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Mapping of atrial fibrillation

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Summary. - Cardiac mapping has been defined as: "a method by which cardiac signals are recorded from multiple sites of the heart and spatially depicted as a function of time in an integrated manner". It requires determination of the local activation time at each electrode and the creation of activation maps which provide a spatial model of the activation sequence. With respect to atrial fibrillation, mapping is useful to gain insight into the underlying mechanism of atrial fibrillation. In this review, we will discuss the mapping studies of experimental and clinical atrial fibrillation.

Key words: acute atrial fibrillation, paroxysmal atrial fibrillation, chronic atrial fibrillation, fragmentation mapping.

Riassunto *(Mappaggio della fibrillazione atriale).* - Il mappaggio cardiaco è stato definito come "un metodo con cui i segnali cardiaci sono registrati da diversi punti del cuore e sono spazialmente descritti come una funzione del tempo in modo integrato". Questo richiede l'individuazione degli istanti di attivazione locale di ogni elettrodo e la creazione di mappe di attivazione che forniscono un modello spaziale della sequenza di attivazione. In relazione alla fibrillazione atriale, il mappaggio è utile per capire in modo più profondo i meccanismi che sottostanno alla fibrillazione atriale. In questa review, si discuteranno gli studi sperimentali e clinici sul mappaggio della fibrillazione atriale.

Parole chiave: fibrillazione atriale acuta, fibrillazione atriale parossistica, fibrillazione atriale cronica, mappaggio.

Introduction

The surface ECG of atrial fibrillation (AF) is characterized by rapid, low-amplitude oscillations and irregular R-R intervals. However, the surface ECG does not provide any information about the possible different underlying mechanisms of AF.

The first experiment demonstrating that AF can result from different mechanisms was performed by Moe and Abildskov [1]. In the isolated canine atria, they compared AF initiated by rapid pacing from the right atrial appendage during either vagal stimulation or application of aconitine. Isolation of the aconitine spot resulted in prompt recovery of sinus rhythm whereas AF continued after isolation of the pacing site during vagal stimulation. This experiment suggested that aconitine-fibrillation is based on an ectopic focus with a high frequency discharge resulting in non-uniform excitation of the atria. This kind of fibrillation was described as "fibrillatory conduction", because perpetuation of AF depended on the persistence of a single rapid focus. On the other hand, acetylcholine-fibrillation continued independently from the site where it was initiated ("true fibrillation").

The features of "true fibrillation" were explained by Moe's multiple wavelet hypothesis [2]. In this hypothesis, it was postulated that persistence of AF depended on the average number of wavelets. If the total number of wavelets increased, the chance of extinguishment and hence termination of AF would become smaller.

True fibrillation can be explained by several different mechanisms, including: 1) single or multiple automatic foci; 2) a single reentrant mother wave giving rise to multiple daughter waves; 3) multiple wandering wavelets, 4) transmural reentry creating 3-dimensional AF [3].

Mapping studies have been crucial to gain insight into the possible underlying mechanisms of AF. Knowledge of the mechanisms of AF can provide a basis for development of better strategies for prevention and treatment. Examples of such new therapies are focal ablation of the origin of ectopic beats [4, 5], isolation of the pulmonary veins [6], and the creation of linear lesions either by surgery or catheter radiofrequency ablation [7-9].

In this review, we will discuss the mapping studies of experimental and clinical AF.

Electrically induced atrial fibrillation

The first experimental evaluation of Moe's multiple wavelet hypothesis was performed by Allessie *et al.* [10] This study demonstrated the presence of multiple wandering wavelets in isolated canine atria during

