

# In search of the sources of cardiac fibrillation

Proclivous towards exploring the unknown, I wanted to be an archaeologist as a child. Later, in my teens, I was inclined towards psychology and therefore entered Medical School. However, in 1979 as a second-year intern in cardiology I discovered my passion: cardiac electrophysiology. I owe that to Jean François Warin, then Professor and Head of the arrhythmia services in Bordeaux.

The fact that a 12-lead ECG trace could describe an invisible electrical mechanism operating within the heart fascinated me. I went to Paris to continue working on cardiology with Professor Philippe Coumel. When I returned to Bordeaux in 1982, intracardiac ablation interventions in arrhythmic hearts had just been reported (Gallagher, 1982; Scheinman, 1982). The results seemed magic. We could not only describe and debate a putative mechanism, but also validate it and treat the condition. Our group had the opportunity to perform the initial intracardiac treatment of simple arrhythmias using localized cardiac electrical shocks. This form of energy was quickly replaced by a more convenient and safer form of radiofrequency current. Ten years later, simple tachycardias caused by focal arrhythmogenic factors were being cured successfully in many centres worldwide.

After Dr Warin passed away, I moved to the Hôpital Cardiologique du Haut-Lévêque under the kind direction of Jacques Clementy, who gave me complete freedom to pursue this complex and developing area of electrophysiology.

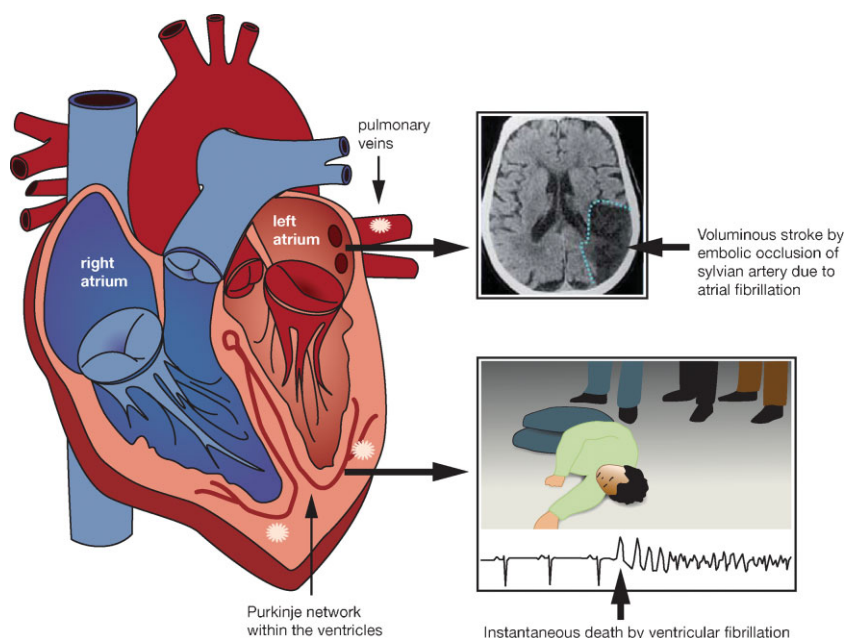
» Fibrillation is the most complex pathology amongst all disorders of cardiac rhythm. «

Once the treatment of most of tachycardias had become routine, we moved towards a new problem: cardiac

fibrillations. Fibrillation is the most complex pathology amongst all disorders of cardiac rhythm (Fig 1). Cardiac fibrillation results in rapid and disorganized contraction of the chamber of the heart it affects. Atrial fibrillation (AF), which occurs in the auricles affects 1% of the population and is the main cause of cardioembolic cerebrovascular accidents. Ventricular fibrillation (VF), which, as the name suggests, occurs in the ventricles is responsible for more than 80% of sudden death cases in adults, amounting to 350,000 annual deaths in Europe involving both young and older adults. In the early 1980s, these disorders were linked to multiple fibrillating wavelets propagating in a chaotic manner. The fibrillating events disturb the cardiac rhythm and render it uncontrollable. Drug therapies have been designed to treat these arrhythmias, but back in those days they were only moderately effective.

