

# Chapter 1

## FIBRILLATION

*Like a handful of worms . . .*

The arrhythmia called fibrillation is introduced as a generalized disordered activity of the cardiac fibers with no actual output of blood from the chambers. Its mechanisms of maintenance are tentatively explained by the reentry, the multiple ectopic foci, or the rotor theories, which are supported only partially by experimental and/or theoretical evidence. By and large, a disturbance starts up the arrhythmia, often in a sensitized heart, but not necessarily always so. Thus, the *setting* of the phenomenon and the *type of disturbance* become relevant, leading to the so-called *clinical fibrillation* (due to disease), *industrial* or *domestic fibrillation* (due to electric accidental shock), and *surgical fibrillation* (due probably to handling). Since the mammalian heart is structurally and electrophysiologically inhomogeneous, a disturbance can be viewed as some added extra-inhomogeneity, which increases the probability of triggering the phenomenon. Thus, electrical, mechanical, chemical, and thermal energies are the different disturbances to add inhomogeneity. Cardiac fibrillation can be classified on the basis of its *etiology* (primary or secondary), *localization* (atrial or ventricular), or *characteristics* (strong or weak). Its clinical and surgical significance is underlined while the fibrillation variables, divided into electrophysiologic and metabolic, are discussed. Since the arrhythmia is a group phenomenon, the concept of minimal mass appears as a pertinent quantity yet to be numerically determined. The minimum magnitude (amplitude in adequate units, of whatever kind) required to trigger fibrillation is called *fibrillation threshold*. When electrically induced, it is called electrical fibrillation threshold (EFT), as a parameter to evaluate and test the sensitivity of the myocardium to the arrhythmia. Single rectangular pulses or train of pulses, either synchronized or not with the QRS complex, can be used as testing signal, wherefrom a time window of weakness called vulnerable period is found, which roughly coincides with the duration of the T-wave. Some numerical illustrative values taken from the literatures are offered.

### 1.1. Definition

Cardiac electrical activity triggers the mechanical activity of the heart — its contraction — both in the atria and in the ventricles. Mechanical contraction absolutely cannot occur without the former while cases of the

opposite situation may be found, that is, existence of electrical activity and no contraction whatsoever. In normal conditions, there is a time sequence of events: First, atrial electrical activity (the P-wave) followed by atrial contraction and, thereafter, ventricular electrical activity (the QRS complex) followed by ventricular contraction and its important physiological consequence, ejection of blood, via the aorta from the left ventricle and pulmonary artery from the right side, to the peripheral and to the lung circulations, respectively. The nomenclature P and QRS belongs to the traditional wave identification in the electrocardiogram (ECG), as established by its founder, Wilhelm Einthoven (1903).

The electrical activity, first in the atria and second in the ventricles, after rapid conduction and distribution throughout the whole myocardial mass takes place in synchronism, thus giving a degree of simultaneity, to the atria first and to the ventricles thereafter — i.e. there is overall depolarization of the fibers — essential for an effective systolic action. Under certain circumstances, however, such synchronism is lost and the atria or the ventricles fall in the state known as *fibrillation*. Therefore, *cardiac fibrillation can be defined as the phenomenon of asynchronous or uncoordinated or chaotic activity either of the atrial or of the ventricular fibers*.

Overall asynchronism is electrical and mechanical, and effective ejection disappears. Figures 1.1 and 1.2 illustrate, respectively, records of atrial and ventricular fibrillation (VF), both recorded from experimental dogs. The electrical activity shows a chaotic nature, with no clear rhythmicity even though frequencies in the order of 300–600 cycles per minute can be detected if the Fourier spectrum is calculated (Clayton *et al.*, 1994); there are, however, reports of somewhat higher values. In fibrillation, the atria do not eject blood any more to the ventricles although ventricular filling is still accomplished due to passive pressure gradient; in the second case, VF, aortic and pulmonary artery pressures, instead, fall rapidly to essentially zero. When the myocardium is looked at, it resembles a handful of moving worms, for which reason sometimes the phenomenon has been described as *worm-like activity*.

In order to illustrate with an analogy (Fig. 1.3), let us consider a team of rowers when competing with their boat in a race. The helmsman, usually a smaller and light guy, steers the boat and acts as pacemaker by rhythmically shouting so that the rowers move their oars in synchronism. If for some reason a disturbance takes place, as for example a bee stings one of the rowers and he slaps it, he may break the synchronism bringing very likely

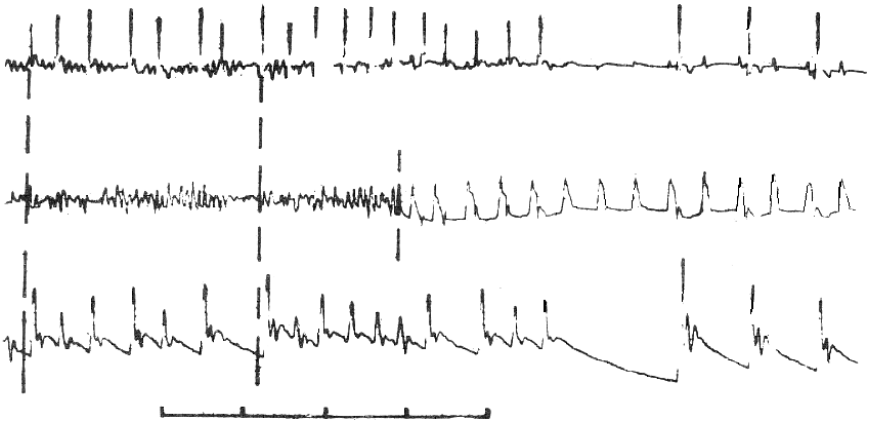


Fig. 1.1. Induced atrial fibrillation in the dog. Top: Surface ECG. Middle: Jugular lead into the right atrium. Bottom: Carotid blood pressure. Time marks below one sec apart. Observe the pulse deficit within the time interval between the two vertical dashed bars on the left when comparing the top and the bottom channels. Spontaneous defibrillation at the third vertical dashed bar followed by AV block. Records obtained by the author at the Laboratory of Bioengineering; reproduced from Valentinuzzi *et al.*, 1986, with kind permission of the publisher.

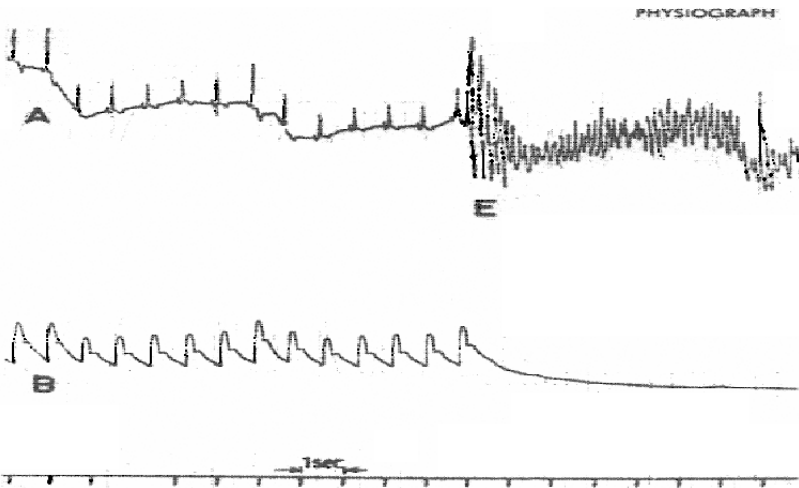


Fig. 1.2. Ventricular fibrillation (VF) in the open chest experimental dog induced by an electric stimulus (E) applied to the myocardium. Channel A is the surface ECG (lead II). Blood pressure, in Channel B, fell rapidly to almost zero level. Obtained by the author at the Laboratory of Bioengineering, UNT, Tucumán. Valentinuzzi *et al.*, 1986, with kind permission of its publisher.



Fig. 1.3. Analogy: A team of rowers needs to row in synchronism if they are to win the race. Here the rowers are shown fully out of phase, that is, they would hardly advance. In similar way, cardiac fibers tend to act on their own when in fibrillation, both electrically and mechanically.

the rest of the team into disorganized movements. Each tends to act on his own, as the fibers of a fibrillating heart with mixed action potentials result in different not coordinated fiber lengths.

## 1.2. Mechanisms

There are two basic and rather simple theories that traditionally try to explain the phenomenon of cardiac fibrillation. The first one was proposed early in the 1900s, independently and within less than one year span, by Mines (1913, 1914) and Garrey (1914). It is known as the **Theory of Circus Motion** or **Reentry**. The second is called the **Multiple Ectopic Foci Theory**. Even a third position claims the arrhythmia to be a consequence of a combined effect of the previous two events. Also Lewis (1925), McKenzie's disciple, in his classical treatise, described these mechanisms. More recent insights, however, say since the 1980s, based on some experimental evidence and mathematical and computer models, have proposed the more complex and still unsettled **Rotor or Vortex Theory** (Rogers and Ideker, 2000; Jalife and Berenfeld, 2004; Massé *et al.*, 2007).

### 1.2.1. Reentry

Figure 1.4 describes a model of this mechanism. On the left, a ring of excitable homogeneous tissue is represented as a circle. At point A, an electrical stimulus is applied triggering the appearance of an action potential that propagates both to the right and to the left. The two excitation waves, one running clockwise and the other counter-clockwise, collide about halfway in their attempt to return to the starting site A and the whole process ends. On the right side of the figure, the same piece of

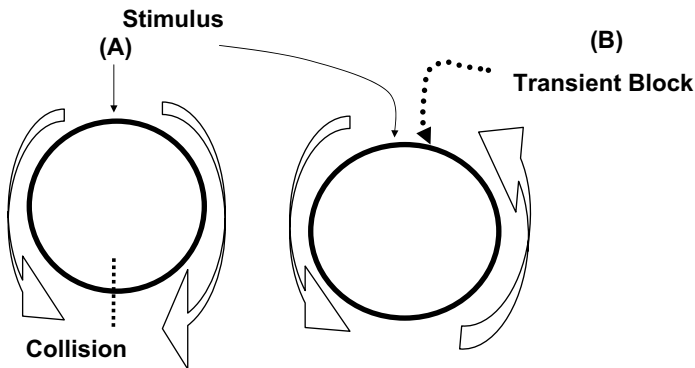


Fig. 1.4. Re-entry mechanism. Left: A ring of excitable homogeneous tissue (circle) is stimulated at point A triggering the appearance of an action potential that propagates both to the right and to the left. Right: The same tissue, but a transient block appears at B at the stimulation moment. Thus, the action potential can only propagate to the left, running the whole circuit to get back to the starting place A.

tissue is depicted but a transient block has appeared at B, at the stimulation moment. In such case, the triggered action potential can only propagate to the left and run the whole circuit to get back to the starting place A. Two possibilities then may occur: the block continues to exist or the block has vanished. If the former happens, the excitation wave dies out; if the latter takes place, the wave re-stimulates site A and a second turn begins so that excitation can keep going on indefinitely establishing a re-entry circuit. Precisely, Mines and Garrey performed experiments with rings of excitable tissue of variable size and they were able to demonstrate the phenomenon. It is, indeed, a beautiful and clear plausible concept. An Old Italian motto says, *se non e vero, è ben trovato* (even if not true, the explanation is nice).

