Ion channels and beating heart: the players and the music

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Soft gentle music accompanies us throughout our lifetime; it is the music of our heart beating. Although at times it is questionable as to who serves as conductor of the orchestra, there is little doubt that our ion channels are the main players. Whenever one of them plays too loudly, too softly or simply off key, disharmony results, sometimes leading to total disruption of the rate and rhythm.

Ion channels can disrupt the music of our heart by different mechanisms. Sometimes their function is correct, but their expression is altered by underlying cardiac diseases (*i.e.* heart failure); sometimes the defect is in their structure, because of an underlying genetic defect, and in this case a channelopathy is present.

Pills of history

Ion channels and ion channel diseases represent one of the most fascinating areas in system biology and clinical medicine. The *ion channel theory* was first hypothesized in the middle of the last century by two British biophysicists (Alan Hodgkin and Andrew Huxley) as part of their Nobel Prize-winning theory of nerve impulse conduction.[1] In subsequent years, pharmacological agents have been used to characterize the function of different ion channels in physiological processes, as pain perception or muscle contraction.[2]

The existence of ion channels was confirmed and *electrically recorded* by Bert Sakmann and Erwin Neher in the '70s using a new and revolutionary technology, called *patch clamp*.[3] They received the Nobel Prize in Medicine in 1991.

The development of patch clamp technology and the discovery of specific mutations of ion channel proteins in the late '80s provided a better classification of ion channel protein families, and a better understanding of their function in normal physiology and diseases. In 1995 the first two genes involved in a cardiac channelopathy were discovered (*SCN5A* and *KCNH2* in long QT syndrome),[4-5] and in the following nine years many of the main genes involved in known channelopathies were identified. To date, almost 25 genes, mainly encoding ion channels or protein modulating ion channel function, have been linked with channelopathies and some of them can cause more than one disease (*one gene, many diseases*). The typical example is *SCN5A*, which has been linked to long QT syndrome, Brugada syndrome, Lev-Lenegre syndrome, atrial standstill, and familial sick sinus syndrome.[6-8]

Disease mechanisms: *strumming on my heart strings*

Over the last two decades, improvements in cardiovascular genetics have resulted in better characterization of disease origin and mechanisms. Most ion channel diseases are mendelian *monogenic* diseases, in which an electrical defect predisposing to life-threatening arrhythmias is present. If the defective ion channel is present on the cellular membrane and is a key player of the action potential, then the basal ECG is usually altered and has specific features that manifest on the ECG. The same gene can be involved in different syndromes (*i.e.* LQTS and SQTS), but the genetic defect will cause opposite changes in the channel function.[7,9] Also, the same genetic defect can cause different channelopathies, and even if the bivalent behavior of such mutations can be supported by patch-clamp findings,[6] we still do not know why some individuals develop a specific phenotype and others a different one (*i.e.* LQT3 and Brugada syndrome).[8,10]

While *membrane channelopathies* are usually characterized by typical ECG features, the only known *sarcoplasmic channelopathy*, catecholaminergic polymorphic ventricular tachycardia (CPVT), is usually characterized by a normal basal ECG. The clinical diagnosis is often possible with an exercise stress test, revealing typical ventricular rhythm abnormalities.[11]

Clinical heterogeneity and incomplete penetrance are other well-recognized features of channelopathies and research is underway to identify these modifying genetic traits (*i.e.* SNPs) and epigenetic mechanisms (*i.e.* miRNA), which could cooperate to explain the different spectrum of clinical presentation and disease outcome.

Genetic testing: the fourth missing season of the clinical concert

Whenever a channelopathy is suspected a complete personal and family history collection is mandatory together with a comprehensive clinical examination. Moreover, physicians should know when and how asking for a molecular screening and what they should expect from its result. The impact of genetic testing may vary, according to different inherited cardiac diseases. In LQTS for instance, the molecular screening is positive in 80% of affected patients and may be helpful for sudden death risk evaluation and for the correct management of the patients;[7] in CPVT the yield of genetic test is high as well (70%), however, despite being useful for diagnosis, it is not useful for making therapeutic decisions.[11] In the case of SQTS, the known disease-associated genes has been shown to account for approximately 30% of probands (unpublished observation); molecular screening is of value in choosing a therapeutic approach, since traditional I_{Kr} blockers, including sotalol and dofetilide are ineffective in many cases of SQT1 because they depend on the inactivated state of the HERG channel (which is lost) in order to exert their inhibitory effect. Quinidine, on the other hand, because it interacts with the activated state of the I_{Kr} channel, is effective in reducing the augmented I_{Kr} responsible for the disease.[12-14]