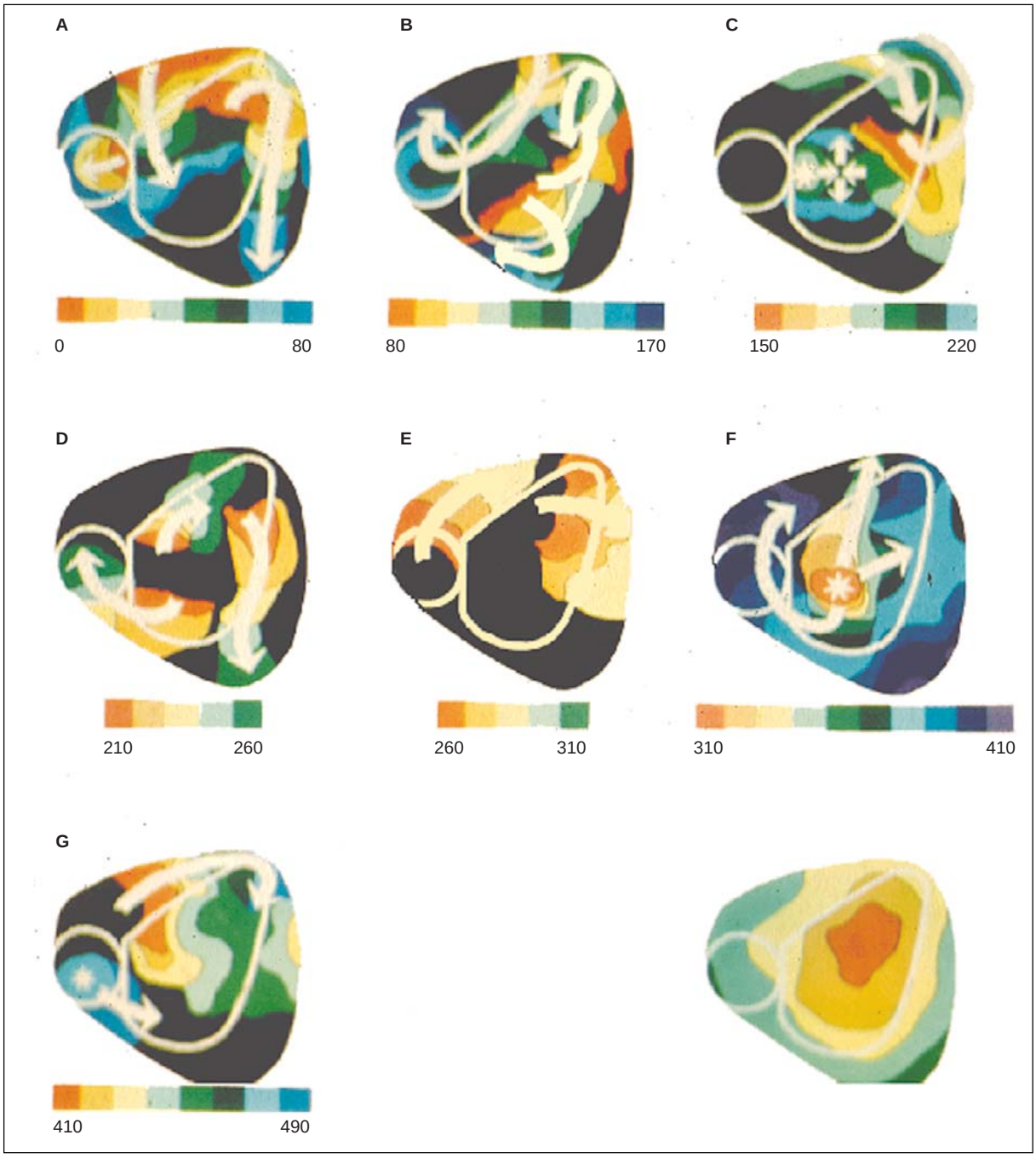

Fig. 1. - Endocardial excitation maps of the right atrium during 0.5 second of self-perpetuating AF in the isolated canine heart. The maps were reconstructed from simultaneous recordings of 192 electrograms from a template containing 480 electrodes with an inter-electrode distance of 3 mm. The propagation pattern is visualized by colors, each representing 10 ms. In the lower right panel, an activation map during sinus rhythm map is given. During AF, multiple wavelets can be clearly identified.The asterisks indicate sites of endocardial breakthrough of impulses probably originating from the left atrium (panel C, F and G). (Reproduced with kind permission from [10]).

acetylcholine-induced AF. Fig. 1 shows a series of consecutive excitation maps of a canine right atrium during 0.5 second of acutely induced AF. For comparison, the right lower panel shows the activation map during sinus rhythm. As can be seen from these maps, there was a continuous beat-to-beat change in activation pattern. The critical number of wavelets in both right and left atria necessary to perpetuate AF was estimated to be between three and six. The asterisks in the activation maps indicate sites of endocardial breakthrough of impulses originating from the left atrium (panel C, F and G).

The first mapping study of electrically induced AF in humans was performed in 1991 by Cox *et al.* in patients with the Wolff-Parkinson White syndrome undergoing cardiac surgery for interruption of their accessory atrio-ventricular pathway [11]. AF was induced by burst-pacing and the right and left atria were mapped using several epicardial templates containing together 160 bipolar electrodes, with an inter-electrode distance varying between 5 and 10 mm. Results of this first clinical study were consistent with the previous experimental studies in the isolated canine heart, supporting reentry at multiple sites as the underlying mechanism of AF. All patients demonstrated non-uniform conduction around regions of bi-directional block resulting in multiple discrete wavefronts. Although anatomical obstacles such as the pulmonary and caval veins were involved in some reentrant circuits, reentry also occurred without the involvement of anatomical obstacles. Sometimes, functional conduction block was associated with specific atrial structures such as the *crista terminalis*. In 6 of 13 patients, a reentrant circuit could be identified in the right atrium around the *sulcus terminalis*. In the left atrium, reentrant circuits were more difficult to document and seemed to occur more fleetingly. In all patients, multiple wavefronts and lines of conduction block were found both in the right and left atrium. A limitation of this first mapping study of human AF was that only single maps were presented and that the beat-to-beat changes in activation during AF were not analysed.

High density mapping of electrically induced AF was performed by Konings *et al.* in 25 patients with the Wolff-Parkinson White syndrome [12]. During cardiac surgery, the free wall of the right and left atrium were mapped consecutively with a spoon electrode containing 244 unipolar electrodes (diameter 4 cm, spatial resolution 2.25 mm). The activation pattern of the right atrial free wall demonstrated a high intra- and inter-individual variation. The activation patterns ranged from well-organized activation consisting of a single planar wavefront to completely disorganized activation by multiple wavefronts propagating in different directions. The degree of organization was related to the frequency of AF, short median AF cycle lengths being associated with a higher degree of disorganization. Based on the complexity of activation, three different types of AF were distinguished. During type I, most of the time single broad wavefronts propagated across the right atrial free wall. Only small areas of slow conduction or conduction block occurred, not disturbing the main course of the large fibrillation waves. This type of AF probably reflects the presence of macro-reentry with involvement of anatomical obstacles. During type II, either one wavefront propagating with marked local conduction delay or two separate wavefronts were present. During type III, multiple fibrillation waves were recorded in the mapping area with a diameter of 4 cm. These multiple wavelets were separated by lines of functional intra-atrial conduction block. The incidence of type I, II and III AF in the small group of 25 WPW-patients was 40, 32 and 28% respectively. During type III fibrillation, leading circle reentry and random reentry were frequently observed. Incidentely, a focal pattern of activation was recorded on the free wall of the right atrium. These patterns of focal activation were only found as solitary events and never occurred repetitively. Electrograms recorded at the site of earliest activation were preceded by a small r wave indicating that the focal activation pattern was most probably due to epicardial breakthrough of an activation wave propagating through one of the pectinate muscles.

