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Review

Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and the major cardiac cause of stroke. Recent studies in patients with paroxysmal AF have shown that the arrhythmia is triggered by focal sources localized usually in one of the cardiac veins. However, in chronic AF, the prevailing theory is that multiple random wavelets of activation coexist to create an unorganized atrial rhythm. Experiments in isolated hearts have demonstrated that stable, self-sustained rotors can exist in the atria and that high frequency activation by such rotors results in the complex patterns of activation that characterize AF. Studies in animals and patients support the view that at least some cases of paroxysmal and chronic AF are the result of the uninterrupted periodic activity of discrete reentrant sites. In this brief review article, we examine historical data and more recent experimental evidence behind the hypothesis that AF may be organized by one, or a small number of high-frequency reentrant sources localized in the left atrium. We then discuss the potential implications and evidence supporting such a hypothesis for human AF. Finally, we suggest future studies designed to unravel the detailed molecular, cellular and pathophysiological mechanisms responsible for AF initiation and maintenance. The work discussed may open potentially exciting new diagnostic and therapeutic possibilities.

Keywords: Arrhythmia (mechanisms); Supraventr. arrhythmia

Fibrillation, like flutter, may also on occasion be terminated in the auricle by cold or pressure very locally applied

Sir Thomas Lewis

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, afflicting over 2 million Americans [1,2], and is the major cardiac cause of stroke [3,4]. Moreover, the rapid heart rate resulting from AF can bring about a number of adverse outcomes including congestive heart failure and tachycardia-related cardiomyopathy [5,6]. Medications are only marginally effective in treating this arrhythmia, and have the potential for serious side effects, including life-threatening pro-arrhythmia. On the other hand, it has recently been demonstrated that patients with paroxysmal AF can be cured by a catheter-based ablation procedure [7]. This is based on the observation that the mechanism of AF in these patients is a focal source localized usually to one of the pulmonary veins [8,9]. However, in chronic atrial fibrillation, the prevailing theory regarding its mechanism is that multiple random wavelets of activation coexist to create an unorganized cardiac rhythm [10]. In this article, we examine recent evidence supporting the hypothesis that, at least in some cases, AF is organized by one, or a small number of high-frequency sources localized to the left atrium (LA). This might make chronic atrial fibrillation amenable to the use of effective therapeutic strategies designed to target prevention of the formation of the reentrant source.

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2. Mechanisms of AF; a historical perspective

2.1. Ectopic foci vs. circus movement

The exact mechanisms underlying AF are still poorly understood despite many years of research and speculation. As early as 1907, Winterberg [11] surmised that AF was due to multiple rapidly firing foci distributed throughout the atria. In 1914, Mines [12] advanced the circus movement theory of reentry. Thereafter, and until the late 1950′s, all of the hypotheses proposed to explain AF were variations of the circus movement and ectopic focus theories [13,14]. However, following publication of the multiple wavelet hypothesis by Moe and Abildskov [10], it became generally accepted that AF was the result of the random propagation of multiple wavelets across the atria, a process that was thought to be independent of the initiating event.

2.2. Multiple wavelets vs. circus movement

Moe and Abildskov [10] strongly argued that both the ectopic focus and circus movement reentry notions were inadequate descriptions of AF. For them it was hard to believe that either mechanism could be endowed with the necessary stability to persist for many years as AF commonly does. Thus, they proposed that the mechanism of AF, whether occurring spontaneously in man or produced experimentally, was fundamentally different from flutter and from automatic ectopic discharge. In 1964, Moe et al. published their classical computer model study on AF [15]. Based on that numerical study and on their previous experimental results [10], they postulated that AF could exist as a stable state, self-sustained and independent of its initiating agency, and also that an independent survival of the arrhythmia was possible only in the presence of inhomogeneous atrial repolarization enhanced by adequate vital activity. The idea of Moe et al. was simple. They considered fibrillation to be a fundamentally turbulent and self-sustaining process, which takes place in a non-homogeneous excitable medium. Such a process could be initiated by an impulse propagating through the medium at a time when some of its components have recovered while others remain partially or fully refractory as a result of a preceding activation. Accordingly, some elements in the medium may be activated while their neighbors may not [10,15].

Experimental support for the multiple wavelet hypothesis had to wait almost 20 years when high-resolution electrode mapping systems were sufficiently developed to allow the recording of electrical activity simultaneously from several hundred different sites on the atrium, giving the possibility of demonstrating turbulent activity during atrial fibrillation. In 1985, Allessie et al. [16] were able to map the spread of excitation in the atria of a dog heart during rapid pacing-induced AF in the presence of acetylcholine, and provided the first demonstration in vivo of multiple propagating wavelets giving rise to turbulent atrial activity. Moreover, these investigators estimated that maintenance of fibrillation in the canine atrium required a critical number of four to six wavelets. Some support of this idea came from the pharmacological experiments of Wang and co-workers [17,18] in which termination of atrial fibrillation by class IC antiarrhythmic drugs was preceded by a decrease in the mean number of wavelets.

Subsequent experiments in dogs [19], as well as more recent intra-operative mapping studies in humans [20], have provided important insight into the characteristics of wave front propagation during fibrillation, and have given support to Moe's idea that multiple wavelets distributed randomly throughout the atria gave rise to the seemingly chaotic activation patterns observed in the electrocardiograms of patients with AF. Finally, the hypothesis was emboldened by the clinical observation that chronic AF could be cured in some patients by the placement of multiple surgical lesions (MAZE) to compartmentalize the atria into regions presumably unable to sustain the multiple wavelets [21]. Indeed, this theory is virtually universally accepted by most clinical electrophysiologists today.

