A new floating sensor array to detect electric near fields of beating heart preparations

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Abstract

A new flexible sensor for in vitro experiments was developed to measure the surface potential, \( \Phi \), and its gradient, \( E \) (electric near field), at given sites of the heart. During depolarisation, \( E \) describes a vector loop from which direction and magnitude of local conduction velocity \( \theta \) can be computed. Four recording silver electrodes \((14 H 9262 m \times 14 H 9262 m)\) separated by 50 \( H 9262 m\), conducting leads, and solderable pads were patterned on a 50 \( H 9262 m\) thick polyimide film. The conductive structures, except the electrodes, were isolated with polyimide, and electrodes were chlorided. Spacer pillars mounted on the tip fulfil two functions: they keep the electrodes 70 \( H 9262 m\) from the tissue allowing non-contact recording of \( \Phi \) and prevent lateral slipping. The low mass \((9.1 mg)\) and flexibility \( (6.33 \text{ N/m})\) of the sensor let it easily follow the movement of the beating heart without notable displacement. We examined the electrodes on criteria like rms-noise of \( \Phi \), signal-to-noise ratio of \( \Phi \) and \( E \), maximum peak-slope recording \( d\Phi/dt \), and deviation of local activation time (LAT) from a common signal and obtained values of 24–28 \( \mu V \), 46 and 41 dB, 497–561 \( V/s \) and no differences, respectively. With appropriate data acquisition (sampling rate 100 kHz, 24-bit), we were able to record \( \Phi \) and to monitor \( E \) and \( \theta \) on-line from beat-to-beat even at heart rates of 600 beats/min. Moreover, this technique can discriminate between uncoupled cardiac activations (as occur in fibrotic tissue) separated by less than 1 mm and 1 ms.

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Keywords: High-density electrode array; Micro mapping; Conduction velocity

1. Introduction

Electrical-mapping techniques of the cardiac activation sequence are based primarily on the spatio-temporal distribution of the potential \( \Phi \) on its surface. The propagating depolarisation produces a biphasic signal \( \Phi \) (Fig. 4b), caused by ion- and capacitive currents flowing from the surrounding volume conductor into the cells. This phase spatially extends just a few hundreds microns (Fig. 2). At a large size scale (mm), the excitation spread can be considered as continuous whereas at the microscopic size scale (<100 \( \mu m \)), the conduction becomes complex and discontinuous in nature (Spach et al., 1992). Discontinuous conduction caused by electrical uncoupling of myocardial fibres due to embedded connective tissue (Fig. 1b) occurs, for example, increasing with the aging process of the heart. Slow conduction, re-entrant excitation waves and even cardiac arrest may be induced by this structural change. Micro-conduction, then, is characterized by complex pathways in the tissue (zig-zag course) hardly to detect with conventional systems.

Macroscopic mapping techniques use arrays covering the entire heart with a large number of electrodes separated by 1–2 mm. Individual signals are digitized with sampling rates less than 2 kHz (Arisi et al., 1992; Schuessler et al., 1992). For each recording site, local activation time LAT can be determined accurately from the negative peak of \( d\Phi/dt \) (Spach and Dolber, 1986) and isochrones can be obtained with interpolation techniques. Since the spatial extent of \( \Phi \) (peak-to-peak) may fall below 100 \( \mu m \), such systems can fail to detect details of the propagating excitation wave, particularly at sites of complex or discontinuous conduction.

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Nomenclature

dΦ/dt derivative of Φ
DD diagonal distance between two of four square-like arranged electrodes
E cardiac near field, components of the gradient of Φ parallel and close to the tissue surface
EMR inter-electrode matching ratio, determined with 20 log(Φ/ΔΦ)
LAT local activation time, discrete value of activation, the instant, when the negative peak of dΦ/dt occurs
SNR signal-to-noise ratio, 20 log(Φpp/Φnpp) given in dB

Greek symbols

Φ surface potential, the potential difference between a site at the heart and a reference electrode placed far from active tissue
ΦACpp peak-to-peak amplitude of the AC-interference signal
Φnpp peak-to-peak amplitude of noise in Φ
Φrms rms-value of noise in Φ
ΔΦ potential difference Φi − Φk recorded with two electrodes i and k, both placed near the active tissue
ΔΦACpp common-mode component of ΦACpp
θ conduction velocity of activation wave front propagating at the tissue surface

Hand-made electrode arrays with sub-millimetre spacing were built using thin wires (Malkin and Pendley, 2000, Witkowski et al., 1993). Ultra high-resolution devices with spacing <100 μm were fabricated with micromachines (Hofer et al., 1994; Kim et al., 2004; Mastrototaro et al., 1992) on rigid substrates. Despite the progress in technology, their application is not trouble-free. The geometrical fitting between the flat surface of the plaque and the variable surface of the tissue showing rifts and complex macrostructures in 3D (see Fig. 1a) remains imperfect. This mismatch may bring some of the electrodes in contact with the tissue and leave the others in a non-contact mode at variable distances. The variable cleft between tissue and array also affects the conduction, or if the plaque is squeezed towards the tissue, it can obstruct the flux of the superfusate. Superfused preparations could then suffer from a lack of oxygen supply. Unless the sensor is transparent, the exact position of the electrodes is uncertain and displacement artefacts during contraction are likely.