Breakthrough patterns were also found in optical mapping studies of the right atrial free wall in the isolated sheep heart during electrically induced AF [13]. Breakthrough sites appeared to be confined to the area of the pectinate muscle bundles. Schuessler *et al.* performed simultaneous endocardial and epicardial mapping of isolated canine atria during sinus rhythm, continuous pacing, premature stimulation and induced tachyarrhythmias [14]. In general, only small differences between endocardial and epicardial activation times (< 1 ms) were found, suggesting that endocardial and epicardial activation occurred simultaneously. Larger differences in endo- and epicardial activation times were associated with the underlying atrial architecture (pectinate muscles and sites with transmural differences in fiber orientation). During reentrant tachycardia, a focal activation pattern was found both on the endocardial and epicardial surface. The sites of earliest activation were spatially disconcordant with a separation of 15 mm between the earliest endocardial and epicardial breakthrough. Hence, this study provided clear evidence of transmural activation during atrial arrhythmias, suggesting the presence of 3-D reentry.

Spectral analysis of optical recordings was used to determine the presence of dominant circuits during electrically induced acetylcholine-AF [15]. The activation pattern of the left atrium was more regular than that of the right atrium. In some cases, sources of periodic activity were found, appearing as stationary rotors or as sites of epicardial breakthrough. Fig. 2 shows 3 consecutive isochronal maps of the left atrium of a sheep as reconstructed from optical recordings of AF. The site of breakthrough was similar in each map. The lower panels show fast fourier transforms of the transmembrane potentials at sites 1, 2 and 3. At the site of breakthrough (1), a single dominant peak of 20.3 Hz. was found. Moving away from this dominant source of rapid impulses, the activation became more irregular and multiple peaks appeared in the spectral analysis. The highest dominant frequency was often found at the left posterior atrial wall where a small stationary vortex was found by optical mapping (micro-reentry) [16]. A higher frequency of these dominant sources was associated with a higher degree of fibrillatory conduction [16]. Wavebreaks occurred frequently at the left atrial appendage and right atrial free wall [17]. The wavelets

had a short lifespan (< one rotation) suggesting that multiple wavelets during AF are generated by breaking up of high frequency waves when they propagate through heterogeneous tissue. From these studies the authors concluded that Moe's multiple wavelet hypothesis did not offer a robust mechanism of maintenance of AF.

However, it should be noted that the frequency of AF in these studies was much higher (20 Hz; 1200/min) then the frequency of atrial fibrillation in humans which ranges between 300 and 420 beats per minute. Thus it remains questionable whether these experimental data can be extrapolated to the clinical situation.

Paroxysmal atrial fibrillation

Epicardial and endocardial mapping during electrically induced AF in dogs with sterile pericarditis showed that unstable reentrant circuits with short cycle lengths were critical for the maintenance of AF [18]. Fig. 3 shows an example of the activation of the right and left atrium during 1.2 seconds of AF. The first two maps show a reentrant circuit located at the right atrial free wall (orange) which disappeared in the third map. A similar circuit reappeared in maps 7-11. Another reentrant circuit (green) was found in the left atrium circulating around the pulmonary veins. In most maps a reentrant circuit comprising the interatrial septum and Bachmann's bundle was present (blue). Based on the hypothesis that this circuit was critical for the maintenance of AF, the conduction through Bachmann's bundle was blocked by ablation. After the ablation of Bachmann's bundle, AF was no longer inducible [19].

Mapping studies in patients with paroxysmal AF showed that AF could be initiated by a rapidly firing focus [20]. The majority of these ectopic atrial premature beats originated from one of the pulmonary veins [21, 22]. Sometimes ectopic beats originating from the superior caval vein, crista terminalis, coronary sinus, or left atrial posterior free wall initiated a paroxysm of AF [23, 24]. Catheter ablation of the focus resulted in a marked reduction of the number of episodes of AF [25].

Recently, the atrial myocardium within the ligament of Marshall has been suggested as another possible site of focal activity [26, 27]. Epicardial mapping (480 bipolar electrodes) of electrically induced AF in dogs located an area with the shortest AF cycle lengths in the ligament of Marshall or one of the left pulmonary veins [28]. In two dogs, spontaneous episodes of AF were recorded. These episodes started with ectopic beats originating from the ligament of Marshall or high right atrium. During the first seconds of AF, atrial activation was still organized but thereafter it converted to AF. The earliest activation during atrial tachycardia and conversion to AF was recorded from the ligament of Marshall.