Several aspects need discussion in the previous model to further clarify it. What variables play a role to actually lead to a circus motion?

- (1) The velocity of propagation  $V_p$  of the action potential is a first element; if it is too high, the excitatory wave will get back to the starting point when the block still persists and will not be able to continue. On the other hand, if such velocity is low enough, the action potential will find point A fully recovered and re-excitation will be possible.
- (2) A second element is the refractory period  $\tau$  of the action potential; if short enough, the possibility of reactivation of the site is clear. However, if it is too long, reentry could not happen for the excitatory wave would find the site unresponsive.

- (3) The third element is the length ( $L$ ) of the circuit, which relates to the heart size (and to the possible wavelength): the longer, the higher the probability of re-stimulation, while the opposite occurs in the case of short pathways.

Thus, after the above-mentioned settings, we may write down the following relationship,

$$V_p = L/\tau \quad (1.1)$$

or, better as inequality, because the pathway must at least be equal to or longer than the solved for product,

$$L \geq V_p \tau \quad (1.1a)$$

as the necessary condition for the establishment of a continuously running action potential, a circus motion or a reentry in a ring-like piece of excitable tissue. Each factor in Eq. (1.1), using the international system of units SI, should be measured in meters (m), meters/second (m/s), and seconds (s), respectively. Expressed in words, **a low propagation velocity, short refractory period, and/or long pathway certainly favor the establishment of a reentrant wave front**. Any action, exogenous or endogenous (as drug injection, cooling, blood flow change, metabolic alteration or the like), affecting any of these three parameters will have an influence, too, on the probability of reentry and, thus, appears as corollary of the latter statement.

How can the appearance of transient blocks be explained? Inhomogeneities may be a first cause, because they tend to hinder normal conduction of the electrical impulse, and cardiac tissue, especially in the mammalian heart, is far from being homogeneous, both histologically and electrophysiologically.

Study of the fibers composing the atria and ventricles clearly shows the existence of different types: contractile, conductive, tendinous, pacemaker-like, of the atrioventricular node, of the sinus node, Purkinje fibers, atrial fibers. They are organized as a *syncytium*, which has a wavy complex structure and is biologically defined as a multi-nucleated mass of cytoplasm not fully separated into individual cells. A unique feature of the heart is the existence of intercalated discs that act as specialized cell junctions, which offer little resistance to the passage of an action potential. Their resistance is very low, so much that ions move freely through the junction allowing the

entire atrial or ventricular mass to function as one huge cell. For this reason, cardiac muscle is frequently referred to as a *functional syncytium*, or a single functional unit. It has been found that abnormal intercellular coupling in the heart, resulting from defects in the expression of *connexin 43*, the major constituent of cardiac gap junctions, plays a key role in the initiation and maintenance of sustained arrhythmias (Cancelas *et al.*, 2000; Gutstein *et al.*, 2005). Gap junctions provide for a unique system of intercellular communication allowing rapid transport of small molecules from cell-to-cell. Such junctions are formed by a large family of proteins named *connexins*. From a cardiovascular viewpoint, cell-to-cell communication, under normal conditions, is essential in cardiac embryogenesis, electrical impulse transmission, synchronization of cardiac contractile activity, transmission of vascular reflex signals, and other biological functions. Under pathological conditions, either by inherited or acquired genetic mutation, intercellular communications participate in the development of congenital cardiopathies, arrhythmogenesis and electrical remodeling, atherosclerosis and myocardial ischemia, arterial hypertension and myocardial remodeling (Suárez and Bravo, 2006). Another important fact refers to the direction the electric impulse moves: conduction velocity along myocardial fibers was found to be usually several times larger than that vertical to them. In pathological conditions, the phenomenon seems to be more marked (Toyomi *et al.*, 1959). In short, structural inhomogeneity and pathways associated with it are facts that may become decisive in triggering fibrillation.

Microelectrode records of cardiac action potentials have demonstrated long time back substantial morphological differences when comparing several fiber types (Hoffman and Cranefield, 1960). Figure 1.5 is a traditional didactic set of intracellular signals based on a long row of careful experiments first published by the previously mentioned authors and, thereafter, reproduced over and over in the literature. They are quite illustrative; the delay between them is clearly discernible. Time marks (shown at the bottom) are 100 ms apart. Not all fibers over the myocardial mass find themselves at one given instant at the same electrophysiological state, due either to temporal shift or to differences in the recovery time. Such differences are more marked during repolarization, which, when looked at from the position of a standard surface ECG, correspond approximately to the location of the T-wave. In short, there is lack of temporal electrophysiological homogeneity and that may favor also the establishment of reentry pathways.

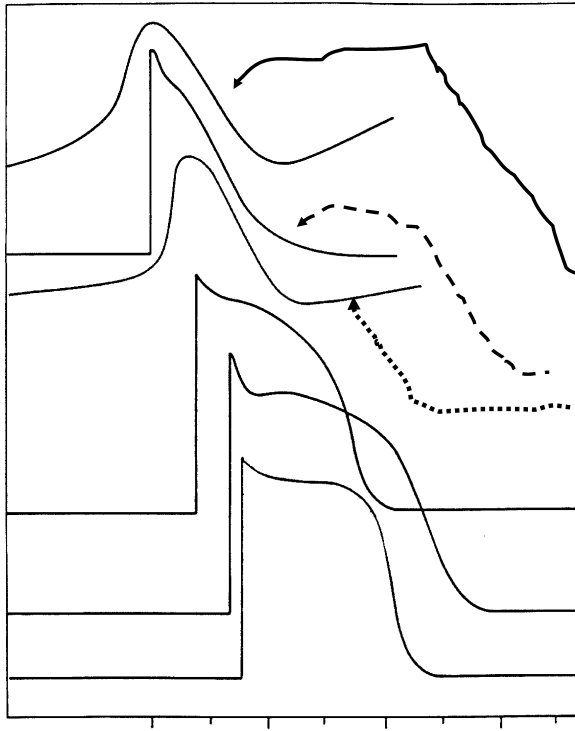


Fig. 1.5. Six cardiac action potentials recorded with microelectrodes from six types of cardiac fibers. They have similar characteristics, but they also show significant differences. Upper one: Produced by one myocyte of the sinoatrial node. The second came from an atrial fiber and the third from a cell located at the atrioventricular node. The lower three action potentials came from the left ventricle: bundle of HIS, distal Purkinje fiber, and a contractile fiber, respectively. Time marks: 100 ms apart (As shown in Hoffman and Cranefield, 1960, and in many textbooks).

### 1.2.2. Multiple Ectopic Foci

A single cardiac electrical impulse out of its anatomical normal site is, by definition, an ectopic beat (from Greek, *ektos*, out of place, formed by *ex* out + *topos* place). It may show up at any myocardial spot and it may trigger or not a consequent contraction. It usually falls also out of the regular expected time, eventually before time (as premature beat) or sometimes rather late in the cycle. Isolated ectopics do not have physiological significance. Young people may have them and, as they grow older, such cardiac manifestations disappear. Their shape is characteristic

and depends on the origin; by and large, the depolarization wave (QRS complex) is opposite in polarity to the recovery wave (T-wave).

A sensitized myocardium (say, ischemic) may produce one or more trains of ectopics; the longer the strip and the more frequent, the more worrying the cardiac condition of the subject because they indicate perhaps tissue injury. If the morphology of the beats making up the tachyarrhythmic episodes changes, it means there are several foci that tend to act as quasi-pacemakers and, at a given time, may easily involve enough muscle mass to turn into fibrillation. Whether such event is the result of just several foci, as some sort of electrical overall bombardment, or a combination of them with reentrant circuits elicited in some other way, becomes a speculative matter of perhaps not much relevance. Figure 1.6 illustrates a basal ectopic beat, Fig. 1.7 points out different places in the myocardium where the unwanted activity might arise and Fig. 1.8 shows a dangerous run of ectopics, also-called extra-systoles or extrasystolia.

### 1.2.3. Rotor Theory

An old idea, put forward by Thomas Lewis in 1925, on the mechanism of fibrillation has re-emerged from theoretical and experimental studies; it says that wave propagation during VF is not totally random. The postulate is that *rotors* or *vortices* (Webster Dictionary says it is *a part that revolves*

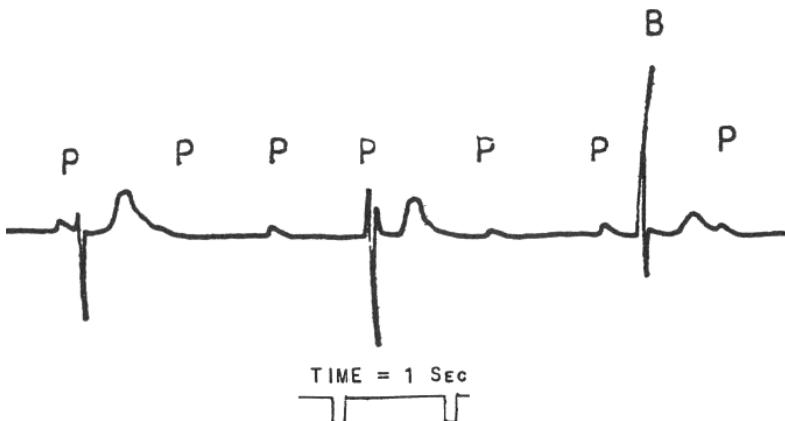


Fig. 1.6. Two ectopic beats originated at the basal region of the ventricles. QRS complexes opposite to T-waves. There is total A-V dissociation. The third beat B is supraventricular and looks very similar to a normal one, but is not. Obtained from an experimental dog at the Department of Physiology, Baylor College of Medicine, Houston, TX.