However, none of the above-mentioned studies gave answers to many critical questions about the origin of the turbulent activity that gave rise to the multiple wavelets in the experiments. For example, while the computer simulations of Moe et al. [15] suggested that 15–30 wavelets were needed at a given time to keep the fibrillatory process going, the experiments of Allessie et al. [16] could show only 4–6 wavelets propagating on the surface of the dog heart. In the presence of such a small number of wavelets, one would expect that, at any given time, a large amount of tissue in both atria would be recovered from previous excitation, which would lead to coalescence of wavelets and eventual termination of AF. In other words, it is reasonable to speculate that, in the experiments of Allessie et al. [16], the arrhythmia could have been in fact the result of a single (or a small number of) high frequency source that was (were) hidden from view. Additional questions include the following: is spontaneously occurring fibrillation the result of a ''mother rotor'' that breaks and fractionates into multiple independent offspring? What are the fundamental structural and electrophysiological characteristics that sustain the wavelets and which enable their coexistence and perpetuation in the form of ''fine fibrillation''? In Moe's model, a random distribution of refractory periods was essential for the establishment of fibrillation, in such a way that closely apposed cardiac cells could have widely different refractory periods. However, our present knowledge about the electrophysiological characteristics of cardiac tissues indicates that such a random distribution of refractory periods is not possible. Clearly, the strong electrical connections that exist between neighboring cardiac cells tend to greatly diminish any differences that might exist in the duration of their action potentials were

such cells not connected to each other [22]. So it seems as though, if any dispersion of refractoriness exists in the myocardial mass, it probably occurs as macroscopic spatial gradients of refractoriness rather than microscopic randomly distributed temporal dispersion of refractoriness [23].

Yet another important question that remains unanswered is what role, if any, do the three-dimensional structure and the complex geometry of the atrial myocardium play in the formation and maintenance of multiple wavelet propagation during fibrillation? In 1993, Schuessler et al. [24] demonstrated that there are specific regions in which the activation of the epicardium and endocardium are discordant, particularly in those areas in which the wall thickness is greater than 0.5 mm. Moreover, such a discordance increases when the excitation frequency is increased which suggests that, during atrial fibrillation, discordant epicardial vs. endocardial activation may become critical and lead to regions of functional block and wave breakup (see below), particularly in those regions in which the three-dimensional anatomy of the atrium is most complex.

Finally, the question of how ordered reentrant flutter can apparently change into fibrillation and vice versa has by no means been settled. Moe et al. [15] argued that circus movement flutter could lead to fibrillation and fibrillation to flutter, even though fundamentally different mechanisms may be involved. Their contention was that since fibrillation is fundamentally a statistical problem, coalescence of multiple wavelets into a single broad wave front might result in flutter, whereas flutter initiated in the setting of temporal dispersion of refractoriness may degenerate into fibrillation. The experiments of Allessie et al. [16] support that contention. However, the alternative possibility that some forms of atrial fibrillation may be the result of high frequency activation by a single reentrant source has also been supported by a number of recent experimental results [25–30].

2.3. Back to the circus movement concept of AF

Recent experimental data [25–28] have led us to revisit the circus movement hypothesis of AF, as postulated many years ago by Lewis et al. [31], who suggested that the mechanism of AF was due to rapid circus movement reentry à la Mines [12], where ''the central wave has a single and accustomed path, from which it is constantly straying a little; when it strays more, as it would do were it to meet a large barrier on its path, this unusual course is not long maintained''. To Lewis [31], the evidence was clear-cut that in AF '' . . . the central excitation wave manifests a strong predilection to move along one channel''. Thus, he proposed that fibrillation was similar to flutter in that a single circuit did exist, but the path followed by the wave front was uneven '' . . . in its detail it constantly alters and sometimes, though for brief periods, the path changes more grossly; but in general, the same broad path is used over and over again''. He also proposed that, in contrast to flutter, in fibrillation the circuit is completed in a shorter time and he explained AF's irregularity on the basis of a shorter excitable gap. This is illustrated in Fig. 1, which shows in panel A Lewis' schematic representation of the flutter wave at a given instant as it circulates around a ring of muscle (see also Ref. [12]). The blackened portions of the ring are thought to be refractory. The wave front travels through partially excitable tissue in the gap, which forms about one-sixth of the ring. Panel B shows a similar representation of the wave during AF. The ring is smaller and the excitable gap relatively shorter. The wave front is deeply interdigitated with its wake and thus, propagation is much more heterogeneous. Accordingly, the result is wave front fractionation, which yields a fibrillatory pattern on the surface electrocardiogram (ECG).

It is important to note that the concept of circus movement reentry as a mechanism underlying AF was a direct product of the use of deductive electrocardiography in the analysis of temporal changes in the electrical axis of the atria which, according to Lewis [31], demonstrated very uniform cycles of rotation with periods of about 123 ms. This concept was subsequently rejected by most other authors because it was considered flawed on the grounds that, on the ECG, changes in the f waves were too unspecific to reflect local atrial activation within a small reentrant circuit [14]. Nevertheless, the circus movement concept of AF is but one example of the truly inspiring deductive abilities that Lewis and his contemporaries demonstrated in their electrocardiographic analyses of cardiac arrhythmias. Today, modern electrophysiologists have the great advantage of being able to access highly sophisticated tools to map cardiac electrical activity and directly observe the nature of the fibrillatory waves with unprecedented spatial and temporal resolution [32,33]. As

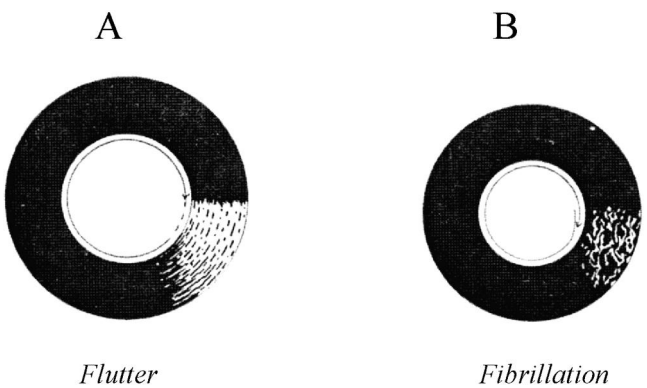

Fig. 1. Lewis' original explanation for the mechanisms of atrial flutter and fibrillation [31]. (A) Flutter results when a circus movement has a sufficiently large partially excitable gap ahead of the wave front (white area). (B) Fibrillation results when the size of the partially excitable gap is diminished due to shorter pathway (smaller ring).

we shall demonstrate below, it is remarkable that despite some qualitative modifications needed to match theory with experimental fact, the newer studies demonstrate that the original concept put forth by Lewis for the nature of AF remains basically correct, at least for certain forms of AF.