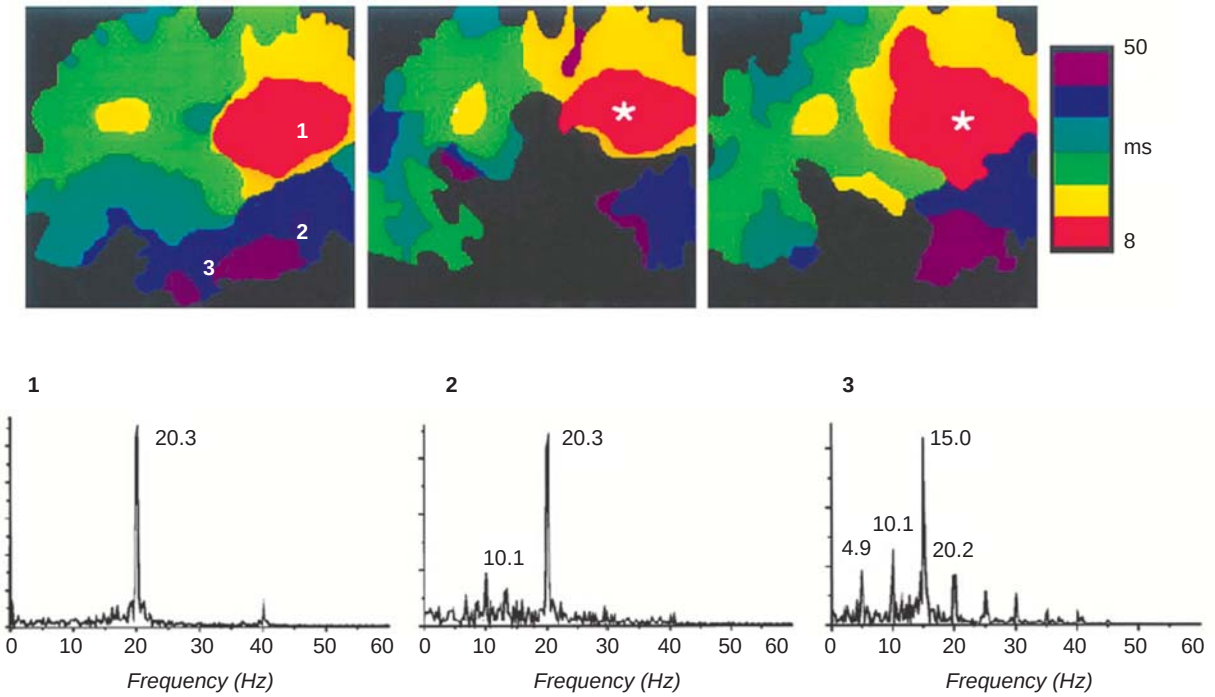

Fig. 2. - Upper panel: three sequential isochronal maps of the left atrium from an isolated sheep heart constructed from optical recordings demonstrating a repetitive focal spread of activation. Lower panel: Fourier transforms of the transmembrane potentials at sites 1, 2 and 3. At all sites, temporal periodicity is demonstrated by the presence of a dominant peak between 15 and 20 Hz. Remote from the dominant source, the activation pattern became more complex reflected by the appearance of additional frequency peaks at sites 2 and 3. (Modified from Skanes *et al.* [15]).