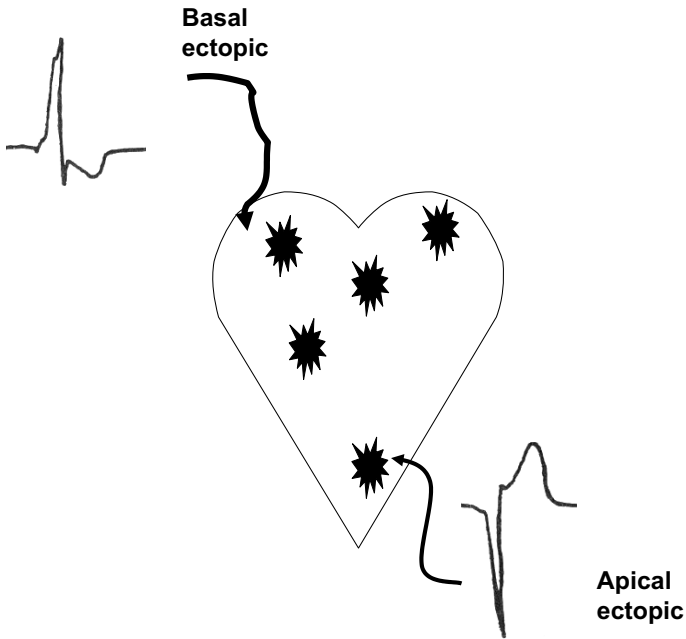


Fig. 1.7. Multiple ectopic foci. Records obtained from experimental dogs.

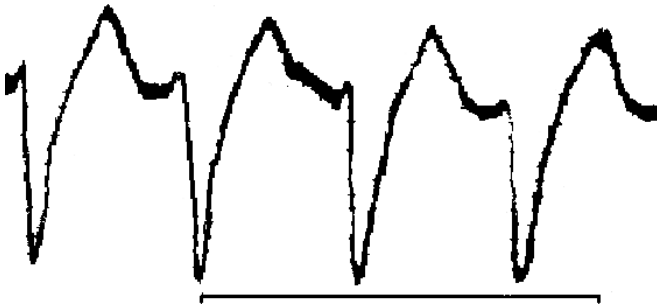


Fig. 1.8. Sequence of apical extra-systoles. It may become a precursor of ventricular fibrillation. Also called extrasystolia. Horizontal bar corresponds to 1 sec. Courtesy of Sofia Berman, MD, Tucuman, Argentina.

*in a stationary part*) are the major organizing centers of fibrillation and that certain specific molecular properties of the cardiac muscle at the ion channel level contribute to the establishment of such rotors and to the overall complexity of the arrhythmia. There is emerging evidence of spatiotemporal organization during early VF. The mechanism is, so far,

unknown in myopathic hearts. The model is based on the theoretical and experimental findings that the heart could maintain electrical waves that rotate about *functional*, rather than *anatomical*, obstacles. These so-called *rotors* were taken as the primary “organizing centers” for fibrillation, and refractory period heterogeneity was considered a secondary factor, possibly modulating and masking the activity of rotors, but not driving the rhythm. Transient unstable rotors might explain VF in terms of how rotors break up to form the turbulent state seen in epicardial maps, that is, there would be “mother rotors” breaking up into “daughter rotors,” which in turn break up in a continual chain of succession (Jalife, 2000; Rogers and Ideker, 2000; Jalife and Berenfeld, 2004; Chorro *et al.*, 2007). Even though somewhat repeating the concept, it deserves quoting the nice description given by the first investigator (Jalife, 2000), from the Department of Pharmacology, SUNY Health Science Center, Syracuse, New York, who says that “traditionally, VF has been defined as turbulent cardiac electrical activity, which implies a large amount of irregularity in the electrical waves that underlie ventricular excitation. During VF, the heart rate is too high (>550 excitations/min) to allow adequate pumping of blood. In the electrocardiogram (ECG), ventricular complexes that are ever-changing in frequency, contour, and amplitude characterize VF. Recent experiments and computer simulations suggest that VF may be explained in terms of highly periodic three-dimensional rotors that activate the ventricles at exceedingly high frequency. Such rotors may show at least two different behaviors:

- (a) At one extreme, they may drift throughout the heart at high speeds producing beat-to-beat changes in the activation sequence.
- (b) At the other extreme, rotors may be relatively stationary, activating the ventricles at such high frequencies that the wave fronts emanating from them break up at varying distances, resulting in complex spatiotemporal patterns of fibrillatory conduction.

In either case, the recorded ECG patterns are indistinguishable from VF”.

The same group called attention to possible dynamic differences in the case of heart failure remodeling, because there is a decrease in VF rate. Besides, acute stretch partially may reverse such effect by a mechanism that is independent of remodeling (Moreno *et al.*, 2005).

Several authors have contributed to the theory. For example, Massé *et al.* (2007) reported that “rotors were present in myopathic hearts studied

during VF and cumulatively lasted a mean of  $(3.2 \pm 2.0)$ s of the  $(7.0 \pm 4.0)$ s of the VF segments analyzed. For each surface mapped,  $(3.6 \pm 2.9)$  rotors were identified for the duration mapped. The average number of cycles completed by these rotors was  $(4.9 \pm 4.9)$ . The longest rotor took  $(10.2 \pm 6.2)$  rotations and lasted  $(2.0 \pm 1.2)$ s. The rotors on the endocardium had a cycle length of  $(192 \pm 33)$  ms compared with  $(220 \pm 15)$  ms on the epicardium". They found centrifugal activation of electrical activity from these rotors, frequently localized at border regions of the myocardium. The subject, however, remains yet unsettled and calls for further and deeper research; no doubt, it is greatly attractive. It might be asked whether a reentry circuit can be considered as a rotor (or is a rotor) and, if not, what the difference between the two phenomena is. The indication seems to be a vortex-like activity moving or shifting along a reentry circuit.

### 1.3. Causes

By and large, a disturbance starts up the arrhythmia, often in a sensitized heart, but not necessarily so. Thus, classification criteria depend on the *setting* the phenomenon takes place and on the *type of disturbance*.

#### 1.3.1. Setting

(a) *Clinical fibrillation*, which etiologically stems mainly in myocardial ischemia or infarct. This is definitely the case of a sensitized myocardium, which speaks precisely of the high-risk patients, candidates to be confined in a coronary unit. Previous clinical studies have diagnosed in them, for example, ventricular hypertrophy or dilatation, hypokinesia, weakened contractility, insufficiency along with very low ejection fraction. Perhaps, they also show hypercholesterolemia and atherosclerosis and a history of hypertension, diabetes, angioplasty, *stents*,<sup>a</sup> smoking habits, and even hereditary factors. It is difficult to determine what the perturbation triggered the arrhythmia, but endogenous catecholamine release due to stress, either physical or psychological, may well be the initial stimulus, or perhaps a minor local metabolic alteration. This fibrillation may not be easy to revert.

---

<sup>a</sup>*Stent*, a short narrow metal or plastic tube often in the form of a mesh that is inserted into the lumen of vessels, as an artery or a bile duct, especially to keep a previously blocked passageway open, apparently introduced by Charles Thomas *Stent*, died 1885, English dentist (Webster Dictionary).

- (b) *Industrial or domestic fibrillation*, which mainly happens at home or in the industrial environment. It is the accidental macroshock (see Chap. 6), due to faulty equipment or installations or improper handling, which most of the time catches a young and healthy heart (because it belongs probably to a worker). Thus, it is not an easy organ to surrender and, if fibrillation is triggered, its probability to be reverted is high. The disturbance in this case clearly is an electrical stimulus.
- (c) *Surgical fibrillation*, which takes place in the operating room, most often during cardiac interventions. The disturbance probably is mechanical handling of a sensitized myocardium, or it may be related to the level and kind of anesthesia. It is simply detected by visual inspection and counter-measures can be applied right on.

### 1.3.2. Type of Disturbance

As described above, the mammalian heart is structurally and electrophysiologically inhomogeneous, which means it is relatively prone to fall into a fibrillary chaotic activity. If, in the form of a perturbation, some extra-inhomogeneity is added, the probability of triggering the phenomenon increases. The question, hence, settles on what kind of disturbance appears as more appropriate. Here is where energy comes up as a handy concept since the cardiac mass during normal and pathological conditions develops metabolic activity involving electrical, mechanical, chemical, and thermal energies. Therefore, these are the different disturbances to add inhomogeneity:

- (a) *Electric energy*, either as a pulse or as a train of pulses, definitely can initiate the phenomenon. In experimental conditions, it represents obviously the best method because it is easy to control, be it in terms of voltage or current.
- (b) *Mechanical energy*, as a thump or several thumps produced with a tool or just with the naked fingers. The resulting minor back and forth compression perhaps produces a redistribution of the membrane electrical charges. Cardiac surgeons are quite familiar with this kind of event.
- (c) *Chemical energy*, as the addition of certain amount of an electrolytic solution containing, for example, potassium ions, or some other exogenous or endogenous agent changing electrophysiological properties. Alcohol feeding is one of the many possible examples (Khedun *et al.*, 1991). Type and amount of anesthesia is another.

- (d) *Thermal energy*, as the addition of certain amount of either warm or cold physiological solution (see Sec. 1.4.2). Gradients of temperature tend to increase the degree of local inhomogeneity by modifying, for example, conductive characteristics of the tissue (Todd, 1983).

There is ample empirical and controlled experimental evidence that any of the above-mentioned perturbations to the heart may lead it into fibrillation.

## 1.4. Types of Fibrillation

Cardiac fibrillation can be classified on the basis of its *etiology*, *localization*, or *characteristics*. Perhaps, these criteria deserve a deeper insight and revision, but they are still useful and have didactic value.

### 1.4.1. Etiology

The word *etiology* refers to the causes of a disease or disorder; thus, we must search for the origin of the specific fibrillation we are faced to. When the origin lies within the heart itself, as ischemia or infarct, it is denominated *primary fibrillation*. Fibrillation triggered by accidental electrocution is usually included in this class.