3. Rotors in the heart

In the early 1990s, Schuessler et al. [34] demonstrated in an isolated canine right atrial preparation that, with increasing concentrations of acetylcholine (ACh), activation patterns characterized by multiple reentrant circuits converted to a single, relatively stable, high-frequency reentrant circuit that resulted in fibrillatory conduction. The circuit may have been established by propagation around a ring formed by a pectinate muscle bridging the atrial wall. Clearly, the anatomy of the atria, with its complex lattice of pectinate muscles, vein orifices and atrioventricular rings is an excellent substrate for sustained circus movement reentry, as originally postulated by Mines [12] and subsequently by Lewis [31]. However, as demonstrated by Allessie et al. in 1973 [35], reentry may be functional and not require an anatomically defined pathway. Subsequent advances in the understanding of functional reentrant rhythms have led to the concept of ''rotors'', which give rise to vortices of electrical waves (spiral waves). Such rotors are self-sustaining and may be stationary or they may drift but subsequently anchor to anatomical heterogeneities in the cardiac muscle. Thus, unlike Lewis' circus movement idea of AF, current concepts derived from the theory of wave propagation of excitable media view the drivers of AF as being relatively stationary vortices rotating around an excitable but unexcited core [25].

Work from our laboratory has focused on rotors as the primary engines of fibrillation [25–28,31,36,37]. We have proposed that fibrillation is a problem of self-organization of nonlinear electrical waves with both deterministic and stochastic components [37]. We have also postulated and subsequently demonstrated that there is both spatial and temporal organization during AF in the structurally normal heart, although there is a wide spectrum of behavior [26–28,38]. At one end of that spectrum, a single drifting rotor can give rise to complex patterns of excitation that are reminiscent of fibrillation [37]. At the other end, acute sustained AF may also depend on the uninterrupted periodic activity of stationary rotors, which activate the atria at exceedingly high frequencies [25–28,38,39]. This is illustrated in Figs. 2 and 3, which we have reproduced from a previously published optical mapping experiment in the isolated, Langendorff-perfused sheep heart [27]. In Fig. 2 bipolar electrodes were placed at selected positions, as indicated on top of each trace. In an effort to localize the AF source (i.e., the site of periodic activity with the highest frequency), power spectral analysis [40] was carried out on each of the recordings using fast Fourier transformation (FFT) to determine the local dominant frequency of activation (largest peak).

The biatrial (BAE) and RA free wall electrograms were irregular, with dominant frequencies (DFs) of 8.2 and 6.9 Hz, respectively. Signals from the region inferior to and from the pulmonary vein (PV) ostium were also irregular, with multiple peaks on their FFTs. Activity recorded from the groove between the PV ostium and the left atrial appendage (LAA) showed more rapid activity, with a DF at 14.7 Hz. The electrogram at the bottom, recorded from the base of the LAA, was rapid and regular, and its FFT showed a dominant peak at 14.7 Hz, suggesting that a stable source might have been present at that site.

Examination of the LA optical movies established the mechanism underlying AF in this episode [27]. In Fig. 3A the isochrone map of optical activity from the LAA shows a vortex rotating clockwise at a period of 67 ms, i.e., frequency 14.7 Hz; the vortex persisted for the entire length of the episode (25 min). The fact that the frequency of this source was equal to the highest DF recorded from all sites (optical and bipolar electrodes) provided direct evidence that it was the mechanism underlying the maintenance of this AF episode. In actuality, single-pixel recordings at three separate locations (Fig. 3B) demonstrated that the entire LAA was being activated at 14.7 Hz. Moreover, all three sites showed identical activation sequences and FFTs, even though only two of the three sites were at or near the location of the rotor. Finally, the electrode that recorded the periodic activity (bottom trace in Fig. 2) was located at the base of the LAA 1 cm away from the rotor. The FFT of this signal showed a single peak at a frequency (14.7 Hz) identical to that of the rotor, indicating that the activity emanating from the rotor propagated to that site in a 1:1 manner.

More recent studies expanded significantly on previous AF work by demonstrating the manner in which interatrial pathways mediate fibrillatory conduction and the establishment of frequency gradients between the left and the right atrium [28]. Bachmann's bundle (BB) and the inferoposterior (IPP) interatrial pathway that underlies the coronary sinus are well-known routes of interatrial electrical communication [41–43]. Although the two sides of the interatrial septum have been shown to be electrically insulated [43], interatrial continuity is present on the superior and inferior aspects of the fossa ovalis, regions that remained intact after both BB and IPP were cut [28].

Our initial optical mapping studies in the isolated sheep heart demonstrated that during AF there were steep activation frequency gradients between the LA and the RA [26,27]. We therefore went on to test the hypothesis that such gradients resulted from the complex, spatially distributed conduction block patterns of the wave fronts generated by the high frequency rotor in the LA as they