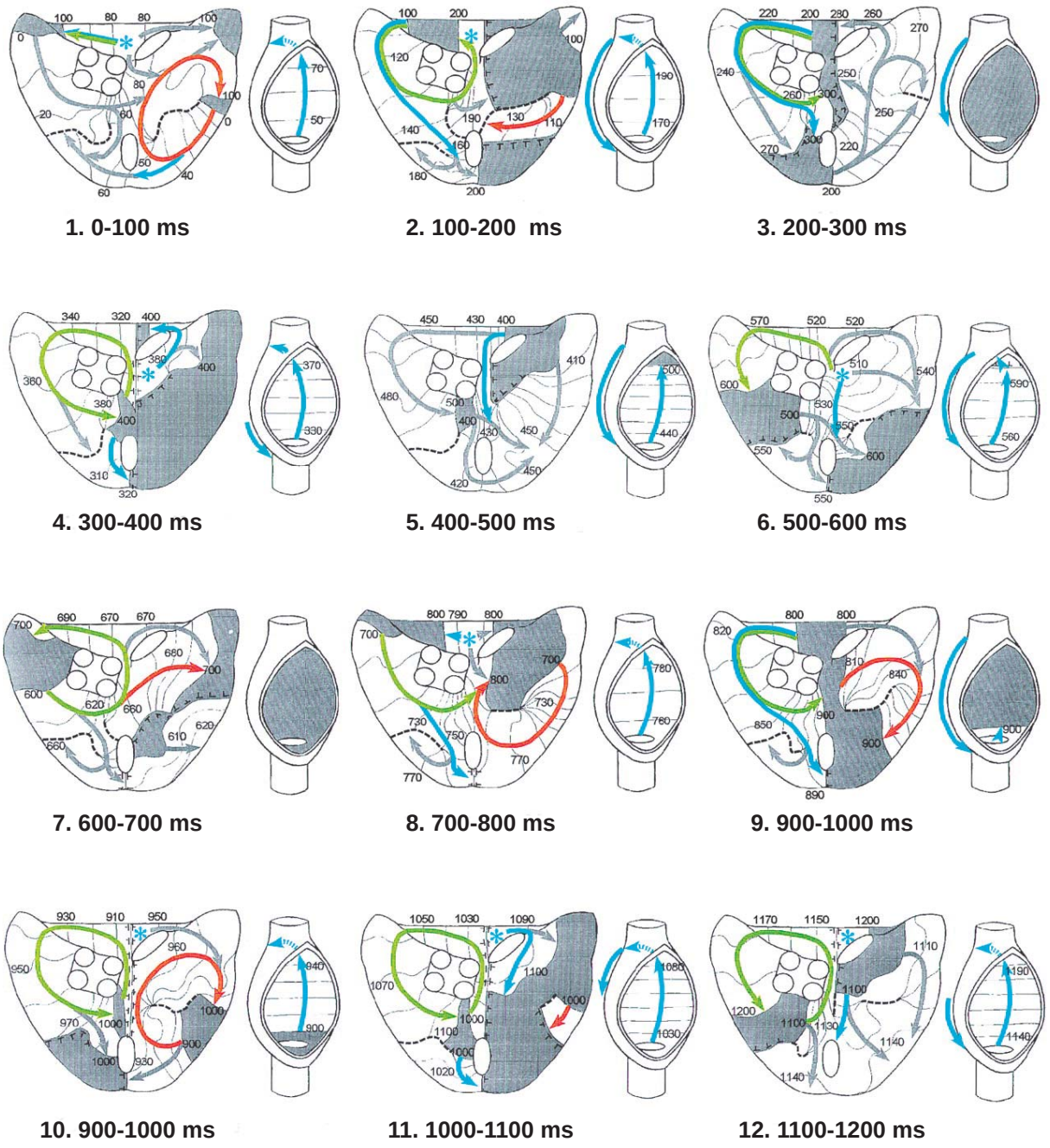

Fig. 3. - Twelve consecutive isochronal maps of both atria during 1.2 seconds of electrically induced AF in a dog with sterile pericarditis. Each map covers a time window of 100 ms. The maps were reconstructed using epicardial templates containing 186 bipolar electrode pairs and endocardial multipolar catheters (12, 20 or 24 poles with an interelectrode distance of 1 or 2 mm). The isochrones are drawn at 10 ms intervals. The colored arrows indicate different unstable reentrant circuits. Dashed lines represent lines of functional block. Asterisks indicate sites of epicardial breakthrough. Regions which are not activated in the time window of 100 ms are gray. (Modified from Kumagai *et al.* [18]).

Chronic atrial fibrillation

Sofar, only 3 mapping studies have been performed in patients with chronic AF during cardiac surgery, mostly for mitral valve disease [29-32]. Holm *et al.* analysed the activation patterns of the right atrial appendage and posterior wall in 16 patients [30]. Using a mapping array of 56 bipolar electrodes, the occurrence of type I, II and III AF was determined. At the posterior free wall, types I, II and III were present in 27, 40 and 33% of the patients. In the right atrial appendage, the incidence was 46, 27, and 27%. The major new finding of this study

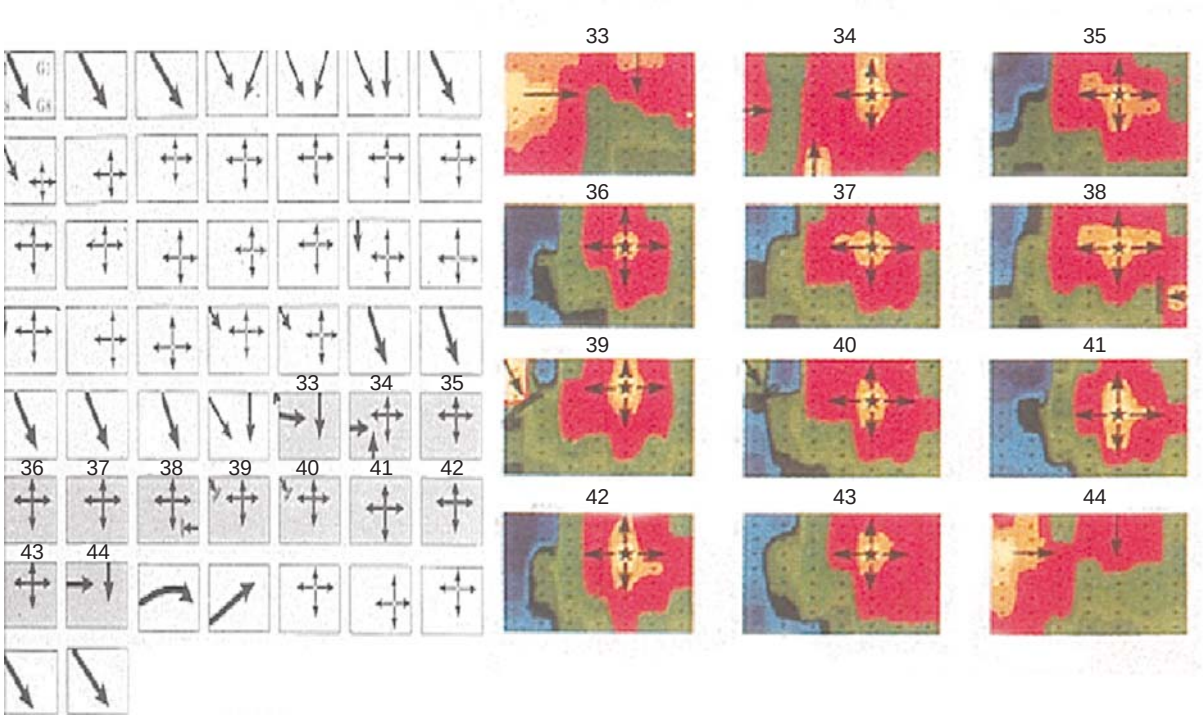

Fig. 4. - Repetitive focal spread of activation of the right atrial appendage in a patient with chronic AF. In the left part, 51 consecutive activation maps are given diagrammatically. The right part shows a series of color maps elucidating a constant site of epicardial breakthrough. The activation maps were reconstructed from an epicardial template of 4 cm containing 56 bipolar electrodes (interelectrode distance of 3 mm). The asterisks indicate the site of earliest activation. (Modified from Holm *et al.* [30]).