*Secondary fibrillation* stems, instead, in other non-cardiac pathologies, as for example in electrolytic imbalance due to renal failure. Diabetes, hormonal disorders, genetic factors, sympathetic over-discharge, or anesthesia may be the underlying causes. Let us illustrate with a few examples:

Resuscitation from cardiac arrest caused by volatile substance abuse is rarely successful. Large doses of catecholamines given during resuscitation, in the presence of butane, may cause recurrent VF. Edwards and Wenstone (2000) reported a case of prolonged resuscitation in a young man, who had inhaled butane. Cardiac output was restored 10 min after the administration of intravenous amiodarone. They suggest that antiarrhythmic agents should be used early during resuscitation to prevent recurrent arrhythmias.

An interesting example is described by Munhoz Da Fontoura Tavares *et al.* (2004), from Brazil: a patient with recurrent VF secondary to an aortic tumor. These tumors can obstruct the coronary arteries, secondarily causing ischemia and VF. Such a mechanism must be considered in the differential diagnosis of sudden death.

Upile *et al.* (2006) reported a rare case of atrial fibrillation (AF) secondary to a mega-esophagus occurring in an old woman. Achalasia (from *a* + Greek *chhalasis*, slackening, herein interpreted as, failure of a ring of muscle, as the anal sphincter or one of the esophagus to relax) is associated with a degeneration of ganglion cells of the *Auerbach plexus* resulting in the absence of esophageal peristalsis and failure of lower esophageal sphincter relaxation. This leads to esophageal dilatation (mega-esophagus). There is a correlation between achalasia and cardiac arrhythmia. Patients with this disorder tend to perform a Valsalva maneuver to aid the transit of food over the stenotic esophageal segment. Besides, recall the anatomical proximity of the esophagus to the left atrium and the possibility of mechanical pressure. More than that, abnormalities of heart rate responses to the Valsalva maneuver (Valentinuzzi *et al.*, 1974), deep breathing, and standing were noted in patients with autonomic defects. This is consistent with the hypothesis that abnormal vagal discharge may contribute to the pathogenesis of achalasia. Vagal firing through acetylcholine release reduces atrial electrical refractory period (the classic negative *bathmotropic* effect), which potentiates AF (Valentinuzzi *et al.*, 1973).

Anyhow, the literature abounds and, unfortunately, often it is not clear enough in its definitions and criteria regarding this matter, pointing out perhaps to a pending subject for revision.

#### 1.4.2. *Localization*

Since the heart is composed of two atria and two ventricles, the phenomenon may take place in any of them or in both simultaneously. In lower species, as herptiles (frogs, lizards, snakes, or turtles) it may occur also in the *sinus venosus* (SV), which is their first cardiac chamber, where the pacemaker is located. While the overall sequence of normal events is well documented, the arrhythmia at the SV, however, is extremely difficult to demonstrate and only in very rare circumstances and for very short periods it can be recorded (Valentinuzzi and Hoff, 1970, 1972; Valentinuzzi *et al.*, 1986; Savino and Valentinuzzi, 1988). Figure 1.9 shows rare VF records obtained from an experimental open chest turtle (*Pseudemys floridana*). The four channels, A, B, C, and D, correspond to ventricular myograms, i.e., the heart was hooked from the ventricular apex and attached by a thin thread at an almost 90 degrees angle to a photoelectric transducer. On the left of A, five normal beats are clearly seen with a rate of about 28/min. Just at the occurrence of the sixth beat (vertical arrow), a brief train of rectangular pulses (10 V,

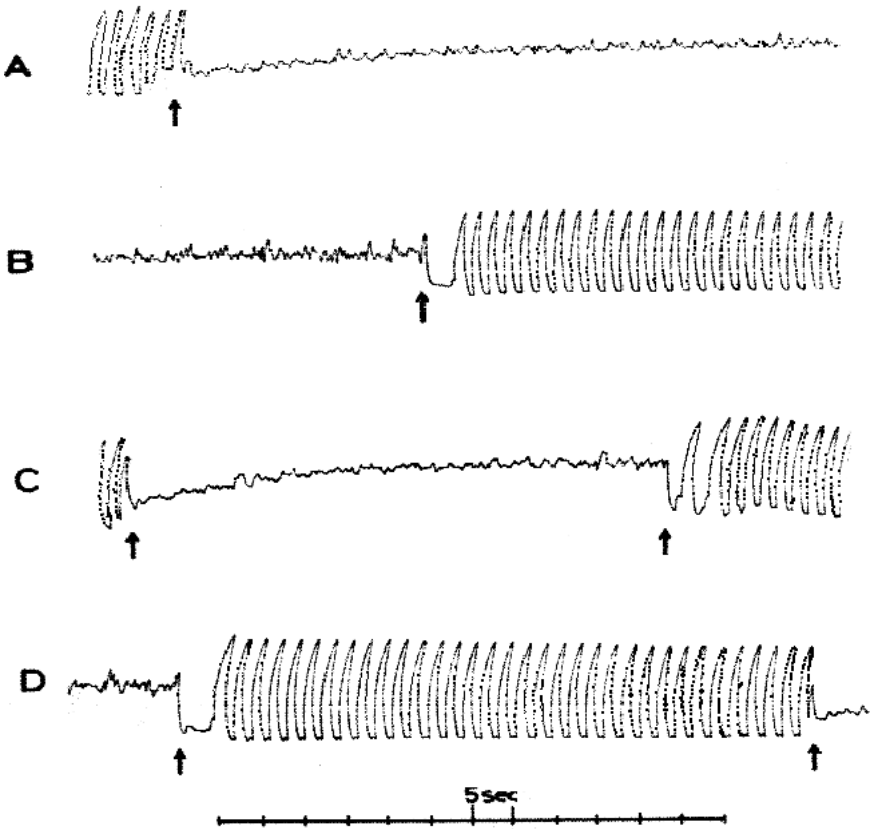


Fig. 1.9. Ventricular fibrillation in an experimental turtle (*Pseudemys floridana*). Time marks below are 5 s apart. See text for details. Obtained by the author at the Department of Physiology, Baylor College of Medicine, Houston, TX, USA, back in the 1960s, during his graduate student years. Also appearing in Valentinuzzi *et al.*, 1986, with the publisher's permission.

2 ms, 25 pps) was directly applied to the ventricles by means of a pair of electrodes triggering the arrhythmia, manifested by the small amplitude grass-like shivering. The second channel B, a continuation of the former above, after 2 min 30 s of fibrillation, displays on the right spontaneous defibrillation (vertical arrow): normal regular beating was resumed. The third channel C, always on the same animal, depicts another episode of fibrillation similar to the first one above, which this time lasted slightly over 1 min and was terminated by the sudden application of cold saline solution. Finally, the lower trace D shows a spontaneous defibrillation on the left (first arrow) followed by another fibrillation triggered with electrical

stimulation. This particular turtle was relatively big, 3 kg of body weight, a fact that could have favored the phenomenon. However, this behavior is far from frequent and no rules can be offered to repeat the experiment.

AF is one of the classical cardiac disorders. It was studied for the first time by James Mackenzie, who is to be considered as the first cardiologist (Hoff *et al.*, 1966). It is a clinical disorder, compatible with life that requires care and medical follow-up because of its persistency and common cause of arrhythmia-related hospitalizations. In addition, it is a major contributor to stroke. Figure 1.1 displays a set of three simultaneous records (surface ECG, semidirect atrial electrogram and arterial blood pressure). Its typical characteristics are clearly seen,

- (1) The ECG does not show the typical P-waves preceding each QRS complex; instead, they have been replaced by a grass-like hum usually termed the *f*-waves.
- (2) Ventricular frequency is high (tachycardia) and irregular. There is tachycardia because of rapid stimulation from the atria to the ventricles via the AV node and it is irregular because not all stimuli can traverse successfully the node, by nature with relatively poor conductive properties.
- (3) There is pulse deficit, that is, when considering an arbitrary time period (say, 30 or 60s), the number of QRS is larger than the number of arterial pulses. In the figure, compare eight beats in channel 1 vs seven in channel 3, when the records between the two vertical bars are inspected. Besides, the pulse amplitude is irregular because some ejections are weak to open the aortic valve (remember Starling's law of the heart); they are too premature and do not allow for an adequate ventricular filling. Clinically, the physician can detect these features by simple peripheral pulse palpation (irregular tachycardia and irregular pulse strength).
- (4) Atrial effective contraction does not exist, meaning that ventricular filling misses the last part. In normal conditions, however, atrial contribution amounts to not more than 20–25% of ventricular filling, hence, and as stated above, the disorder is compatible with life.

AF may persist during many years (10, 20, or more), it needs treatment, and it leads to atrial hypertrophy and rarely, if ever, at least in man, reverts spontaneously to normal rhythm. It is considered serious. In the dog, probably due to heart size, most of the time does not last longer than a few minutes.

In an editorial article, Efimov and Fedorov (2005) discussed quite clearly four traditional and still challenging questions: (1) Is AF myogenic or neurogenic in nature?; (2) Is AF maintained by reentry or by focal activity?; (3) Is AF maintained by a single source, or are multiple sources required?; and (4) Is there a critical mass of myocardium required to maintain AF? They suggest possible avenues of research as well as requirements that might be needed to reach full answers. One important outcome is that AF appears as not fully similar to VF.

An even more recent review article highlights groundbreaking work in AF genetics that has provided with a better understanding of the origins of this dysrhythmia (Damani and Topol, 2009). Historically, many studies have identified the familial predisposition for AF, however, up to 30% of patients are affected without any known familial association and the absence of any other risk factors, such as hypertension or diabetes. Other studies found mutations associated with the disease, but it was not until recent work using sequencing technology, that the 4q25 locus was recognized as a susceptibility factor for AF. The gene *PITX2*, which is known to have a role in embryonic cardiac development, has also been identified as the causal variant within the 4q25 susceptibility locus. Translation of these findings will lead to improved screening, prognosis, and treatment, as well as the future possibility of a personalized approach for the treatment of AF.