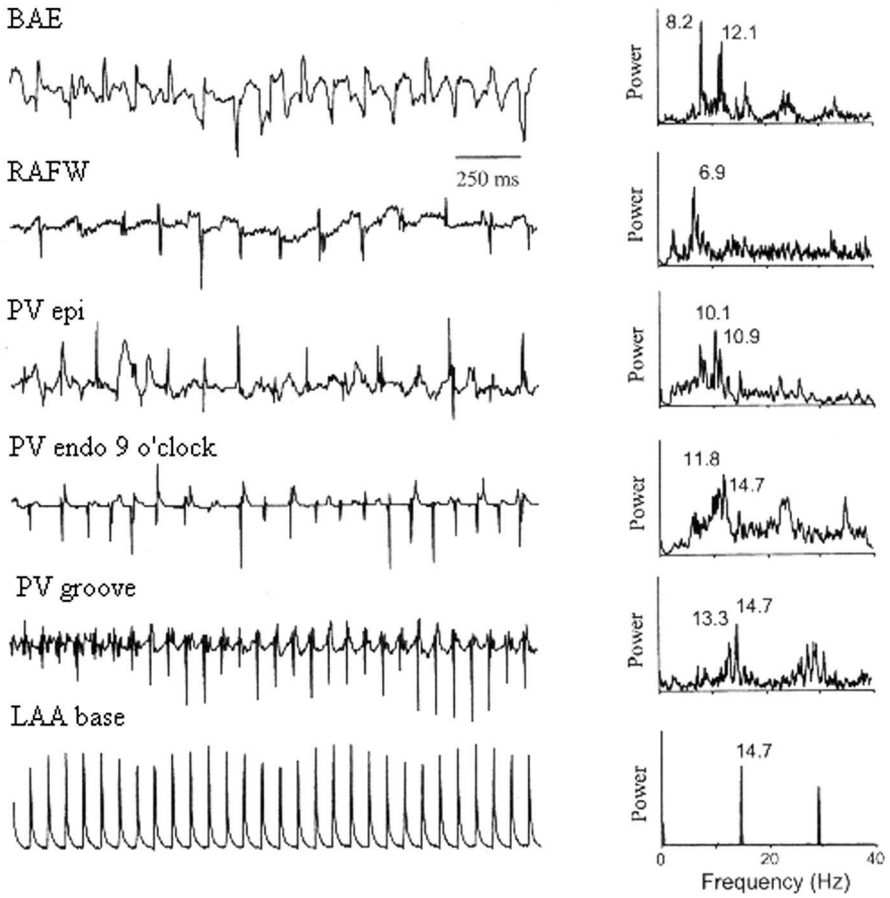

Fig. 2. Simultaneously recorded electrograms with corresponding FFTs during an AF episode. BAE indicates biatrial electrogram; RAFW, RA free wall; PV epi, epicardial surface of PV; PV endo 9 o'clock, PV endo at 9 o'clock position; PV groove, groove between LAA and PV ostium; LAA base, low base of LAA. Reprinted from Ref. [27], with permission of the American Heart Association.

propagated through interatrial pathways (BB, IPP), the crista terminalis and the complicated lattice of pectinate muscles in the right atrium [28].

An example of LA-to-RA frequency gradient is illustrated in Fig. 4, which shows electrograms and corresponding power spectra obtained from the LA and RA and the left and right sides of BB in a 3-s episode during AF (see Ref. [28] for details). The optical electrogram from the LA (Fig. 4A) shows rapid activity, with a DF of 18.8 Hz. In Fig. 4B, the recording on the left end of BB shows a DF of 18.7 Hz. Moving further to the right, the DF at the right end of BB (Fig. 4C), is 14.5 Hz, and finally, the RA (Fig. 4D) shows a DF of 9.8 Hz. Fig. 4E shows optical DF maps of the LA and RA in which the different gray areas represent DF domains, together with their corresponding values (in Hz). These data again demonstrated higher AF frequencies in the LA than in the RA [26–28,40]. Moreover, the results indicated that the largest decay in frequency occurred close to the junction between BB and the RA, strongly suggesting that the intricate architecture of the network of pectinate musculature may have been the substrate for fibrillatory propagation on the RA free wall [28,44]. Further support for the above hypothesis was sought by monitoring the direction of conduction along BB and IPP over a distance covered by a minimum of three consecutive electrodes, i.e., 2 cm over BB and 2.6 cm over IPP [28]. Fig. 5A illustrates an example of left-to-right propagation along BB during a 3-s episode of AF (see top trace). In Fig. 5B, quantification of this finding revealed that wave fronts propagated from left to right in 81 and 80% of the analyzed activations along BB and IPP, respectively. On the other hand, right-to-left propagation occurred in a significantly smaller percentage of cases.

4. Atrial structure and propagation

Studies in animals at the macroscopic level suggest that the complicated three-dimensional structure of the atrium is an essential component that contributes to the complexity of propagation patterns identified by high resolution mapping during AF [25,44,45]. However, the information about how heterogeneous electrophysiology and heteroge-

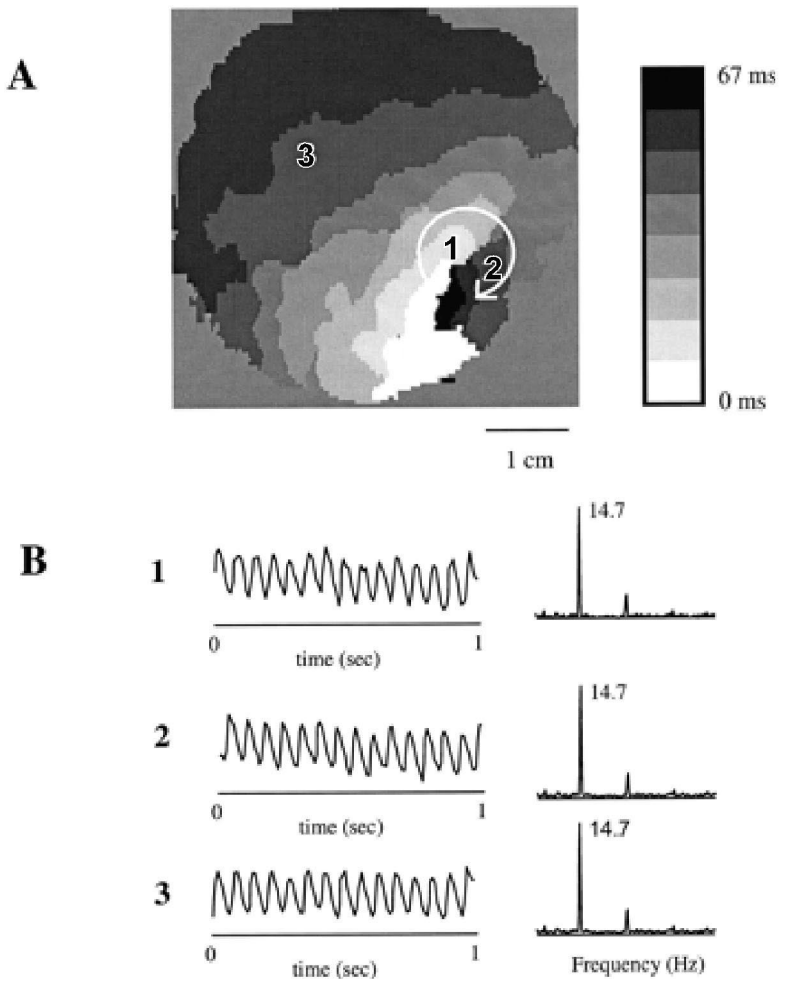

Fig. 3. Microrentrant source of AF. (A) Isochrone map of optical activity from the LAA, which shows a vortex rotating clockwise. (B) Optical signals and corresponding FFTs from sites marked 1 to 3 on isochrone map. Reprinted from Ref. [27], with permission of the American Heart Association.

neous anatomy interact to lead to AF initiation, maintenance or perpetuation is incomplete at best. Advances have occurred in the understanding of geometrical factors, such as wave front curvature [46] and sink-source relationships at areas of tissue expansion [47], and in the application of nonlinear dynamics theory to the spatial and temporal organization underlying complex cardiac arrhythmias [48,49], particularly during both atrial and ventricular fibrillation. Such advances may be relevant to the ultimate understanding of the mechanisms of initiation of AF by the interaction of the propagating wave fronts with anatomic or functional obstacles.