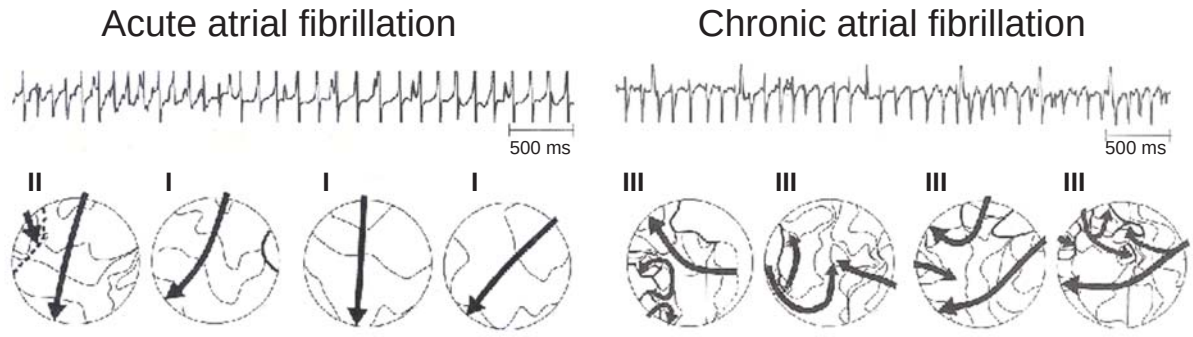

Fig. 5. - Right atrial unipolar electrograms and consecutive activation maps of the right atrial free wall obtained during acute (left panel) and chronic AF (right panel) in the goat. Isochrones are drawn at 10 milliseconds intervals. Thick lines represent arcs of conduction block and dashed lines collision of fibrillation waves. Arrows indicate the direction of activation of (multiple) fibrillation waves. During acute AF, the mapping area was mostly activated by single broad wavefronts. Only small arcs of conduction block were present (thick line). During chronic AF, the median cycle length was shorter and the right atrial free wall was activated by multiple wavelets. (Modified from Konings *et al.* [35]).

was that during chronic AF in humans, focal activation of the right atrium occurred *repetitively*. The origin of this focal activation pattern was consistently located at the right atrial appendage. An example is given in Fig. 4. The left part gives a schematic representation of the activation of the right atrial appendage during 51 consecutive beats. In the right part of the figure, the color maps of beats 33-44 are shown. During beat 33, two wavefronts entered the mapping area from different directions. In the next beat, the mapping area was again invaded by 2 wavefronts but now a third impulse arose from the center of the mapping area (*). During the next beats, a focal activation pattern arose from this site and repeated itself until beat 43. During beat 44, the mapping area was again activated by two wavefronts entering from different directions.

