult especially in young children. The first line of therapy is beta-blockers but ICDs are indicated for patients with aborted SCD or CPVT during exercise and in adolescents with incompletely controlled CPVT despite a high dose of medications [33]. Nowadays, more than 200 pathogenic alterations have been reported in 8 genes (*ANK2*, *CALM1*, *CALM2*, *CALM3*, *CASQ2*, *KCNJ2*, *RyR2* and *TRDN*) (**Figure 1**) and a comprehensive genetic analysis explains around 60% of CPVT cases. The main gene associated with CPVT is *RyR2*, being responsible of nearly 50% of all cases [34]. The ryanodine receptor is an intracellular calcium channel that is located in the sarcoplasmatic reticulum and activated by the influx of small amounts

of calcium, thereby allowing the outflow of stored calcium, being crucial in triggering heart muscle contraction. A negative autopsy of a young case died suddenly during exercise could be caused by this arrhythmogenic entity (**Figure 2**).

5. Brugada syndrome

This inherited disease was identified in 1992 by Pedro and Josep Brugada [35]. It is characterized by an ECG pattern consisting of coved-type ST-segment elevation in atypical right-bundle branch block in leads V1 to V3 (often referred to as type-1 Brugada ECG pattern), and an increased risk for SCD resulting from episodes of polymorphic ventricular tachyarrhythmias. The ECG pattern can be baseline or intermittent, and it can be unmasked during a drug test (class IC sodium channel-blockers). The prevalence of the disease is 4–12% of all SCD causes. The penetrance and expressivity of the disorder are highly variable, although it is considered a disorder involving mainly young male adults (about 40 years old), and SCD typically occurring during sleep. Patients with BrS usually remain asymptomatic and modulating factors such as fever, exercise or drugs (www.brugadadrugs.org), may play a major role in the dynamic nature of the ECG. After surviving a cardiac arrest or the occurrence of syncope, the only treatment having any proven effect on the prevention of sudden death is the implantable cardioverter-defibrillator (ICD) [36]. However, ICD implantation in symptomatic is not free from controversy, especially in children [37]. The first genetic alteration was identified in 1998 [38]. Nowadays, 24 genes have been associated to the disease (*ABCC9*, *CACNA1C*, *CACNA2D1*, *CACNB2b*, *GPD1-L*, *HCN4*, *HEY2*, *KCND2*, *KCND3*, *KCNE3*, *KCNE5*, *KCNH2*, *KCNJ8*, *LRRC10*, *PKP2*, *RANGRF*, *SCN10A*, *SCN1B*, *SCN2B*, *SCN3B*, *SCN5A*, *SEMA3A*, *SLMAP* and *TRPM4*) (**Figure 1**) but a comprehensive genetic analysis only identify the genetic alteration in a 35% of cases. Approximately 30% of patients with BrS carry a loss of function genetic alteration in *SCN5A* (BrS type 1) [37]. This gene is responsible for the phase 0 of the cardiac action potential, a key player in the cardiac electrical activity. Hence, current guidelines only recommend genetic analysis of this gene [29]. A negative autopsy of a young case died during night could be caused by this arrhythmogenic entity (**Figure 2**).

6. Short QT syndrome

This arrhythmogenic disease was reported in 2000 [39]. It is a rare and highly lethal arrhythmic disease entity characterized by a short QT interval in ECG (<330 ms), with a high sharp T wave and a short interval between the peak and the end of the T wave, leading some clinical manifestations from lack of symptoms to syncope, and even SCD. Clinical manifestations may appear in infants and young population, being considered one of the main causes SIDS [40]. Nowadays there is no pharmacological therapy of proven efficacy to prevent arrhythmias and the implant of an ICD is the only alternative for high-risk cases. Nowadays, few pathogenic alterations have been identified in 6 different genes encoding potassium and calcium ion channels (*KCNQ1*, *KCNJ2*, *KCNH2*, *CACNA1C*, *CACNB2* and *CACNA2D1*)

(**Figure 1**), following an autosomal dominant pattern of inheritance [41]. It should be a high penetrance and a comprehensive genetic analysis identifies the genetic alteration in nearly 60% of clinically diagnosed cases. A negative autopsy of an infant case (less than 2 years) died suddenly could be caused by this arrhythmogenic entity (**Figure 2**).