Thus, several investigations [24,28,42,50] have focused on the role of the subendocardial anatomical structure of the atria in the mechanisms of cardiac arrhythmias. Spach and Kootsey [50] showed that structural discontinuities of a scale >1 mm in the muscle structure play an important role in the establishment of unidirectional block and the initiation of reentry. Schuessler et al. [24] demonstrated discordant activation of the epicardium and endocardium, particularly in areas of the atrial wall that were thicker than 0.5 mm. Discordance increased with increased excitation frequency, up to ~5.9 Hz, which suggested propensity to reentry during AF, particularly in those regions in which the three-dimensional anatomy of the atrium was most heterogeneous. Gray et al. [44] showed that the crista terminalis and the pectinate muscles were sites of preferential propagation whose frequency dependence (cycle lengths above 150 ms) enabled disparity between endocardial and epicardial activation as well as reentry, with local block at branch points and epicardial breakthroughs. Subsequently, Wu et al. [51] used isolated canine isolated RA in the presence of acetylcholine to conclude that the pectinate muscles form a substrate for conduction block allowing stationary reentry with increased organization of the overall atrial activity. Altogether, the above studies support the importance of the anatomical structure in determining frequency dependence of impulse conductions and the idea of a common mechanism for atrial flutter and fibrillation [25,31].

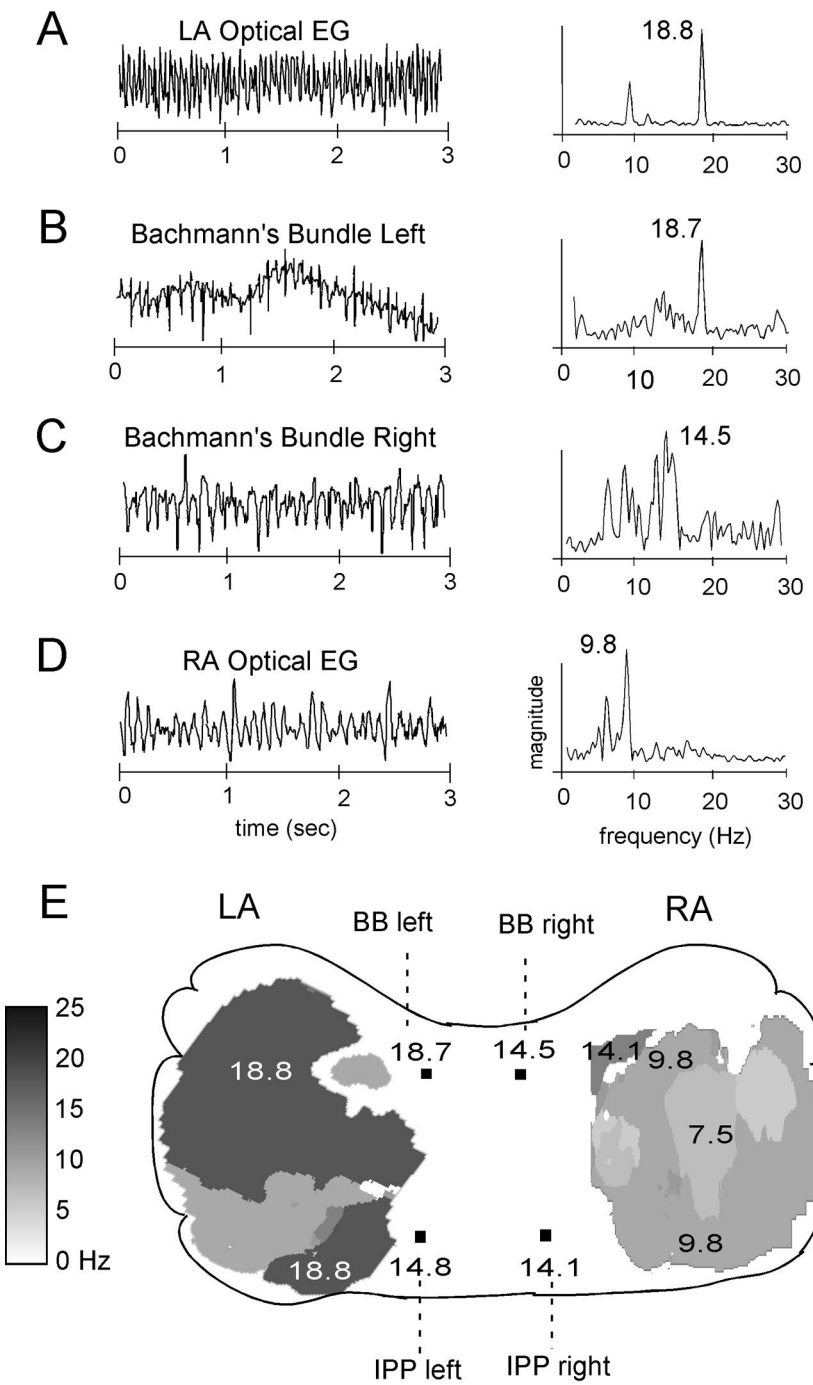

Fig. 4. Left-to-right decrement of dominant frequencies. (A) Optical activity in the LA (LA optical EG) with its corresponding FFT; (B)–(D) electrode recording and FFT from: (B) left end of Bachmann's bundle (BB); (C) right end of BB; (D) optical activity in the RA. (E) Dominant frequency maps of the epicardial surfaces of LA and RA, with values of dominant frequencies along BB and IPP (inferoposterior pathway). The areas of the frequency maps indicate the optical mapping field. Small areas in red (one in the LA and two in the RA) have frequency value of 60 Hz and represent noise artifact. Reprinted from Ref. [28], with permission of the American Heart Association.

