Sudden cardiac death with “normal” heart: molecular autopsy

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Several culprits may be identified at postmortem in young sudden death (SD) victims, including coronary artery, either acquired or congenital, myocardial, valve, conduction system and congenital heart diseases. However, in up to 20% of cases, the heart is grossly and histologically normal (unexplained SD or “mors sine materia”) and inherited ion channel diseases have been implicated (long and short QT syndromes, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia). These channelopathies are nowadays regarded as inherited cardiomyopathies with isolated electric dysfunction, and are due to defective proteins of sodium and potassium ion channels at the sarcolemma level or receptors for intracellular calcium release.

Long QT syndrome, in both autosomal and recessive forms, is characterized by prolonged QT interval, mostly due to potassium channel dysfunction in terms of delay of intracellular potassium current during repolarization. On the opposite, in short QT syndrome, a hereditary disease with autosomal dominant transmission, the potassium reentry is accelerated during repolarization. Both conditions are at risk of SD: the more the length or shortness of the QT interval, respectively, the higher the risk of ventricular fibrillation.

Brugada or Martini-Nava-Thiene syndrome is an inherited autosomal dominant cardiomyopathy, featured by non ischemic ST segment elevation, due to delayed sodium exit during repolarization. Whether there are structural alterations associated with Brugada syndrome is still a matter of controversy.

At difference from the previous ones, catecholaminergic polymorphic ventricular tachycardia presents with normal ECG at rest; ventricular arrhythmias arise only during effort or emotion, when the heart frequency exceeds the threshold of 120-130 beats/min. It is also an inherited disease with autosomal dominant pattern. Molecular investigations disclosed mutations in genes coding the calcium receptors (ryanodine
receptor 2 and calsequestrin), located in the membrane of the smooth sarcoplasmic reticulum and in charge of calcium release for electromechanical coupling. Unfortunately, the stress test, which should trigger the ventricular arrhythmias thus unmasking the disease, may result false negative, so that only mutation screening in the family may detect asymptomatic carriers and allow preventive strategies. Overall, 30-40% of the diseases at risk of SD in the young are genetically, potentially recurrent cardiac disorders, and they include both structural and non structural heart diseases which can account for SD as first clinical manifestation in previously asymptomatic apparently “healthy” people. Thus, autopsy may still represent the first opportunity to make the proper diagnosis and the employment of molecular biology techniques even at postmortem may be of help, particularly to solve the puzzle of “mors sine materia”. Molecular autopsy, carried out in a large cohort of SD cases, was able to achieve the diagnosis in one third of otherwise unexplained SD cases (14% RyR2, 16% KCNQ1 or KCNH2, 4% SCN5A).

Archived formalin-fixed, paraffin embedded tissue (FF-PET) is the easy way of storage and transport, and thus is typically the only source of DNA available for procurement. However, postmortem genetic testing can be performed only using “DNA-friendly” autopsy material such as EDTA-preserved blood or fresh frozen tissue. More in details, 10 ml of EDTA blood and 5 g of heart and spleen tissues should be frozen and stored at −80°C.

In conclusion, the employment of molecular techniques at autopsy is becoming nowadays an essential tool in the setting of unexplained cardiac SD. To this aim, proper sampling of blood and tissues has been recommended in the guidelines for autopsy investigation proposed by the Association for European Cardiovascular Pathology.

**BULLET POINTS:**

- Up to 20% of SD cases in the young present a grossly and histologically normal heart (unexplained SD or “mors sine materia”)
- 30-40% of the diseases at risk of SD in the young are genetically, potentially recurrent cardiac disorders
- Autopsy investigation of cardiac SD in the young should always include sampling for molecular investigation
- “DNA-friendly” autopsy material such as EDTA-preserved blood or fresh frozen tissue is recommended for genetic screening purposes

**REFERENCES:**


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