## Atrial fibrillation

Our team included Pierre Jais, Méléze Hocini, Dipen Shah and many bright and passionate colleagues from around the world who studied the genesis of these two pathologies. We started with AF and chose the unconventional route of exploring the very beginning of the arrhythmia by mapping the premature beat that sparks the fibrillatory rhythm in a normally beating heart. We discovered that, in our patients, the sources of the ectopic beats observed in AF were not only the heart auricle but in the majority of cases the pulmonary veins. Once we recognized this, we explored patients with episodes of other types of AF by placing recording catheters into their pulmonary veins in anticipation, often for long hours, of a spontaneous onset of AF. We also recorded the onset of pharmacologically induced AF and confirmed the importance of the



**Figure 1.** Scheme of atrial and ventricular fibrillations. The scheme illustrates the location of the sources of the fibrillation event in atrial and ventricular fibrillation, the pulmonary veins and Purkinje cells, respectively as well as their clinical risks.

pulmonary veins in the initiation of AF. We found that, in most cases the sources of ectopy were discharges emanating from cells situated in the external wall of the pulmonary veins. Surprisingly, the electrical impulse came from a simple vein that was believed to be electrically inert and of no possible interest to an electrophysiologist. Importantly, these foci responded to ablation treatment with radiofrequency (Haissaguerre, 1998).

### » Our work opened a new avenue in treating AF... «

After a phase of scepticism, this discovery was confirmed in numerous studies, involving both normal hearts and hearts exhibiting multiple pathologies. Our work opened a new avenue in treating AF and has brought considerable hope for the treatment of VF leading to sudden death. It also provides a wonderful example of 'Reverse translational research'. Stemming from these observations, the architecture and the properties of the cells involved in the onset of fibrillation have now been described in an attempt to explain their ability to generate ultra-rapid discharges (400/min) which act as 'triggers' for the fibrillation event. This research was also interesting from a conceptual standpoint as it demonstrated that a highly complex phenomenon, which was thought to derive from some sort of 'chaos' theory, had instead discrete and definite sources. In addition to drug therapies, AF can now be tackled by cryo or thermoablative therapy that eliminates the venous cells causing the fibrillation. The number of patients managed in this manner is growing constantly and reached 150,000 in 2009.

In persistent forms of AF, the contribution of the pulmonary veins is less prominent and is shared with different structures in the atrial tissue. The progression of an episodic form of AF to a persistent one is marked by structural alterations in the atrial tissue brought about by co-morbidities like aging, diabetes, heart failure and hypertension. These alterations in the atrial

substrate are certainly accelerated by fibrillation itself, but they usually begin before the arrhythmia progresses to persistent form. To be able to prevent this progression, we must focus on identifying risk factors and tissue biomarkers in early stage patients.

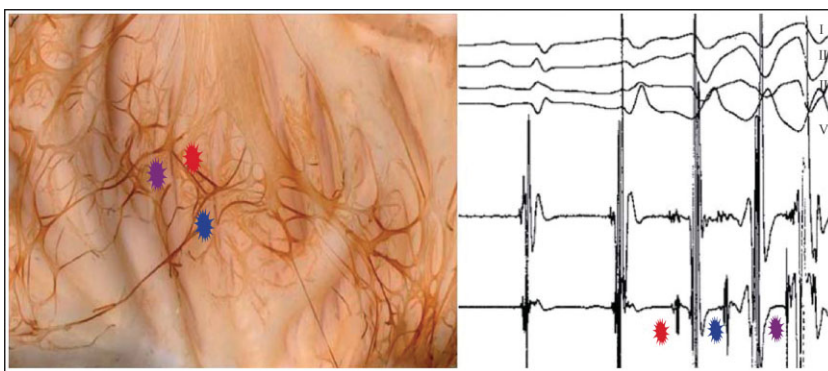
### Cellular and genetic bases for cardiac fibrillation