5. Cholinergic input and mechanism of acute AF maintenance

Both vagal stimulation and administration of ACh have been shown to result in AF [52,53]. In experimental animals, vagal stimulation results in sustained AF as long as the vagus nerve is continuously stimulated [54–56]. This has been attributed to the heterogeneous distribution of vagal innervation throughout the atria, which increases spatial dispersion of refractory periods [53]. However, any hypothesis put forth to explain mechanism of maintenance of AF must contend with the fact that local frequencies in

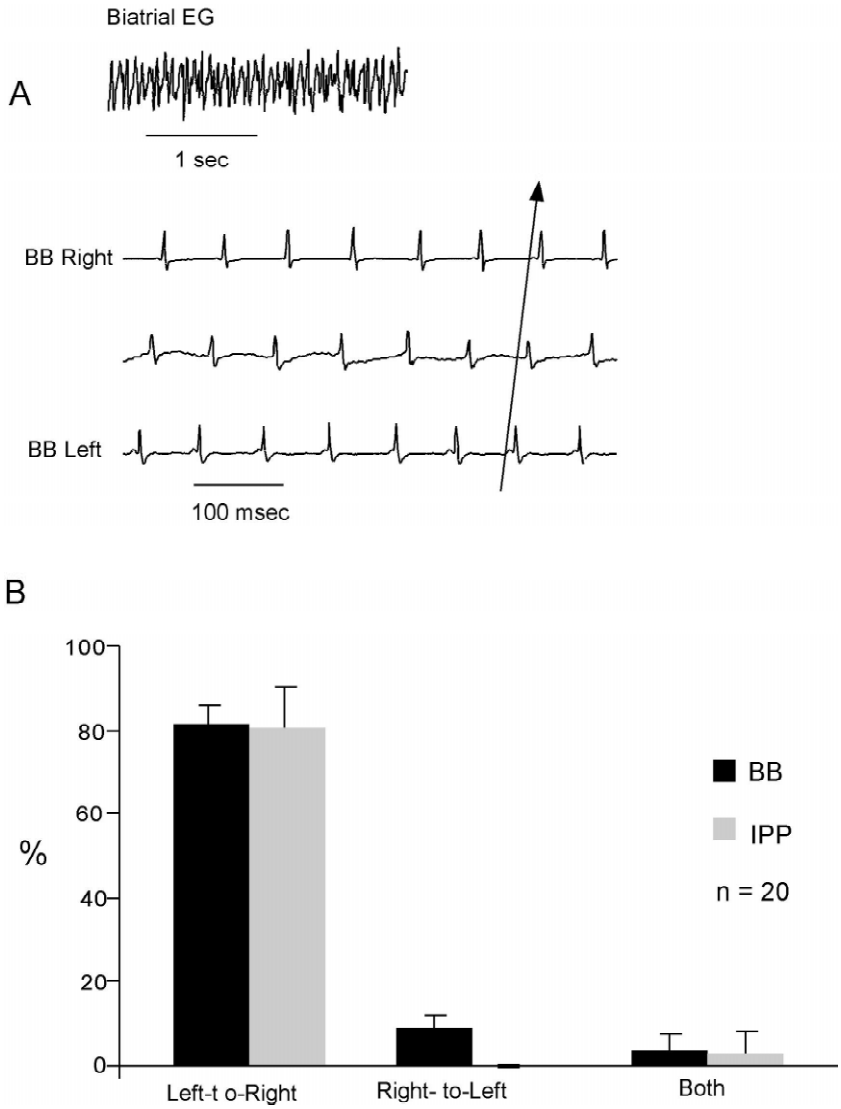

Fig. 5. Left-to-right directionality of impulse propagation. (A) Recordings from three electrodes along Bachmann's bundle (BB), the tracing in the bottom being most leftward. (B) Quantification of direction of propagation along BB and the inferoposterior pathway (IPP). Reprinted from Ref. [28], with permission of the American Heart Association.

some parts of the left atrium sometimes reach values as high as 16–18 Hz [27,28,40]. This means that action potential durations at those sites must abbreviate to about 60 ms or less in order to activate repeatedly at such frequencies in a 1:1 manner. Recently, Li et al. [57] demonstrated significant intrinsic differences in the APD of LA myocytes with respect to RA myocytes of the dog heart. In addition, they showed that LA myocytes have a larger I_{Kr} density and greater ERG protein expression compared to the right atrium. At a frequency of 6 Hz, APD in the LA and RA were ~100 ms and 110 ms, respectively. It is possible that such differences contribute somehow to the establishment of LA-to-RA frequency gradients during acute AF in the structurally normal heart through the resultant LA-to-RA differences in ERP. Yet, intrinsic APD differences alone are insufficient to explain the mechanism of AF maintenance or the exceedingly high frequency that can be achieved in some parts of the LA. A frequency of 16–18 Hz means that, somewhere in the LA, the atrial APD during AF is less than 60 ms, which cannot be explained on the basis of a relatively large I_{Kr} whose time constant is about 135 ms at +10 mV [57]. Thus, under acute condition, continuous vagal stimulation, ACh perfusion or other manipulations that are capable of abbreviating atrial APD to extreme values are necessary for the arrhythmia to be established and maintained. We surmise that such a pro-fibrillatory effect of ACh is related to the inherent spatially heterogeneous response of the atria to muscarinic activation, which leads to an increase in AF source frequency on the one hand, and spatial dispersion of local frequencies on the other; the end result being complex patterns of activation and wavelet formation [53].

We base this contention on recently published data in the Langendorff-perfused sheep heart which showed that increasing ACh concentration from 0.2 to 0.5 μM, did increase the frequency of the dominant source as well as the LA-to-RA frequency gradient [28], suggesting that the LA and RA are indeed different in their response to ACh. Thus we hypothesize that these effects are the result of two distinct mutually complementary mechanisms: first, ACh greatly abbreviates APD, and thus should lead to an increase in the stability and frequency of rotation of microreentrant sources in the LA [27,28] by reducing wave front-wave tail interactions and allowing rapid curling of the wave front near the center of rotation. Second, ACh increases resting membrane conductance and threshold current. Therefore it should reduce excitability in the two atria. Consequently, outside of the rotor domain (i.e., the region of 1:1 activation), ACh should enhance sink-to-source mismatch at branching sites and other areas of changing cell-to-cell coupling and/or geometry and facilitate the development of spatially distributed delays and intermittent block, the hallmark of fibrillatory conduction.