This year, two consensus documents from the Canadian Society of Cardiology[15] and the European Society of Cardiology/Heart Rhythm Society[16] have been released, recommending a class of indication for molecular screening in the clinical management of patients with known ion channel diseases and cardiomyopathies. Importantly, the class of indication may differ between probands and their family members. When a disease-causing mutation is identified in a family, the screening of family members is always recommended as a class I indication, in order to facilitate making a diagnosis and establishing preventive measures. By contrast, the indication for screening of probands depends on the disease

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phenotype. Screening is recommended when the positive predictive value is high and/or when the genetic test provides either diagnostic or prognostic information or when it influences therapeutic choices. In channelopathies screening is recommended as a class I indication only in LQTS and CPVT probands, whereas it is in class IIa for Brugada syndrome, in class IIb for progressive cardiac conduction disease and SQTS and it is not indicated (class III) for atrial fibrillation.[16-17] Because of rapid advances in molecular genetics, some of the recommendations of the consensuses documents are already out of date and need to be revisited.

Accurate clinical identification of patients affected by channelopathies is quite important before pursuing molecular screening. Patients should be informed about the specific role of genetic testing in their specific disease; genetic counselling is desirable before collecting blood samples as well as during communication of the genetic results. A comprehensive clinical examination should be performed by experienced physicians in dedicated clinics (*Sudden death clinics* or *Inherited arrhythmias clinics*) that should have knowledge and experience in the interpretation of genetic data.

The ethical, legal, and psychological aspects of genetic testing, particularly in children, are complex. Therefore, the choice of timing for molecular screening in children should be guided by the natural history of the disease and by the availability of effective prophylactic treatments.[18]

In conclusion, molecular genetics is no longer a simple research tool, but, despite its complexities, is entering the phase of utility in clinical evaluation of patients with inherited cardiac arrhythmia syndromes, together with anamnesis, physical examination and instrument-assisted evaluation. The *four seasons* are now composed.

A new science growing from *the sound of silence*: molecular pathology

Sudden cardiac death (SCD) can be the first clinical manifestation of an inherited channelopathy and autopsy may represent the first and last opportunity to make the proper diagnosis, which is critically important for family members. However, a standard autopsy is typically negative in channelopathies and therefore not helpful at reaching the correct diagnosis in the proband, which is essential for the identification of affected family-members, potentially at risk of SCD.[19-20]

Many deaths *sine materia*, often sudden, and in young apparently healthy people, are designated as *undetermined* by pathologists (*autopsy-negative sudden unexplained death*, SUD). However, the *silence* of these hearts sine vitae, have been recently broken by the sound of a new science, *molecular pathology*, which includes a molecular autopsy designed to uncover the gene mutation underlying a channelopathy.

The importance of molecular autopsy is supported by the observation that one third of unexplained SCD cases are of genetic origin.[21-22] Furthermore, the role of channelophaties has recently been heightened, with the identification of a significant percentage of sudden infant death syndrome (SIDS) cases[23-25] and stillbirth cases,[26] other examples of *mors sine materia*.[27]

Basso *et al.* addressed this issue in two different publications.[28-29] In the first, the Association for European Cardiovascular Pathology was involved[28] and the employment of molecular biology techniques has been recommended in guidelines for autopsy investigation of sudden death (SD). In the most recent one[29] the role of molecular autopsy in SD was reviewed and practical information on how and when the pathologist should proceed with the genetic screening of channelophaties was provided.

However, to become reality in clinical practice it is important that not only pathologists, molecular biologists, and clinicians expert in the field, cooperate in this direction, but that all cardiologists and family physicians, that are more likely the principal interface with family members, become aware of the importance of such a procedure.

Conclusion and introduction to the theme

Our principal aim in planning this issue was to focus on the interest, utility and readability of the selected topics for the *users* (*i.e.* cardiologists interested in cardiovascular genetics; geneticists and biologists interested in ion channel disorders). We believed that starting from the *phenotype* or *disease* (*i.e.* Brugada syndrome, etc.) is probably easier than starting from the *genotype* (*i.e.* Sodium Channel Gene Diseases, etc.). Each section contains a comprehensive and up-to-date description of the molecular basis, pathogenesis, clinical aspects (diagnosis and management) of the single disorder. We hope the reader will find this special issue useful for his/her research and clinical practice.

And now, let's start with the *music*!

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