AF may have an inheritable component as family history has been identified in approximately 5% of patients with AF (Fatkin, 2007). The same holds true for VF as inheritable forms of VF constitute approximately 10% of sudden unexplained deaths, including dilated cardiomyopathy, long-QT, short-QT and Brugada syndromes and catecholaminergic polymorphic ventricular tachycardia (Chugh, 2008). In familial forms of both types of cardiac fibrillation, mutations involving genes encoding  $K^+$  and  $Na^+$  channel proteins, connexin and other peptides have been discovered. These mutations alter the flow of transmembrane  $Na^+$  and  $K^+$  currents or the intracellular  $Ca^{++}$  handling (Workman, 2008). This common linkage into their molecular mechanisms may explain the high prevalence of AF associated with inherited syndromes of VF, more than 100 times higher than the general population (Sakhuja, 2009).

### Ventricular fibrillation

Our team adopted the same approach of searching for the fibrillation origin to study the VF. However, heart mapping in this case was considerably more difficult due to the strikingly lethal nature of the disorder, which calls for immediate defibrillation of the patient using electric shocks. We had no more than a few seconds to map the heart but nevertheless managed to observe that these 'electrical tornadoes' emanated from the arborized tissue of the ventricular Purkinje cells (Fig 2), which account for only 2% of the total cardiac mass (Haissaguerre, 2002a).

By targeting the responsible cells using thermo-ablation, we could extinguish the arrhythmias in 36 of 38 patients treated and subsequently monitored using implanted devices. The first intervention of this nature took place 8 years ago and the patients involved have suffered no relapses so far, providing proof of concept of the approach (Haissaguerre, 2002b; Knecht, 2009) However, the impossibility of creating more elaborate maps forces us to rely on experimental and theoretical modelling studies of this lethal condition. The Purkinje tissue is characterized by specific ionic and conduction properties that make it an optimal target both for local energy delivery and most importantly for widely applicable drug therapy.



**Figure 2.** Ventricular fibrillation. A Purkinje network in the heart (left) and intracardiac recordings (right) of the Purkinje discharges (stars) leading to extremely fast cardiac rhythm (280 beats per minute) resulting in the death of the affected person in a few minutes. The likely sites of origin of these beats within the Purkinje network are marked in the picture (left) and the potentials recorded (right) from the respective sites are marked by the coloured stars. Adapted from Haissaguerre et al (2002).

It is now important to focus on the identification of the mechanisms that lead to firing of discharges, understand the properties of the Purkinje tissue and its interaction with the myocardial tissue. Again, to be able to recognize individuals susceptible to develop VF is crucial as they may succumb from the episode. We believe that in addition to triggering beats, it is most likely that the susceptible ventricle harbours electrical 'faults' which may be identified by processing of electrocardiographic signals, functional imaging techniques, pharmacological provocative tests and evaluation for genetic predisposition (Haïssaguerre, 2008, 2009).

The pathophysiology of the electrical trigger interacting with the vulnerable ventricle to cause arrhythmic sudden death must be evaluated using basic electrophysiology approaches with optical mapping and computer simulation facilities. Optical mapping offers the highest spatial and temporal mapping resolution while computer simulations will allow the manipulation of any of the multiple electrical parameters involved in the genesis of VF. Novel tools must also be developed. For example, customized catheters with the ability to record multiple monophasic action potential recordings during intracardiac procedures would allow the creation of maps of electrical repolarization disharmony of the ventricular myocardium and a multi-

lead high resolution mapping system capable of reconstructing epicardial electrograms from the chest surface, non-invasively. Our ultimate goal is to define screening and therapeutic protocols to manage sudden but potentially preventable arrhythmic death currently claiming over half a million lives each year in Europe and North America.

The author declares that he has no conflict of interest.



**Michel Haïssaguerre**

Michel Haïssaguerre is awarded the 2010 Louis-Jeantet Prize for Medicine for his work on the origins of cardiac fibrillation. He is Professor of Cardiology at the University Victor-Segalen Bordeaux 2 and head of the Department of Cardiac Arrhythmias at the University Hospital of Bordeaux.



Hôpital Cardiologique du Haut Lévêque – Université Bordeaux II, PESSAC, France  
E-mail: michel.haïssaguerre@chu-bordeaux.fr

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