6. Pathophysiological implications

If applicable to human AF, the studies discussed above may open potentially exciting new diagnostic and therapeutic possibilities. Arguably, the recent success in localizing foci that trigger AF in certain patients has rendered the arrhythmia amenable for termination by radiofrequency ablation [7–9]. Similarly, ability to localize the ''engine'' that maintains AF should make that engine a more vulnerable target for specific therapies, whether ablative, electrical, pharmacological, or hybrid. However, caution must be exerted when attempting to extrapolate to the clinical situation data that have been obtained from experiments in normal hearts with acute AF under the artificial conditions of isolation and crystalloid perfusion [26–28]. Moreover, we are not proposing here that a single rotor in the LA maintains all forms of AF. It is more likely, in fact, that the underlying mechanisms vary according to species and that, in man, multiple mechanisms prevail. Nevertheless, strong support for the idea that AF may be the result of discrete sources giving rise to high frequency excitation in the LA, with fibrillatory conduction toward the RA, can be found in observations made during radiofrequency ablation of AF in humans [7–9,58,59]. Clearly, in some patients with paroxysmal AF, impulses initiated by ectopic pacemaker or triggered discharges by a focal source of activity propagate from an individual pulmonary vein into the LA (see Fig. 6A) to encounter heterogeneously recovered tissue. As illustrated in Fig. 6B, one would expect that the initiation and maintenance of AF under these conditions should depend on the formation of relatively sustained rotors in the LA, which generate high frequency impulses that travel to the remainder of the atria as fibrillatory waves [25–28].

Therefore a strong argument can be made that most, if not all, patients with AF have a focal (e.g., pacemaker or triggered discharges originated in one of the pulmonary veins) or reentrant mechanism as the initiating cause of the arrhythmia. Also it is possible that, in a significant number of patients, a rotor or a small number of rotors are the drivers that maintain the arrhythmia. As such, perhaps the only differences between paroxysmal and chronic AF are the rotation frequency and stability of such sources; that is, when the driving site is most stable and its frequency is highest due to both electrophysiological and structural remodeling [60–62], the clinical scenario of chronic AF would be manifest. While this hypothesis has not been tested, there is evidence in the literature that supports it strongly. Specifically, one experimental report described the profound antiarrhythmic effect of cryoablation (using a hand-held probe) to areas of shortest cycle lengths in the posterior LA in open chest dogs with chronic AF [63]. While Morillo et al. [63] attributed their success to the fact that the ablated areas were large enough to prevent reentry of multiple wavelets, this could really have represented empiric elimination of potential high-frequency sources. We base such an interpretation on a careful analysis of the

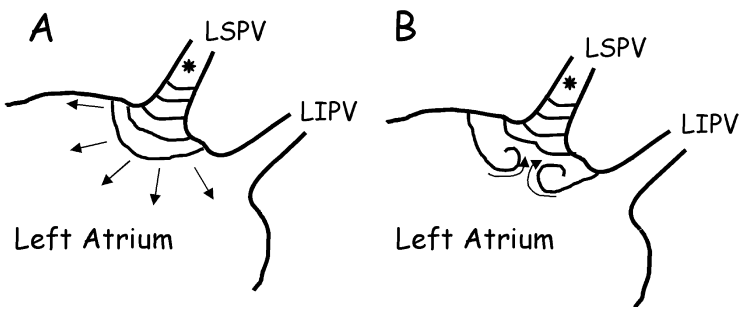

Fig. 6. Schematic representation of proposed mechanism of initiation of paroxysmal atrial fibrillation by rapid ectopic discharges. (A) Rapidly succeeding wave fronts emanating from an ectopic focus in the left superior pulmonary vein (LSPV) invade the left atrium. Arrows indicate direction of propagation. (B) When conditions of heterogeneity are appropriate, the wave fronts brake and initiate two counter-rotating vortices (curved arrows indicate direction of rotation) which, if stable enough, become the engines that maintain VF. Alternatively (not shown), only one of the vortices survives and keeps AF going by generating wave fronts at an exceedingly high frequency (typically ~15 Hz in the LA of the sheep heart). LIPV: Left inferior pulmonary vein.

data presented in the article of Morillo et al. [63], which reveals a substantial gradient of frequencies between the LA and RA in the chronic AF dog model. We have reproduced in Fig. 7 one of their experiments to illustrate this point. The highest frequency was found in the PV region (11.1 Hz), followed by the posterior left atrial wall (10.6) and left atrial appendage (9.1). The lowest frequencies were localized to the smooth portion of the right atrial wall (7.2 Hz) and tip of right atrial appendage. Thus, despite quantitative differences in the absolute frequency values, these data in the chronic AF dog demonstrate a remarkable resemblance with those obtained in the acute, cholinergically mediated AF model of the sheep heart (see Fig. 4 above).

Additional support for the single source hypothesis is found in the work by Roithinger et al. [64], who used radiofrequency ablation to show that selective left atrial linear lessions reduced significantly AF frequency in a canine model of AF, whereas right atrial lesions did not. A recent article by Wu et al. [65] confirmed the presence of left-to-right frequency gradients in a canine model of AF and suggested that the pulmonary veins and ligament of Marshall act as high frequency sources that maintain the arrhythmia. Other studies have shown that refractoriness is shorter in the LA than in the RA [66,67]. Very recent experiments by Li et al. [57] strongly suggest that LA to RA differences in refractoriness at low frequencies correlate strongly with intrinsic differences in the APD recorded from cells obtained from the two atria. A larger density of the rapid delayed rectifier current (I_{Kr}) in the LA seems to explain nicely such chamber specific differences in APD during pacing at relatively low frequencies [57]. Whether such differences explain the ability of the LA to activate at frequencies as high as 18 Hz as well as the LA-to-RA gradient of frequencies during AF [28], remains to be determined.