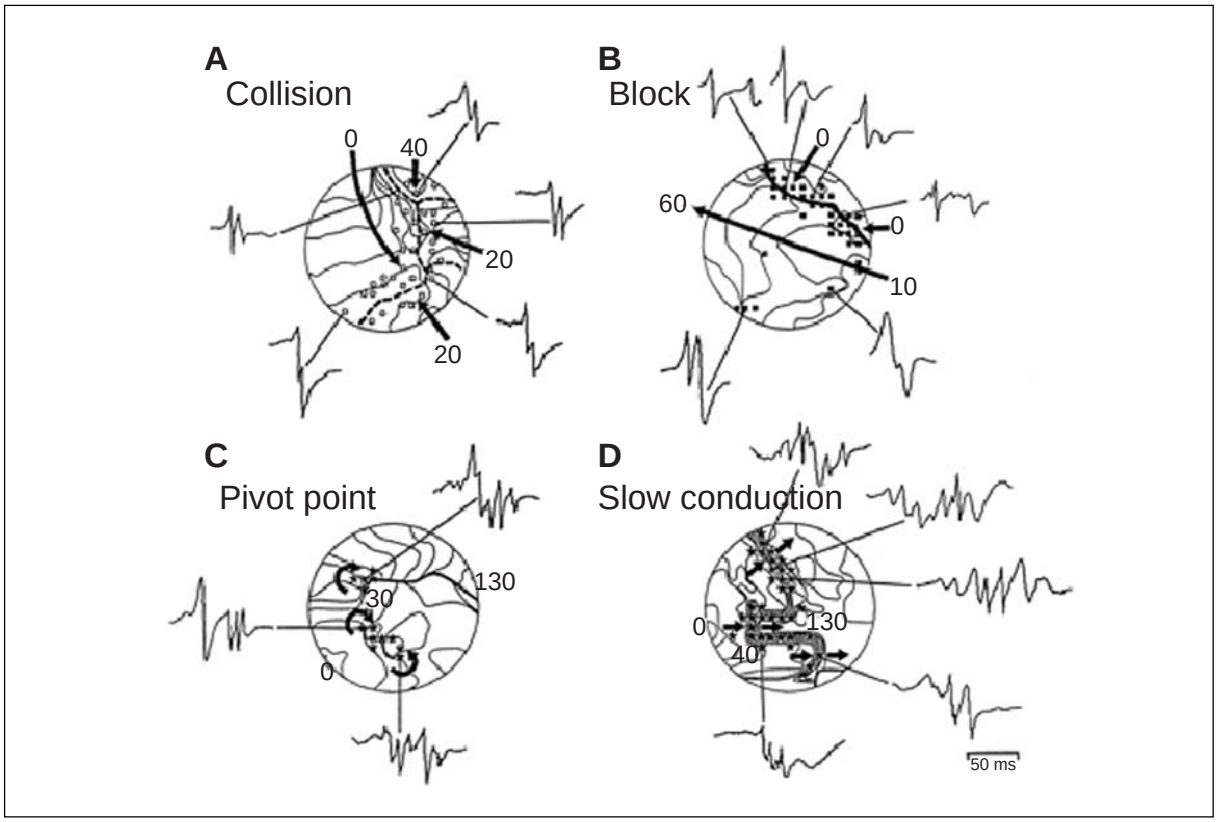

Fig. 6. - Four isochronal maps of the right atrial free wall during acute human AF together with examples of double and fragmented unipolar electrograms. The maps were reconstructed from 244 electrograms recorded with a spoon shaped electrode. Isochrones are drawn at 10 milliseconds interval. The arrows indicate direction of activation. In panel A, four wavefronts entered the mapping area from different directions and collided at the dashed line. Short double potentials (□) were recorded at either site of the line of collision. In the upper part of the map in panel B, long-double potentials (■) were recorded at a line of functional conduction block. Panel C and D show fragmented electrograms (⁎) recorded at different pivot points and areas of slow conduction (crowding of isochrones). (Modified from Konings *et al.* [40]).

Non-contact mapping of the right atrium, both during induced (no. = 8) and chronic AF (no. = 3) confirmed 3 different types of AF [33, 34]. In this study, the majority of patients showed a type III AF pattern. In all patients, the right atrium was activated by wavefronts emerging from the coronary sinus or Bachmann's bundle.

Other mapping studies of chronic AF compared right and left atrial activation [31, 32]. Surprisingly, in most patients, the activation of the left atrium seemed to be more organized. In 3 patients, organized and disorganized activation occurred alternately in the right atrium. However, since the mapping resolution of these studies was rather low (only 30 unipolar or 24 bipolar electrodes) conduction abnormalities occurring in small areas with disorganized conduction might easily have been missed.

Two experimental studies evaluated the difference in degree of organization between acute and chronic AF [35, 36]. The first study compared acute and chronic AF (142 ± 55 days) in the goat [35]. During acute AF the free wall of the right atrium was activated mainly by broad planar wavefronts (type I AF). In contrast, during chronic AF activation of the right atrium was characterized by type III AF. During chronic AF, the median fibrillation interval was shorter and the incidence of fragmented electrograms was higher. Fig. 5 shows a unipolar fibrillation electrogram and four consecutive activation maps of the right atrial free wall during acute and chronic AF in the goat. Another recent mapping study compared right and left atrial activation during acute and chronic AF in the dog, using several epicardial templates with a total of 240 unipolar electrodes [36]. The atrial rate was higher and activation was more disorganized during chronic AF than during acute AF. During acute AF, in the left atrium the cycle length was slightly shorter than in the right atrium. During chronic AF this difference was enhanced. The activation pattern of the right atrium was similar during acute and chronic AF. On the other hand, in the left atrium during acute AF frequently linking of successive fibrillation waves was seen, whereas during chronic AF the left atrium was activated by more complex activation patterns.