*Atrial flutter* can be considered a variant of the former arrhythmia, even though it shows lower frequency components and appears as more regular, its hemodynamic effects, however, are similar to those of AF. It is a common tachycardia that can be caused by scarring in the heart resulting from prior cardiac disease or heart surgery, but it can also occur in some patients with no other identifiable heart problems. During atrial flutter, instead of the electrical activity starting in the sinus node, electrical activity begins in that chamber. The rapid beating of the atria can in turn cause the ventricles to beat rapidly. It typically originates from the right atrium and most often involves a large circuit that travels around the area of the tricuspid valve that is between the right atrium and the right ventricle. This type of flutter is referred to as *typical atrial flutter*. Less commonly, atrial flutter can result from circuits in other areas of the atria. Flutter that results from these less common types of circuits is referred to as *atypical atrial flutter* (Boyer and Koplan, 2005). Figure 1.10 illustrates a clinical example.

VF spreads throughout the ventricular mass (Fig. 1.2). It was observed in 1543 by Andrea Vesalius, author of the first modern anatomy treatise.

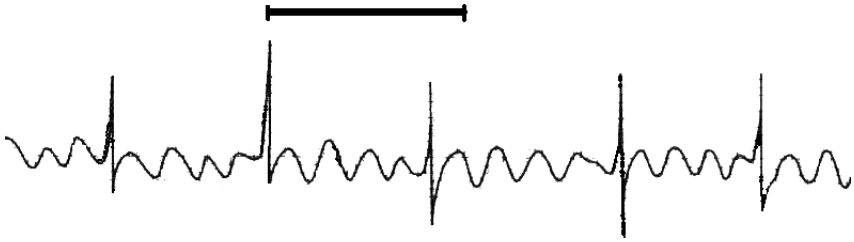


Fig. 1.10. Atrial flutter. The horizontal bar above corresponds to 1 second. QRS complexes are clearly shown while the atrial P-waves have been replaced by a rather regular high rhythm in the order of 300 per minute. Courtesy of Gabriela Feldman, MD, Tucumán City, Argentina.

Hoffa and Ludwig triggered it electrically in 1850 in the experimental animal searching for “tetanic contraction of the heart”, which is now well-known that it cannot take place due to its long refractory period. In 1874, Edmé Félix Alfred Vulpian (1826–1887, French neurologist) coined the term *mouvement fibrillaire* and John A. MacWilliam, a physiologist trained under Karl Ludwig, gave an accurate description in 1887. Clearly, this arrhythmic arrhythmia is incompatible with life posing a serious emergency to be attended to within no longer than a few minutes. Most of the commonly named “heart attack” or “heart collapse” falls in this category. It is the typical emergency of the cardiac surgeon, of the coronary unit, of the street collapse, of the domestic, or industrial accidental electrocution.

### 1.4.3. Characteristics

Once the ECG is disrupted into the fibrillatory waves, its characteristics change suddenly and sharply, from the periodic three-component polymorphic form to the irregular already described pattern. By and large, the first 2–3 min of fibrillation appear as composed of high frequencies with relatively high amplitudes. If the heart is visible, the uncoordinated movements impress as strong and vigorous; this is referred to as *Fibrillation Type 1*, with good possibilities for reversion. As time goes by, the fibrillary contractions weaken as does the probability of reversion. The electrical signal loses amplitude, too, and lower frequency components prevail. It is called *Fibrillation Type 2*. Emergency personnel well know by experience the importance of the fastest possible intervention for the defibrillating procedure to succeed. Animal experimentation has led to the same

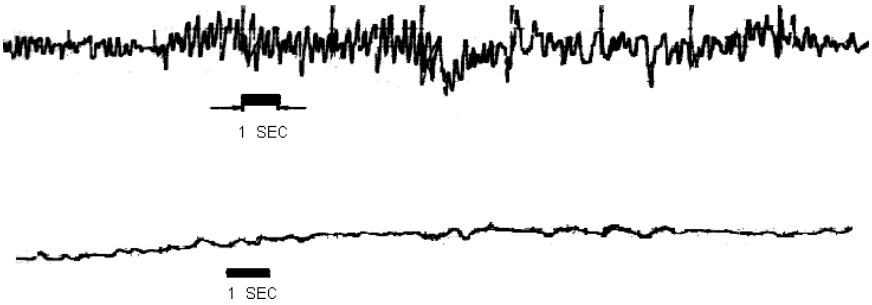


Fig. 1.11. Type 1 (upper trace) and Type 2 (lower trace) Ventricular Fibrillation in the dog. Observe the higher frequencies and amplitudes in the former as compared to the latter, which seems to be fading off. Obtained by the author in the Laboratory of Bioengineering, Universidad Nacional de Tucumán, Argentina.

conclusion. Figure 1.11 depicts both types recorded from an experimental dog. Up to here, the above description is purely qualitative.

A good number of reports fill the literature determining quantitatively the fibrillation frequency components under different conditions. Not all coincide fully; however, ranges are not too far off. It has been found, for example, that during cardiopulmonary by-pass and after inducing VF at a core body temperature of  $34^{\circ}\text{C}$  (normothermia) or at a core body temperature of  $29.8^{\circ}\text{C}$  (hypothermia), by using fast Fourier transform of the ECG signal, median fibrillation frequencies were 5.4 Hz and 3.6 Hz, respectively (Strohmenger *et al.*, 1997).

A team from Austria and Norway (Strohmenger *et al.*, 2001) evaluated VF frequency and amplitude variables in 89 patients with out-of-hospital cardiac arrest. ECG recordings of 594 countershock attempts were collected and analyzed. By using fast Fourier transformation analysis of the VF ECG signal — and quoting from that paper — median frequency, dominant frequency, spectral edge frequency, and amplitude were as follows: 4.4 (2.4–7.5) Hz, 4.0 (0.7–7.0) Hz, 7.7 (3.7–13.7) Hz, and 0.94 (0.24–1.95) mV, respectively, before successful countershock ( $n = 59$ ). These values were 3.8 (0.8–7.7) Hz, 3.0 (0.3–9.7) Hz, 7.3 (2.0–14.0) Hz, and 0.53 (0.03–3.03) mV, respectively, before unsuccessful countershock (number of cases,  $n = 535$ ). In patients in whom bystander CPR was performed ( $n = 51$ ), VF frequency and amplitude before the first defibrillation attempt were higher than in patients without bystander CPR ( $n = 38$ ) (median frequency, 4.4 (2.4–7.5) vs 3.7 (1.8–5.3) Hz, dominant frequency, 3.8 (0.9–7.7) vs 2.6 (0.8–5.9) Hz; spectral edge frequency, 8.4 (4.8–12.9) vs 7.2 (3.9–12.1) Hz; amplitude, 0.79

(0.06–4.72) vs 0.67 (0.16–2.29) mV. Clearly, the unsuccessful interventions were dealing with fibrillations of the second type.

### 1.5. Clinical and Surgical Significance

Sudden cardiac death (SCD) stems in primary cardiac causes, often without previous symptoms. In the USA, about 325,000 people (about 0.2% of the population) a year die of coronary heart disease without being hospitalized or admitted to an emergency room. Most of these are deaths caused by cardiac arrest and are due to ventricular tachycardia or VF or both. Some cardiac arrests, however, are due to extreme slowing of the heart or *bradycardia*. The figures herein cited are approximately the same for the Western countries, all perhaps strained and stressed by similar socio-economic and labor problems. Economic crises, unemployment, and crime increase in big cities are combined factors that have built up a sensation of lack of security. Globalization seems to impose a toll on humankind, giving quite a piece of material not only for the medical sciences but also for psychologists and social workers alike. Politicians should take a look, too, and be concerned at least.

The incidence of SCD parallels the incidence of coronary artery disease (CAD), with the peak of SCD occurring in people aged 45–75 years. The incidence increases with age in men, women, whites, and non-whites. However, the proportion of deaths that are sudden from CAD decreases with age. In the Framingham study (<http://www.nhlbi.nih.gov/about/framingham/>), the proportion of CAD deaths that were sudden was 62% in men aged 45–54 years, but this fell to 58% in men aged 55–64 years and to 42% in men aged 65–74 years ([www.americanheart.org/presenter.jhtml; www.emedicine.com/med/topic276.htm](http://www.americanheart.org/presenter.jhtml?www.emedicine.com/med/topic276.htm)).

Fibrillation, either atrial or ventricular, is no doubt a cardiologic clinical problem of current standings. If we recall what is presented in the previous paragraphs above, it is also a potential surgery event; occasionally, it may be deliberately triggered to quiet down the contracting heart, which, during an intervention under the control of a heart–lung machine, acts as a disturbance. However, it is a controversial issue and some authors favor hypothermia or cardioplegic solutions as stabilizing methods during cardiac surgery. By definition, **cardioplegia** is the intentional and temporary cessation of cardiac activity. Most frequently, it is obtained by injection of a cold crystalloid because it protects the myocardium from damage. Sometimes, the patient is first exposed to hypothermia and, thereafter,

iced solution of dextrose and potassium chloride is introduced into the heart (<http://en.wikipedia.org/wiki/Cardioplegia>).

All this points out to a whole battery of associated laboratory and imaging studies to complement and back up a therapeutic decision: ECG to help identify ischemic or pro-arrhythmic conditions, serum electrolyte levels (including calcium and magnesium), cardiac enzymes to identify myocardial injury, complete blood count (CBC) to detect possible anemia, arterial blood gases to assess the degree of acidosis or hypoxemia, and even the determination of eventual toxic substances. Images include the traditional X-rays or any of the more sophisticated single photon emission computed tomography (SPECT), positron emission tomography (PET), nuclear magnetic resonance (NMR), and/or Doppler echocardiography to identify hypokinesia, aspiration pneumonia, pulmonary edema, cardiomegaly, or injury, as secondary to cardiopulmonary resuscitation CPR.

## 1.6. Fibrillation Variables

The fibrillating arrhythmia can happen either in the atria or in the ventricles or simultaneously in both. Qualitative description is usually the case (as up to here in this text, interspersed with a few quantitative parameters), but no absolute quantification has so far been developed, as with other physiological variables (for example, blood pressure, blood flow, or concentration of substances). We cannot offer a statement like “this fibrillation is very serious because it measures so many units or because it is of grade 3 or 4”; at most, Types 1 and 2 are feebly distinguished, as described before. The only true statement refers to just a normally beating heart or to a fibrillating heart, as states. Besides, some stimuli (see above) may induce the passage from one state to the other, either way, and there are factors or variables that favor the transition. Finally, once the transition takes place (from normal beating to fibrillation or vice versa), the stimulus does not have to be maintained, for either spreading of fibrillation to the whole mass or reversion to the regular beat, act by themselves, as self-sustained events.