7. Next generation sequencing

The genetic revolution was initiated 20 years ago, firstly with the knowledge of the human genome and in last 10 years with the advances in genetic technology that have permitted the development of massively parallel sequencing (also called next generation sequencing). Hence, current NGS technologies allow a massive sequencing of genes, even whole exome and genomes. The advance is the reduced time and the cost-effective way in comparison to traditional Sanger sequencing. Traditional Sanger sequencing has high fidelity but is slow and quite expensive compared with next generation methods. However, Sanger remains as a gold standard in validation of alterations as well as family segregation. In recent 5 years, NGS technology has been implemented in forensic area, allowing a comprehensive post-mortem genetic analysis. Hence, molecular autopsy using NGS has identified the cause of the death in a large part of cases with a no conclusive cause of death after comprehensive autopsy protocol without genetic analysis [42]. Current guidelines recommend use of molecular autopsy in young cases classified as negative after an autopsy [29]. The NGS analysis requires a certain DNA quality and quantity; the best approach is obtaining DNA from post-mortem blood, conserved at 4°C. DNA from tissue can be also an option but the conservation should be at -20°C. Currently, DNA from formalin-fixed, paraffin-embedded (FFPE) is not an option due to formalin destroy DNA and no proper amplification is possible for NGS technology. After NGS analysis, the next challenge is the interpretation of data identified. Most part of alterations remains as ambiguous significance and an exhaustive analysis of each variant should be performed before translation into clinical practice [43–45]. This will require sustained collaboration between geneticist, cardiologist and forensics for genetic data interpretation, to optimize cause of death in a negative autopsy but also in family members in order to adopt personalized therapies.

8. Conclusions

In infant and young population, unexpected SD remains as a main problem because usually the first manifestation of the disease is the death. In last 10 years, negative autopsy cases are being progressively more studied in order to identify the cause of death, especially in young population. Cases usually classified without conclusive cause of death have been comprehensively analyzed and resolved. However, molecular autopsy is not performed in all forensic centers and large percentage of cases remains without a cause of death. Use of genetics in forensic area has improved diagnosis of negative autopsies, but also identification of relatives at risk of SCD. Early identification of individuals at risk allows adoption of therapeutic measures in prevention of new lethal episodes in infant and young population.

Acknowledgements/funding

This work was supported by Fundació La Marató TV3 (358/U/2015), Obra Social 'La Caixa', Fundació Daniel Bravo and Fondo Investigación Sanitaria (FIS PI14/01773) from the Instituto de Salud Carlos III (ISCIII). The CIBERCV is an initiative of the ISCIII, Spanish Ministry of Economy and Competitiveness.

Author details

Georgia Sarquella-Brugada¹, Sergi Cesar¹, Anna Fernandez-Falgueras², Maria Dolores Zambrano¹, Anna Iglesias^{2,4}, Josep Brugada^{1,3,4}, Ramon Brugada^{2,4,5,6} and Oscar Campuzano^{2,4,5*}