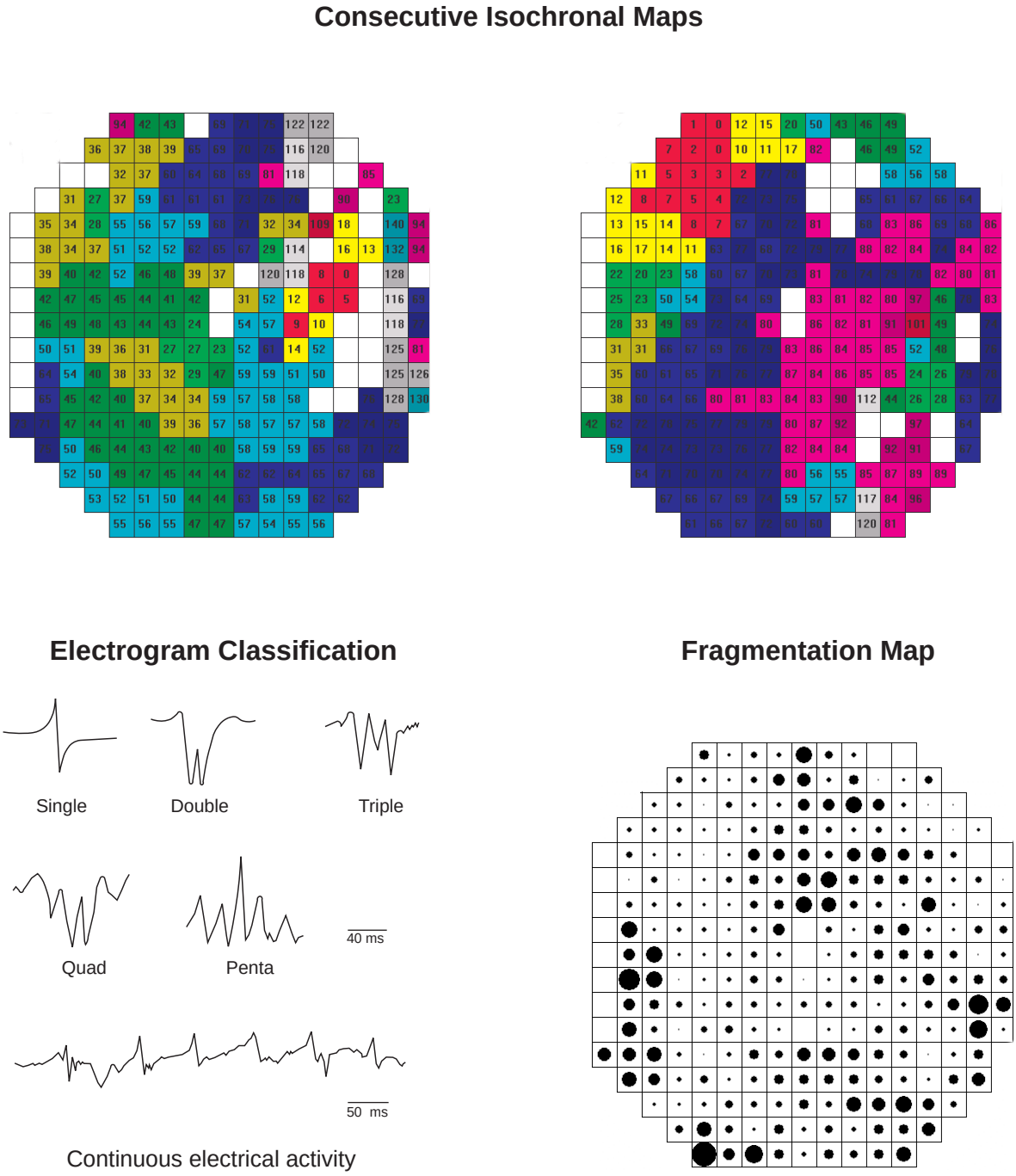

Fig. 7. - Upper panel: Activation maps of two successive beats during chronic AF recorded from the free wall of the right atrium in a patient with mitral valve disease. The maps were reconstructed from recordings obtained with a spoon-shaped electrode (244 unipolar electrodes, interelectrode distance 2.4 mm). Colors indicate activation time. Lower left panel: Classification of the degree of fragmentation of unipolar fibrillation electrograms. Lower right panel: Fragmentation map of the right atrial free wall during chronic AF. The size of each dot indicates the local incidence of fragmentation.

Fragmentation mapping

Bipolar atrial electrograms recorded in patients during AF occurring after cardiac surgery were classified by Wells *et al.* [37]. Type I electrograms were discrete electrograms separated by an isoelectrical baseline free of perturbations. Type II electrograms showed small perturbations around the isoelectrical baseline between discrete atrial signals. No discrete electrograms could be distinghuised in type III electrograms. Type IV electrograms were a mixture of type I, II and III electrograms.

The anatomic distribution of different types of electrograms and its relation to the refractory period during electrically induced AF was examined in two dog models

one with sterile pericarditis and one after 6 weeks of rapid atrial pacing [38]. Bipolar fibrillation electrograms were categorized according to the classification of Wells *et al.* In both groups, disorganized atrial electrograms were found at sites with the longest effective refractory period (right postero-lateral atrium) whereas organized atrial electrograms were found at sites with the shortest effective refractory period (left atrial sites, right atrial appendage).

The complexity of endocardial atrial activity during electrically induced AF in humans was analysed by Jais *et al.* using a multipolar catheter (14 bipolar electrodes, 3 mm inter-electrode distance) [39]. The study population consisted of 25 patients with paroxysmal AF. The "complex electrical activity time" was defined as the ratio of the total duration of electrograms with fibrillation intervals smaller than 100 ms and the total recording time. Atrial activity was more complex in the left than in the right atrium. In the right atrium the disorganized left atrial activity changed abruptly into more organized activity at the crista terminalis. In the left atrium, atrial activity in the septum and the area between the pulmonary veins was more disorganized than in the appendage and anterior left atrium. Thus, organized fibrillation appeared to be confined to the trabeculated parts of the right and left atrium.

The relation between the morphologies of unipolar fibrillation electrograms and the spatial activation pattern during AF was first studied by Konings *et al.* [40]. Fibrillation electrograms were classified as singles, short doubles, long doubles and fragmented potentials. It was found that long double potentials occurred along long lines of functional conduction block whereas fragmented potentials were recorded either during pivoting of fibrillation waves around the end of a line of block or at areas of slow conduction. Short double potentials were recorded when fibrillation waves collided (Fig. 6). In normal human right atria, no preferential sites for double potentials or fragmented electrograms were found.

Kuck *et al.* used an electro-anatomical mapping system (CARTO) to analyse bipolar fibrillation electrograms in patients with paroxysmal AF [41]. Fibrillation electrograms were recorded during 45 seconds at 36 ± 12 sites in the left atrium. Electrograms were classified as either type A (regular activation separated by a clear isoelectrical baseline), type B (irregular activation with perturbations of baseline and/or highly fragmented electrograms) or type C (alternation between type A and type B). Type B and C electrograms were equally present throughout the left atrium whereas the incidence of type A electrograms was higher in the upper left pulmonary vein.

In our institution, we are presently analysing the degree of fragmentation of unipolar electrograms obtained during mapping of the right and left atrium in patients with chronic AF undergoing cardiac surgery. In Fig. 7 an example is given. The upper panels show two successive activation maps of the right atrial free wall during chronic AF in a patient with mitral valve disease. Multiple wavefronts enter the mapping area from different directions. The wavefronts frequently change direction or collide with each other. In the lower left panel, examples of different degrees of fragmentation of fibrillation electrograms are shown. In the right lower panel a total fragmentation map is given representing the incidence of fragmented electrograms at each recording site. Fragmented electrograms were recorded at almost all electrodes. However, some recording sites showed a higher incidence of fragmentation than others. It is yet unknown to what extent this spatial dispersion in fragmentation is due to the normal atrial architecture. It is a challenge for the future to apply fragmentation mapping of chronic AF to diagnose the underlying electro-anatomical substrate.

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