### 1.6.1. *Electrophysiological Variables*

Everything related to the movement of charges *in* and *out* of or *along* the cardiac fibers belongs to this group. Hence, diastolic potential, action potential amplitude, action potential duration (APD) (refractory period), propagation velocity, diastolic depolarization, and depolarization rate, are

to be taken into account. Membrane permeabilities to sodium, potassium, and calcium ions are also members of the set. In short, all that encompasses the electrophysiological behavior of the myocardium.

### 1.6.2. *Metabolic Variables*

Cardiac tissue consumes energy and delivers work. All the complex processes involved in such actions include availability, synthesis, processing, and breaking down of a variety of substances such as oxygen, carbon dioxide, adenosine triphosphate (ATP), enzymes, chemical and hormonal mediators, and the like. They influence the above-mentioned variables, sometimes very deeply, as hypoxia would do. Over 30 years ago, attention was called over some of these factors including hypothalamic influence, too (Verrier *et al.*, 1975; Obeid *et al.*, 1978).

All variables influencing the probability of triggering fibrillation are no doubt inter-related and not precisely in a simple form. The best we can do is trying to qualitatively anticipate how high that probability is in a particular individual given a number of previously measured variables and cardiac history. This is the way to classify a patient as of “high or medium cardiac risk”.

### 1.6.3. *Myocardial Mass*

Garrey (1914) proposed the concept of *critical mass* as essential in the establishment of the fibrillatory waves and estimated a value not in weight but in square units, suggesting 400mm<sup>2</sup> as possible figure. In fact, MacWilliam long before, in 1887, advanced the same idea. The size of the heart is obviously related to the possible length of the reentry circuits and it is easily visualized that a longer pathway tends to facilitate the phenomenon. Small hearts would not fibrillate easily or would not at all. The opposite should hold true. Homogeneous hearts (that are small, too), as those of lower animals, would not either; however, there are reports of uncontrolled cases in which the phenomenon was sporadically seen (Valentinuzzi *et al.*, 1986; Savino and Valentinuzzi, 1988; see also Fig. 1.9).

A few investigators have tried to numerically estimate that *minimum fibrillating mass*. Moe and Abildskov (1959), for example, claimed it is in the order of 1g; much later, Ruiz and Valentinuzzi (1994) considered a *minimal defibrillating mass* (perhaps around 11–12g), that is — and anticipating the concept to be discussed in the chapter on defibrillation — the smallest mass (in essence, number of fibers) to depolarize in order

to revert the phenomenon; such mass is conceptually similar but not necessarily numerically the same as the former.

Nolasco and Dahlen (1968) reported that if the relation of the APD and its preceding diastolic interval (the so-called *restitution relation*) is equal or larger than 1, electrical alternans may show up, while the latter phenomenon does not take place when such relation is smaller than 1. Recall that alternans may well become a preliminary event to fibrillation; recall also that if a heart is driven by slowly increasing the stimulation frequency, the diastolic interval gets shorter and, as the process continues, repolarization of one pulse touches at some instant the depolarization phase of the following pulse so signaling in all probability the beginning of fibrillation. In such case, the electrical diastolic interval  $T_D$  tends to zero or becomes zero and  $APD/T_D$  tends to a large value. Years later, and following Nolasco and Dahlen's lead, Wu *et al.* (1999) studied how the restitution characteristics might influence the *fibrillation critical mass*, since the latter might be influenced by the former. The goal of these authors was to evaluate the relationship between repolarization characteristics and critical mass for VF in diseased human cardiac tissues. Hearts from transplant recipients were used. After a rather sophisticated methodology, it was found that at baseline, VF did not occur either spontaneously or during rewarming, and it could not be induced by electrical stimulation. Reproducing now almost verbatim from their paper: "The mean APD at 90% depolarization at a cycle length of 600 msec was  $(227 \pm 49)$  msec, and the mean slope of the APD restitution curve was  $0.22 \pm 0.08$ . The weight of these samples averaged  $(111 \pm 23)$  g (range 85 to 138). However, after cromakalim infusion, sustained VF (>30 min in duration) was consistently induced. As compared with the baseline in the same tissues, cromakalim shortened the APD at 90% from  $(243 \pm 32)$  msec to  $(55 \pm 18)$  msec and increased the maximum slope of the restitution curve from  $0.24 \pm 0.11$  to  $1.43 \pm 0.10$ . They concluded that at baseline, the critical mass for VF in diseased human hearts *in vitro* is >111 g. However, the critical mass for VF can vary, as it can be reduced by shortening APD and increasing the slope of the APD restitution curve". Observe that this value is more than 100 times higher than that estimated by Moe and Abildskov 40 years ago, although it admits different figures, presumably lower, if the APD shortens.

Winfree (1994) predicted 100–200 mm<sup>2</sup>, i.e., one-fourth to one-half smaller than Garrey's value, basing his assumption on the vortex-like reentry; he also advanced 12 cm<sup>3</sup> or 12 g, as possible value for the critical mass. He expressed the idea in a different way, too: a minimum size of

six times the rotor diameter, which would lead to a volume of about 12g, although it is not clear how the latter figure was actually obtained. Vaidya *et al.* (1999), in a beautifully presented article, reflectively state that sustained fibrillation should not be possible in the mouse heart with ventricular areas of some 100 mm<sup>2</sup> and masses around 200 mg. They wanted to determine whether arrhythmias are possible in the adult mouse ventricle and, after careful experimental design, they found that such Langendorff perfused heart can, indeed, sustain rotors and VF. The result is surprising because the wavelength (10–30 mm), as the authors themselves assert, is larger than the available length, which may mean that wavelength is not a good fibrillation predictor, at least in the mouse. The paper offers several previous references that suggested reentry in small pieces of cardiac tissue and concludes that an area just larger than that required for reentry could support fibrillation. The latter sounds quite sensible.

In a not too clear paper, Fatema *et al.* (2008) sought to compare the predictive power and reproducibility between minimum and maximum left atrial (LA) volume for the development of first AF or flutter. It was a prospective study in 574 adults (mean age  $74 \pm 6$  years), in sinus arrhythmia, with no history of prior atrial arrhythmias. After a mean follow-up period of ( $1.9 \pm 1.2$ ) year, 30 of them (that is, 5.2%) developed either AF or flutter. Without giving actual volume values or explaining how such parameter was determined (apparently, echocardiography was used), these authors concluded that “*minimal LA volume was an independent predictor of first AF/flutter*”. Is this contribution related to the concept of minimal fibrillating mass? The answer tends to the affirmative, but from the information made available it becomes rather difficult to assess. A large volume does not necessarily mean a large mass for it may be due to blood overload of the cavity.

Panfilov (2006) put forward the concept of *effective size*, which takes into account the wavelength of reentry, as determining factor. The paper deserves a more detailed consideration because its ideas are attractive, indeed. From Eq. (1.1) above, such wavelength  $L$  in a physical pathway is given by the refractory period  $\tau$  multiplied by the velocity  $V_p$  (or  $L = \tau V_p$ ). However, cardiac reentry is usually characterized by a spiral shape, with a specific geometry, so that wavelength  $L$  is defined in a slightly different way, as this author clearly says. For isotropic tissue far from the spiral wave core, such shape can be approximated in polar coordinates ( $r, \varphi$ ) as  $r \cong \lambda \varphi 2\pi$ ; in the latter, the wavelength  $\lambda = V_p(T)T$ , where  $T$  stands for the period of spiral wave rotation and  $V_p(T)$  represents the wave propagation velocity at

that particular period  $T$ . Hence, the spiral wave depends only on  $\lambda$ , which in turn means that the number of spiral turns is a function of the tissue size  $S$  relative to  $\lambda$ , so that Panfilov (2006) defines the *effective size*  $S_e$  as  $S/\lambda$ . However, tissue size (or heart size) is a rather undetermined parameter because of the complex shapes involved that calls for further elaboration if a quantitative value is searched for. Panfilov, then, very ingeniously proceeds assuming that the shapes of two different ventricles or atria have the same ratios relative to their respective anisotropic properties. In such situation, relative sizes can be estimated from the cubic roots of their masses (Winfree, 1994). Heart weight can be measured or approximated as 0.6% of the body weight, while the spiral wavelength is the period of the tachycardia or fibrillation (easily obtained from the ECG). Unfortunately, data regarding the propagation velocity *at the arrhythmia frequency* are rarely, if ever, available, meaning that an exact computation of the wavelength is not possible. Panfilov, again quite slyly, states that arrhythmia wavelengths can be compared by comparing their periods under the approximate assumption that conduction velocities are the same, and so defines for a particular species the relative effective size of the heart  $S_{re}$  as,

$$S_{re} = \frac{\sqrt[3]{(HW)}}{T}. \quad (1.2)$$

The above expression is a rough approximation, as he clearly recognizes, but gives the possibility of comparing VF of different animals, including man. With Eq. (1.2), Panfilov (2006) estimated effective sizes for rabbit, dog, pig, and human hearts during VF reporting the following  $S_{re}$  values:

Rabbit,	$33.2 \pm 12.9$ ,	estimated heart weights,	(18 to 30) g
Dog,	$53.1 \pm 15.3$ ,	estimated heart weight,	(150 $\pm$ 40) g
Pig,	$59.4 \pm 12.7$ ,	estimated heart weight,	(210 $\pm$ 40) g
Human,	$37.4 \pm 9.3$ ,	estimated heart weight,	(420 $\pm$ 60) g

Observe how the relative effective size grows to a maximum falling back to almost the initial value as the heart weight increases (Fig. 1.12). The maximum corresponds to approximately 250 g and, while the range of mass is rather wide, between 25 and 500 g, the range of the effective fibrillating size appears as considerably narrower, only from 30 to 60, the former being about 16 times larger than the latter. Anyhow, speculating on this interesting proposal would not lead anywhere. It must be underlined, too, that in Eq. (1.1), there are two overlapping concepts: one is  $L$ , the

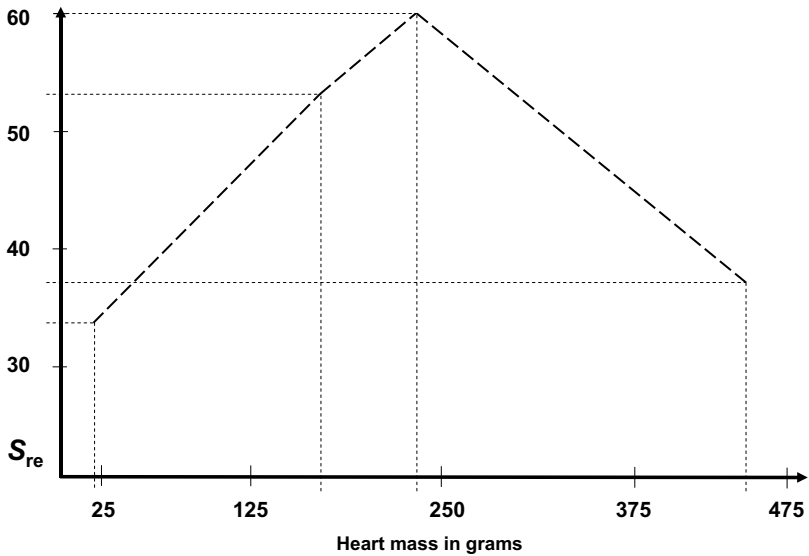


Fig. 1.12. Relative effective heart size  $S_{re}$  vs heart mass. Inspired in Panfilov's Figure 1b (2006) and using his average data. With the latter author's kind permission.

physical available length over the tissue; and  $\lambda$ , the wavelength of the electrical circulating signal, that at first sight ought to fit into the former path, even though, as reported above by some authors, is not always so.