*Address all correspondence to: oscar@brugada.org

1 Arrhythmia Unit, Hospital Sant Joan de Déu, Barcelona, Spain

2 Cardiovascular Genetics Center, University of Girona-IDIBGI, Girona, Spain

3 Cardiovascular Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain

4 Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain

5 Medical Science Department, School of Medicine, University of Girona, Girona, Spain

6 Cardiology Service, Hospital Josep Trueta, Girona, Spain

References

- [1] Lawler W. The negative coroner's necropsy: A personal approach and consideration of difficulties. *Journal of Clinical Pathology*. 1990;**43**:977-980
- [2] Basso C, Burke M, Fornes P, et al. Guidelines for autopsy investigation of sudden cardiac death. *Virchows Archiv*. 2008;**452**:11-18
- [3] Oliva A, Brugada R, D'Aloja E, et al. State of the art in forensic investigation of sudden cardiac death. *The American Journal of Forensic Medicine and Pathology*. 2011;Mar;**32**(1):1-16
- [4] Tfelt-Hansen J, Winkel BG, Grunnet M, Jespersen T. Cardiac channelopathies and sudden infant death syndrome. *Cardiology*. 2011;**119**:21-33
- [5] Campuzano O, Sanchez-Molero O, Allegue C, et al. Post-mortem genetic analysis in juvenile cases of sudden cardiac death. *Forensic Science International*. 2014;**245C**:30-37

- [6] Wedekind H, Schulze-Bahr E, Debus V, et al. Cardiac arrhythmias and sudden death in infancy: Implication for the medicolegal investigation. *International Journal of Legal Medicine*. 2007;**121**:245-257
- [7] Behr E, Wood DA, Wright M, et al. Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. *Lancet*. 2003;**362**:1457-1459
- [8] Tan HL, Hofman N, van Langen IM, et al. Sudden unexplained death: Heritability and diagnostic yield of cardiological and genetic examination in surviving relatives. *Circulation*. 2005;**112**:207-213
- [9] Behr ER, Dalageorgou C, Christiansen M, et al. Sudden arrhythmic death syndrome: Familial evaluation identifies inheritable heart disease in the majority of families. *European Heart Journal*. 2008;**29**:1670-1680
- [10] Michaud K, Mangin P, Elger BS. Genetic analysis of sudden cardiac death victims: A survey of current forensic autopsy practices. *International Journal of Legal Medicine*. 2011;**125**:359-366
- [11] Klaver EC, Versluijs GM, Wilders R. Cardiac ion channel mutations in the sudden infant death syndrome. *International Journal of Cardiology*. 2011;**152**:162-170
- [12] Dettmeyer RB, Kandolf R. Cardiomyopathies—Misdiagnosed as Sudden Infant Death Syndrome (SIDS). *Forensic Science International*. 2010;**194**(1-3):e21-e24. doi: 10.1016/j.forsciint.2009.10.010
- [13] Podrid PJ, Myerburg RJ. Epidemiology and stratification of risk for sudden cardiac death. *Clinical Cardiology*. 2005;**28**:I3-I11
- [14] Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. *Circulation*. 2012;**125**:1043-1052
- [15] Arzamendi D, Benito B, Tizon-Marcos H, et al. Increase in sudden death from coronary artery disease in young adults. *American Heart Journal*. 2011;**161**:574-580
- [16] Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. *Circulation*. 2012;**125**:620-637
- [17] Oliva A, Grassi VM, Campuzano O, et al. Medico-legal perspectives on sudden cardiac death in young athletes. *International Journal of Legal Medicine*. 2017;**131**:393-409
- [18] Sarquella-Brugada G, Campuzano O, Cesar S, et al. Sudden infant death syndrome caused by cardiac arrhythmias: Only a matter of genes encoding ion channels? *International Journal of Legal Medicine*. 2016;**130**:415-420
- [19] Fernández-Falgueras A, Sarquella-Brugada G, Brugada J, et al. Cardiac channelopathies and sudden death: Recent clinical and genetic advances. *Biology (Basel)*. 2017 Jan 29;**6**(1). pii: E7. doi: 10.3390/biology6010007. Review. PMID: 28146053