A number of studies in patients also support the idea that the left atrium may be the driver for AF. Harada et al. [68] mapped atrial activation in 10 chronic AF patients who were undergoing mitral valve surgery. They demon-

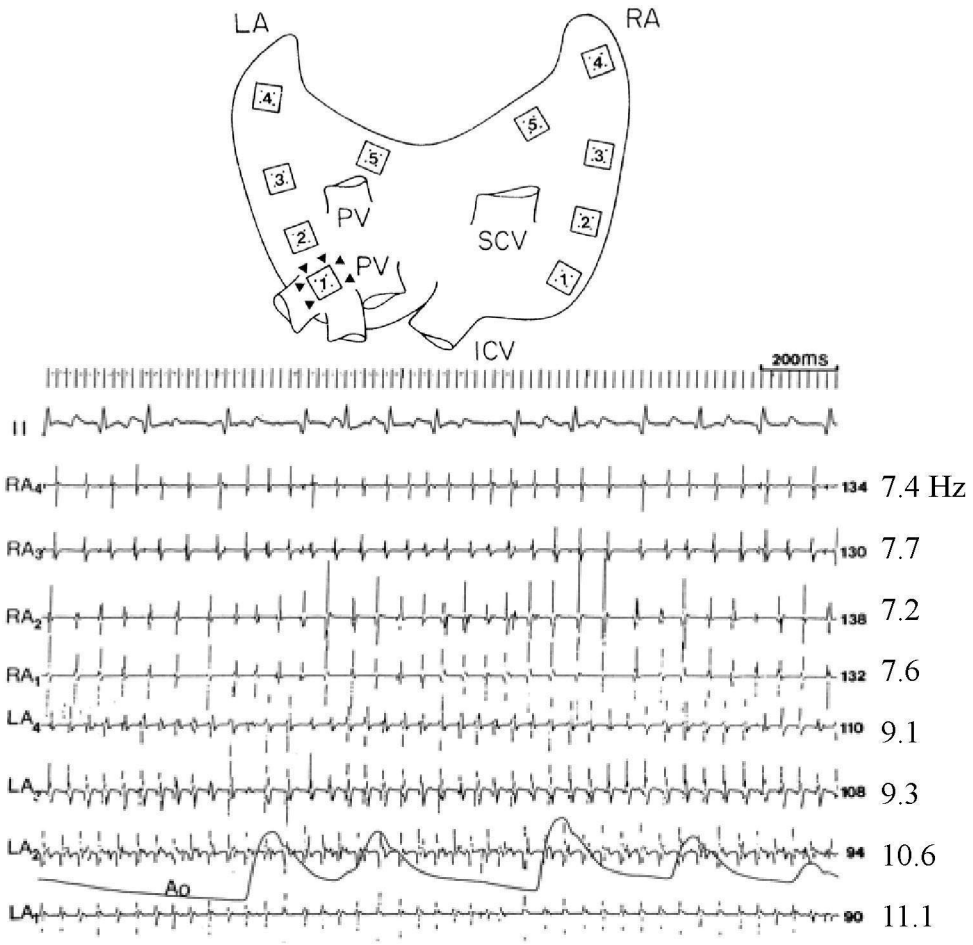

Fig. 7. Electrical recordings from a dog during sustained AF [60]. Top, distribution of the epicardial electrodes on both atria. Shortest atrial fibrillation cycle length is localized to the inferoposterior left atrium (LA_1=90 ms). Bottom, electrograms showing sustained atrial fibrillation induced by programmed electrical stimulation. Signals are from surface ECG lead II and eight bipolar epicardial electrograms. Mean atrial fibrillation cycle length and frequency are shown on the right. Electrodes 1 to 4 on RA and LA correspond to positions from posterior wall towards the appendages. Ao, Aortic pressure. Modified from Ref. [63], by permission of the authors and the American Heart Association.

strated that the LA underwent regular and repetitive activations with cycle lengths that ranged between 131 and 228 ms. By contrast, the activation sequence in the RA was extremely complex and dysrhythmic. More recently, the same authors [69] demonstrated that resection of the LA appendage and/or cryoablation of the orifice of the left pulmonary vein terminated AF in 10 of 12 additional patients with mitral valve disease. On the other hand, Pappone et al. [70] demonstrated termination of chronic AF in humans by isolating the PV, confirming that areas in the posterior LA may act as drivers for AF.

Together, the above experimental and clinical data strongly support the hypothesis that at least some cases of chronic AF may be due to a single or, at most, a few high frequency periodic sources of activity in the posterior left atrium. However, to our knowledge, the detailed molecular, cellular and pathophysiological mechanisms that determine the predilection of the highest frequency sources to remain in the LA and the PV region remains a mystery. Hence, there is a need to integrate studies describing phenomena ranging from the molecular level to membrane channels, cells and tissues to the whole body to address this interesting and clinically relevant question.

7. Some suggestions for future study

Experiments in isolated hearts have demonstrated that stable, self-sustained rotors can exist in the atria and that high frequency activation by such rotors results complex patterns of activation that characterize AF [26–28]. Studies in animals and patients support the view that, at least some cases of paroxysmal and chronic AF, are the result of the uninterrupted periodic activity of discrete reentrant sites [63,64,68,70]. This revived knowledge raises the possibility that even patients suffering from chronic AF may be amenable to more effective therapeutic strategies in the not too distant future. However, achieving that goal will require a much better understanding of the detailed molecular, cellular and pathophysiological mechanisms of AF initiation, perpetuation and termination. Therefore, while work on AF seems to be going in the right direction, there is an urgent need to integrate studies describing phenomena ranging from the molecular level to membrane channels, cells and tissues to the whole body. Importantly, new strategies should be developed to achieve more rigorous quantitative understanding of frequency dependent behavior of atrial muscle. Studies are needed as well to delineate the mechanisms of spontaneous initiation of AF by premature beats, by rapid focal discharges originating at the cardiac veins, or even at the sinoatrial node. Multidisciplinary approaches will be essential to advance knowledge of how heterogeneous electrophysiology and heterogeneous anatomy interact to lead to AF initiation, maintenance and perpetuation. In addition, new numerical and experimental tools, including mathematical modeling, as well as optical and multiple electrode mapping approaches should be used in our attempts to improve comprehension of the complex dynamics of excitation and electrical wave propagation in the atria. Specifically, appropriate tools should be used to elucidate the role played by such parameters as curvature/velocity relationships [46,71,72] and sink-source properties at junctional and branching sites [73,74], as well as excitability and refractoriness in the dynamics of initiation and maintenance of AF. Moreover, it will be important to expand on current knowledge and develop new methodologies, including tissue culture and transgenic animals, to advance knowledge of biophysical, molecular and genetic bases of bioelectrical phenomena relevant to triggering and spontaneous initiation of AF. Further, advanced computational tools should be developed to enable integration of molecular mechanisms of ion channel behavior and structure/function of cells with knowledge about AF in multicellular and whole animal preparations. Finally, advanced methods for detection and analysis of electrical signals with high spatial and temporal resolution at the organ systems level are needed, possibly combining information acquired using bioelectric, chemical, acoustic, optical and motion analysis techniques.

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