Closing this section, we underline that whatever the actual value of the critical mass, it is clear that fibrillation is a *group concept*, in the sense that for one fiber the phenomenon does not have meaning, even for just a few fibers it would be questionable. Obviously, it calls for more and quite attractive research, both experimentally and theoretically. Besides, heart and body weights are related and it has been known for a long time that obese people tend to have larger hearts, which are easier to fibrillate and more difficult to defibrillate (DeSilva and Lown, 1978).

## 1.7. Electrical Fibrillation Thresholds (EFTs)

### 1.7.1. Definition

The minimum magnitude (amplitude in adequate units, of whatever kind) required to trigger fibrillation is called *fibrillation threshold*. A small increment assures fibrillation, while the same decrement will never produce the event. It is like walking on the borderline of a step ladder: a bit to the flat side, and we are safer; a bit to the cliff side, and we fall off. Perhaps a better

definition should state: *That amplitude with 50% probability of triggering the phenomenon is the fibrillation threshold.* It is interesting to note that as early as 1940, Wiggers and Wegria proposed the fibrillation threshold concept as a parameter to quantitatively evaluate myocardial susceptibility or sensitivity to the arrhythmia, which no doubt continues as valid practical piece of information; an ischemic ventricle, for example, requires less current than a healthy heart to fall into the uncoordinated activity.

To deepen into the concept two aspects need further discussion: *Methods of Stimulation* and the so-called *Ventricular Vulnerable Period*.

### 1.7.2. *Methods of Stimulation*

Cardiac stimulation is frequently used in experimental physiology and in clinical studies as a method to evaluate the effects of drugs or the responses in a given pathology. The outstanding saga of electrophysiologists, among a wealth of superb contributions, has led to the now fully recognized rectangular waveform as the best controllable electrical stimulus.

As a *single pulse*, the stimulus is characterized primarily by its duration and amplitude and, secondarily, by the rising and falling times, usually defined as the times elapsed between the 10% and 90% levels of the maximum amplitude. The two latter time parameters are more than met by the current electronic technology, i.e., they are short enough and negligible in comparison with the durations found in cardiac electrophysiology, which at most covers a range of 10–500 ms. In other words, the pulse behaves as if it were a perfect rectangle.

As a *train of rectangular pulses*, the stimulus needs two other characteristics to be specified: the *repetition frequency* and the *on-off ratio*. The former is measured in number of pulses per second or pulses per minute (p/s or ppm) and the latter as a number between 0 and 1, which describes the ratio of the time current (or voltage) is applied to the repetition period; thus, a 0.5 or a 50% ratio would mean pulses that apply current during one-half of the total cycle. Sometimes, it is also-called the *stimulation duty ratio* or *duty cycle*. Besides, the train has always an *overall duration*, from start to end, which includes a definite total number of pulses.

### 1.7.3. *Vulnerable Period*

A single electrical pulse can trigger fibrillation, however, to study the conditions for this to happen requires the exploration of the cardiac cycle, from QRS to QRS complex; say, from beat  $N$  to beat  $(N + 1)$ . A pair of

electrodes picks up the ECG and this signal is connected to the stimulator trigger input. Besides, the output from the stimulator is connected via adequate electrodes to the myocardial mass. When the stimulator is manually turned on, it does not yet deliver the stimulus but it waits a predetermined time — an *adjustable delay* — being triggered by the next and immediately oncoming R-wave. In this way, all the cycle is explored, from zero delay, i.e., applying a stimulus to the heart in coincidence with the R-wave, up to the following (R + 1)-wave. For each cycle location, the stimulating single pulse is raised from zero amplitude up to the value that actually triggers fibrillation or to a maximum value in the case fibrillation is not met. A given pulse width must be selected (say, 1, 2, or 5 ms or longer, if necessary) and either voltage (in Volts) or current (in mA) should be chosen as the electrical parameter to apply. Plotting those pulse amplitudes vs the cycle location would produce the threshold curve for fibrillation (Fig. 1.13); those values on the upper region should always lead to fibrillation while values below never will. Values at the far left or at the far right will never trigger fibrillation because the ventricles are in the refractory period. However, there is a clear region where the curve falls off rather sharply showing a definite minimum, precisely in coincidence with the T-wave of the ECG. In other words, with one single pulse, either of voltage or of current, at a given pulse width, a definite duration in the order of 30 ms (roughly the duration of the T-wave) is found over each beat where fibrillation is more likely to occur. Like a window letting bad air

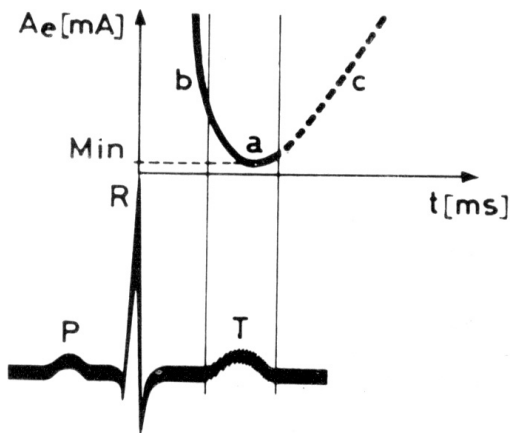


Fig. 1.13. Ventricular Vulnerable Period. The T-wave duration of each cardiac beat is more sensitive to a single electrical stimulus. Amplitudes above display a clear minimum at *a*. Vertical axis can be expressed either in mA or in volts as well.

in, that is the *vulnerable period* of the heart. Thus, the *electrical fibrillation threshold (EFT) to single pulse stimulation* is that minimum amplitude with a 50% probability of triggering the phenomenon when directly applied to the myocardium during the vulnerable period.

A train of pulses can also be synchronized with the QRS complex (Fig. 1.14, lower panel) or can be applied at any random instant. Depending on its overall length, the train may fully cross the T-wave region or it may fall short. Most of the time, however, pulses bombard all through the vulnerable period greatly favoring the discharge of the arrhythmia. A fibrillation threshold is also defined for this situation and, as expected, this second value is always considerably lower than to single pulses. In other words, a burst of electrical pulses is more likely to produce cardiac fibrillation than an isolated pulse; this conclusion has relevance when electrical safety is considered (alternate current is more dangerous than direct current). With single pulse, the probability of hitting the vulnerable period is low, about  $D_T/T_C$ , where the numerator stands for the ECG T-wave duration and the denominator represents the cardiac period, roughly 10% at the most.

Hence, EFTs depend on many factors, patho-physiological, pharmacological, technological, and procedural (Ruiz *et al.*, 1987); numerical values are only illustrative, as orienting references, and should not be taken as absolute. Comparisons are acceptable exclusively when similar conditions are met. Let us offer examples reported in the literature. Some papers published before 1986 dealing with this specific subject are referred to in Valentinuzzi *et al.* (1986).

Aupetit *et al.* (1993) found a beneficial effect of calcium antagonists when studying the vulnerability to fibrillation. The threshold intensity for fibrillation electrically induced with impulses of 100 ms and 180 ppm (3 Hz) was measured during the course of ischemias obtained by total occlusion of the left anterior descending coronary artery near its origin in open-chest pigs. The variations of EFT with ischemia duration (30, 60, 120, 180, 240, 360)s were compared under control conditions and after diltiazem. EFT was not influenced by diltiazem before, but raised during ischemia, particularly from the 60th second, from 1.7 to 4.0 mA. In six pigs out of eight, fibrillation was even avoided in the longest of the ischemic periods considered (360s). These experimental results obtained with diltiazem are consistent with the clinical effectiveness of calcium antagonists recently observed in the prevention of post-infarction sudden death, provided that myocardial contractility is not too much adversely affected.

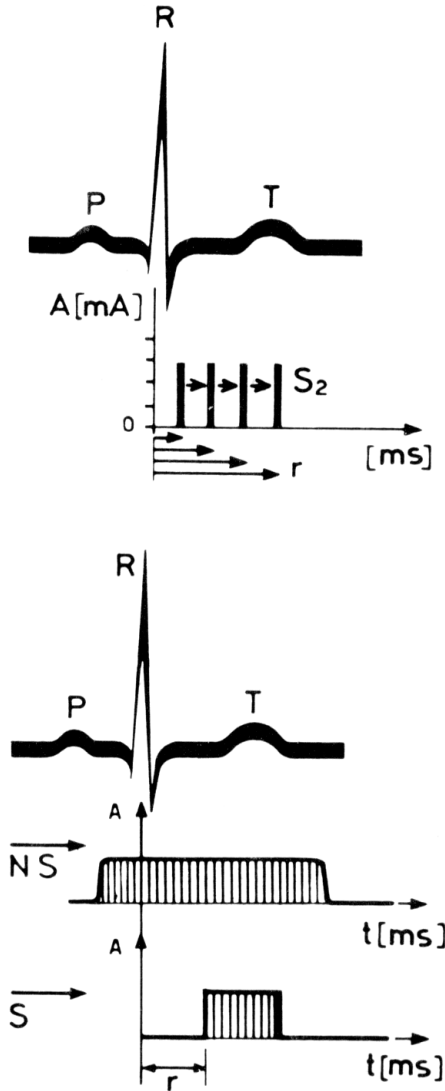


Fig. 1.14. Upper part: Synchronized single stimulus with adjustable delay. See also the preceding Fig. 1.13. Lower part: Non-synchronized (NS) and synchronized (S) trains of pulses; the latter with adjustable delay.