- [20] Schimpf R, Veltmann C, Wolpert C, Borggrefe M. Channelopathies: Brugada syndrome, long QT syndrome, short QT syndrome, and CPVT. *Herz*. 2009;**34**:281-288
- [21] Campuzano O, Sarquella-Brugada G, Brugada R, Brugada J. Genetics of channelopathies associated with sudden cardiac death. *Global Cardiology Science & Practice*. 2015;**2015**:39
- [22] Roberts R. The number one cause for sudden cardiac death in the young unravels. *Cardiology*. 2010;**115**:46-48
- [23] Campuzano O, Allegue C, Partemi S, et al. Negative autopsy and sudden cardiac death. *International Journal of Legal Medicine*. 2014;**128**:599-606
- [24] Lupoglazoff JM, Denjoy I, Guicheney P, et al. Congenital long QT syndrome. *Archives de Pédiatrie*. 2001;**8**:525-534
- [25] Moss AJ, Shimizu W, Wilde AA, et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. *Circulation*. 2007;**115**:2481-2489
- [26] Mizusawa Y, Horie M, Wilde AA. Genetic and clinical advances in congenital long QT syndrome. *Circulation Journal*. 2014;**78**:2827-2833
- [27] Behere SP, Shubkin CD, Weindling SN. Recent advances in the understanding and management of long QT syndrome. *Current Opinion in Pediatrics*. 2014;**26**:727-733
- [28] Nakano Y, Shimizu W. Genetics of long-QT syndrome. *Journal of Human Genetics*. 2016;**61**:51-55
- [29] Priori SG, Blomstrom-Lundqvist C. 2015 European Society of Cardiology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. *European Heart Journal*. 2015;**36**:2757-2759
- [30] Refaat MM, Hassanieh S, Scheinman M. Catecholaminergic polymorphic ventricular tachycardia. *Cardiac Electrophysiology Clinics*. 2016;**8**:233-237
- [31] Mohamed U, Napolitano C, Priori SG. Molecular and electrophysiological bases of catecholaminergic polymorphic ventricular tachycardia. *Journal of Cardiovascular Electrophysiology*. 2007;**18**:791-797
- [32] Ylanen K, Poutanen T, Hiippala A, et al. Catecholaminergic polymorphic ventricular tachycardia. *European Journal of Pediatrics*. 2010;**169**:535-542
- [33] Imberti JF, Underwood K, Mazzanti A, Priori SG. Clinical challenges in catecholaminergic polymorphic ventricular tachycardia. *Heart, Lung & Circulation*. 2016;Aug;**25**(8):777-783
- [34] Laitinen PJ, Brown KM, Piippo K, et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. *Circulation*. 2001;**103**:485-490

- [35] Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. A multi-center report. *Journal of the American College of Cardiology*. 1992;**20**:1391-1396
- [36] Benito B, Brugada R, Brugada J, Brugada P. Brugada syndrome. *Progress in Cardiovascular Diseases*. 2008;**51**:1-22
- [37] Sarquella-Brugada G, Campuzano O, Arbelo E, et al. Brugada syndrome: Clinical and genetic findings. *Genetics in Medicine*. 2016;**18**:3-12
- [38] Brugada P, Benito B, Brugada R, Brugada J. Brugada syndrome: Update 2009. *Hellenic Journal of Cardiology*. 2009;**50**:352-372
- [39] Gussak I, Brugada P, Brugada J, et al. Idiopathic short QT interval: A new clinical syndrome? *Cardiology*. 2000;**94**:99-102
- [40] Pereira R, Campuzano O, Sarquella-Brugada G, et al. Short QT syndrome in pediatrics. *Clinical Research in Cardiology*. 2017; Jun;**106**(6):393-400
- [41] Behere SP, Weindling SN. Inherited arrhythmias: The cardiac channelopathies. *Annals of Pediatric Cardiology*. 2015;**8**:210-220
- [42] Sanchez O, Campuzano O, Fernandez-Falgueras A, et al. Natural and undetermined sudden death: Value of post-mortem genetic investigation. *PLoS One*. 2016;**11**:e0167358
- [43] Campuzano O, Allegue C, Fernandez A, et al. Determining the pathogenicity of genetic variants associated with cardiac channelopathies. *Scientific Reports*. 2015;**5**:7953
- [44] Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine*. 2015;**17**:405-424
- [45] Amendola LM, Jarvik GP, Leo MC, et al. Performance of ACMG-AMP variant-interpretation guidelines among nine laboratories in the Clinical Sequencing Exploratory Research consortium. *American Journal of Human Genetics*. 2016;**98**:1067-1076