Ruiz and Valentinuzzi (1994) determined in a group of 17 dogs an average EFT of  $(14.1 \pm 4.3)$  mA applying with spoon electrodes ( $664 \text{ mm}^2$ , i.e. a current density of  $0.21 \text{ mA/mm}^2$ ) directly to the ventricles non-synchronized train of pulses of 2 ms width, 50 Hz repetition rate and overall

duration of 1 s (meaning that 50 pulses were delivered). In a group of 33 animals, instead, the average EFT was  $(0.91 \pm 0.44)$  mA with the same type of stimulus but using hook electrodes inserted on the myocardium ( $11 \text{ mm}^2$ , i.e. a current density of  $0.08 \text{ mA/mm}^2$ ). On the other hand, with synchronized single pulses of 5 ms duration using hook electrodes, the average value over the same group of 33 dogs was  $(16.8 \pm 7.4) \text{ mA/mm}^2$ , or a density of  $1.53 \text{ mA/mm}^2$ . Obviously, a single pulse was less effective than a train to trigger fibrillation; besides, hook electrodes were more effective than large electrodes applying trains because the former concentrate the stimulus on a small spot creating a focalized inhomogeneity. In the previous report, the threshold for each animal was obtained from the threshold band concept (Valentinuzzi *et al.*, 1984), that is, the applied current attempting fibrillation was plotted as a function of time. A band can be bounded between the maximum value that did not trigger fibrillation and the minimum that did produce the arrhythmia. The mid-range value of such band was taken as the ventricular EFT for that particular animal. The width of the band can well be considered as an estimator of intra-animal repeatability. Numerical data collected from dogs, sloths, and cats yielded that the mid-range value does not differ significantly from the average value within the band. This “fibrillation band” contains values that may or may not trigger the phenomenon with a 50% probability of success. Thus, this definition would take account of the random variations intrinsic to the threshold concept.

Opposite to diltiazem, as described above, myocardial ischemia sensitizes the cardiotoxic effects of bupivacaine, especially the propensity to VF. In anesthetized, open chest pigs, determination of EFT was performed with impulses of 100 ms duration at the rate of 180 bpm, in the absence of ischemia and at the end of increasing periods of ischemia (30, 60, 120, 180) s obtained by complete occlusion of the left anterior descending coronary artery, that is, similar conditions as described by the same group (Aupetit *et al.*, 1993). Bupivacaine significantly increased the fibrillation threshold before coronary occlusion from approximately 7.0 to 9.5 mA. In contrast, during ischemia, the fibrillation threshold was shifted to the left and down, with a hastening of spontaneous fibrillation. Recording of monophasic action potentials in the ischemic area revealed that conduction time was prolonged by more than 100% under the combined influence of ischemia and bupivacaine, whereas the major enhancement of excitability due to ischemia was not attenuated by bupivacaine. Therefore, bupivacaine should be used with caution in the condition of ischemia, especially if

heart rate is rapid. Besides, tachycardia may be another factor in the enhancement of bupivacaine effects on conduction (Freysz *et al.*, 1995).

Left ventricular hypertrophy (LVH) is associated with an increased risk of death, susceptibility to ventricular arrhythmia, and multiple electrophysiological abnormalities. Do such susceptibility and electrical abnormalities persist after regression of hypertrophy? Rials *et al.* (1995) placed constricting bands on the ascending aorta of cats or performed sham operations. Serial cardiac echocardiography was performed to measure left ventricular wall thickness. After LVH had developed in the banded animals, the constricting bands were removed and serial echocardiograms were used to monitor for regression of hypertrophy. Cats with persistent LVH had a higher incidence of ventricular tachycardia compared with those that regressed or with sham and had lower VF thresholds ( $9 \pm 2$ )mA against ( $17 \pm 4$ )mA or ( $16 \pm 3$ )mA. Persistent LVH was associated with prolongation of epicardial monophasic action potential duration (MAPD). Dispersion of refractoriness was greater in the group with no regression vs the other two groups. The authors concluded that LVH produces multiple electrophysiological abnormalities and increased vulnerability to inducible polymorphic ventricular arrhythmia.

The latter same group (Rials *et al.*, 1997) addressed the possible regression of ventricular hypertrophy using captopril, including its vulnerability to fibrillation. They used rabbits which had undergone unilateral renal artery banding and contralateral nephrectomy to induce LVH or were placed in the control group. Their description states: "Both groups were studied 3 months later by *in vivo* and *in vitro* electrophysiological techniques. Banded rabbits had increased mean arterial pressure, increased left ventricular weight and wall thickness, increased dispersion of refractoriness, and lower ventricular fibrillation thresholds than control rabbits. Action potential duration and cell capacitance were also greater in the banded group. Additional rabbits were treated beginning 3 months after banding with either captopril or vehicle added to their diet for an additional 3 months. These rabbits and age-matched controls were then studied by *in vivo* and *in vitro* electrophysiological techniques. In banded rabbits that received vehicle and were studied 6 months after banding, increased dispersion of refractoriness, a lower ventricular fibrillation threshold, and action potential prolongation persisted and were unchanged from animals studied 3 months after banding. Captopril, started 3 months after banding, caused regression of hypertrophy and normalization of the *in vivo* and *in vitro* electrophysiological abnormalities.

Addition of captopril to the tissue bath during *in vitro* electrophysiological study showed no effect on cells from control or banded rabbits. That is, pharmacological regression of LVH with captopril normalized the *in vivo* and *in vitro* electrophysiological abnormalities of ventricular hypertrophy and reduced the vulnerability to ventricular fibrillation”.

## 1.8. Conclusions and Review Questions

The fibrillation process is a complex and still not well understood phenomenon, even though at least three theories have been so far proposed: re-entrant and persistent excitatory waves, appearance of many pacemaker sites, and formation of relatively organized vortices that tend to generate other vortices as they wander. Perhaps, the latter are a different and more sophisticated way of looking at the circular motions. Several causes have been identified that can be placed either in the clinical, industrial (or domestic), or surgical setting; in the end they amount to the concept of disturbance or to added inhomogeneity to a tissue which is by nature highly inhomogeneous. The latter leads to the traditional four kinds of applicable energies: electric, mechanic, chemical, or thermal. Primary and secondary fibrillations are also distinguished as according to its anatomical localization, that is, atrial or ventricular, the former compatible with life and considered as clinical, and the latter classified as an urgent emergency. The so-called fibrillation variables were introduced along with the not yet well-documented idea of critical fibrillatory mass. Finally, EFT, which can be widely changed by a number of parameters and by methods of stimulation, was presented; it is linked to the extremely important concept of vulnerable window.

*Review questions* (T = True; F = False)

- |  |   |   |
|--|---|---|
| 1. Mechanical contraction of the ventricles means the presence of previous electrical activity.  | T | F |
| 2. During normal cardiac activity the sequence of events is: <i>sinus node-atrial/atrial contraction/AV node-ventricular conduction system-ventricular mass/ventricular contraction.</i> | T | F |
| 3. Cardiac fibrillation is the phenomenon of asynchronous or incoordinated or chaotic activity either of the atrial or of the ventricular fibers.  | T | F |

4. Atrial fibrillation is not compatible with life while ventricular fibrillation is. T F
5. The circus motion theory of fibrillation says essentially that many hyper-excitabile points all over the myocardial mass tend to take over the control of cardiac action. T F
6. Cold may slow down the propagation of action potentials along the myocardial fibers, while acetylcholine may hinder conduction across the AV node. T F
7. Mammalian myocardial tissue is inherently homogeneous, very much like in a lower heart. T F
8. A vigorous fibrillation, that is, with high frequency components and good amplitude, has better probability of being reverted. T F
9. A single cardiac fiber may enter into fibrillation. T F
10. An electrical stimulus with amplitude having 50% probability of triggering fibrillation is called electrical fibrillation threshold or EFT. T F
11. A sudden accidental human body connection to a direct current power generator . . .  
 (A) will very likely trigger cardiac fibrillation.  
 (B) will never trigger cardiac fibrillation.  
 (C) may trigger cardiac fibrillation.  
 Finish the above statement with either (A), (B), or (C), as the most appropriate form to express the concept.
12. The ventricles of a mammalian heart are electrophysiologically more unstable during the duration of the T-wave. T F
13. A short action potential . . .  
 (A) does not have any effect on the probability of fibrillation.  
 (B) tends to favor the arrhythmia.  
 (C) does not favor the arrhythmia.  
 Finish the sentence above with the most plausible option.

14. Abnormal intercellular coupling in the heart, resulting say from defects in the expression of *connexin 43*, plays a key role in the initiation and maintenance of sustained arrhythmias. T F
15. Electrical waves rotating around functional obstacles act as primary organizing centers for fibrillation.  
ABSOLUTELY TRUE PERHAPS TRUE  
ABSOLUTELY NO
16. Ventricular hypertrophy or dilatation, hypokinesia, weakened contractility, insufficiency, low ejection fraction, atherosclerosis do not favor the probability of fibrillation. T F
17. The type of anesthesia may favor ventricular fibrillation. T F
18. Mark at least three possible etiologic factors favoring cardiac fibrillation:  
CATECHOLAMINES BRONCHITIS  
VAGAL FIRING DEPRESSION  
AORTIC TUMOR
19. Lower animals fibrillate very easily. T F
20. Fibrillation of the second type is characterized by . . .  
(A) high frequency components.  
(B) a wide spectrum.  
(C) low frequency components.  
Select the best answer.
21. Fibrillation is a group phenomenon, that is, one single fiber cannot fibrillate. T F
22. A minimum mass of cardiac tissue is needed for fibrillation to take place. T F
23. An electrical amplitude with 50% probability of triggering the phenomenon is called the electrical fibrillation threshold. T F

24. The electrocardiographic T-wave marks a period of . . .

- (A) no susceptibility to electrical pulses.
- (B) high susceptibility to electrical pulses.

25. Is cardiac fibrillation a fully understood arrhythmia?

YES      NO