We propose a new approach to avoid these difficulties, namely to measure E at a given site of the heart with an ultra-lightweight sensor floating with the movement of the beating heart. E reflects the very local conduction process in a sub-millimetre area around the recording site, and is represented by a vector loop indicating the direction of propagation (see Fig. 2).
computed the technical requirements for proper measurement of \( E \) with two orthogonal pairs of electrodes (Plank and Hofer, 2000) and obtained crucial limit values of diagonal distance \( DD \) (>100 \( \mu m \)), sampling rate (>50 kHz) and signal-to-noise ratio \( SNR \) of \( \Phi \) (>40 dB). Electrode response has to be optimized to ensure that each recording channel is able to follow the fastest slope expected (200 V/s). The small dataset of four depolarisation signals can easily be used to obtain parameters of local conduction without time-consuming signal processing techniques and allows monitoring in a beat-to-beat manner, even at heart rates of 600 beats/min.

The time course of \( E \) at a given site allows an “electro-anatomical characterisation”, reflecting the microstructure of the tissue under study. This fact might be of relevance in future developments of intra-cardiac catheters, serving as pathfinders of complex conduction and could lead to improved diagnostic techniques in the heart. The development of an appropriate near field sensor is a first step towards this vision.

We describe the design, the fabrication, and mechanical and electrical testing procedures of this new sensor and demonstrate, shortly, its experimental application in vitro.

2. Methods

2.1. Fabrication of sensors

2.1.1. Geometrical design and wafer production

Sensor and carrier should meet the following criteria: (1) the geometry (needle-like form) has to ensure easy access to every recording site, even in complex tissue; (2) the stiffness needs to be strong enough to allow exact positioning of the tip but without affecting the tissue; (3) inter-electrode distances have to be <100 \( \mu m \) to ensure proper computation of \( E \) from local potential differences \( \Delta \Phi \) (Plank and Hofer, 2000); (4) \( SNR \) has to be kept <40 dB to warrant appropriate accuracy in computing \( LAT \) and \( \theta \) (Plank et al., 2003); and (5) ultra-small latencies of the signals in the range of a few microseconds have to be detectable by the system. A sketch of the layout showing the four electrodes separated diagonally with \( DD \) (criterion 3) is given in Fig. 3. Polyimide (Upilex UBE Industries, Japan) was chosen due to its outstanding physical and chemical properties. Experiments with dummy devices with thicknesses of 25, 50 and 125 \( \mu m \) were performed to test criterion 1 and 2. Foils with 50 \( \mu m \) have been proven to be best feasible due to a good balance between desired flexibility and sufficient rigidity for handling during in vitro experiments. The films were cut into sheets of 100 mm \( \times \) 100 mm. Pre-stress during the production process resulted in a bending of the wafer, which was released by thermal annealing at 370 °C.

After thermal annealing, the wafer was pre-cleaned with ethanol in an ultrasonic bath for 1 h and subsequently immersed in 10% RBS50-solution (Carl Roth GmbH, Germany) for 8 h. Finally, it was rinsed with deionised water and dried with a wafer spinner.

2.1.2. Backside processing

The major part of the wafer was covered on the backside by metal layers for optional electrical shielding of the sensor.

2.1.3. Microelectrodes

Electrodes, conducting lines, and solderable pads were patterned by a lift-off process using an image reversal resist (TI 35 ES from Clariant Corp., USA). Spin coating during 40 s was followed by hard-baking of the resist at 95 °C for 1 min. Afterwards, the polyimide layer was hard-baked in a vacuum oven at 370 °C for 1 h.

The region of the sensor around the tip was left off this process to avoid contact between shielding plane, bath ground and recording electrodes via the conductive liquid. The metal layers (100 nm adhesion layer from titanium plus 500 nm shielding layer from silver) were evaporated. The metal plane was isolated with a polyimide resist (Durimid 112A, Fujifilm Electronic Materials, Japan), then spin coated at 4000 rpm and dried at 130 °C for 1 min. Then, the polyimide layer was removed and the metal layers (adhesion layer of 100 nm titanium followed by a 500 nm thick silver layer) were deposited by evaporation (Balzers BAK 550
The movement in the z-plane during contraction was determined by analysing a digital video sequence (Olympus CamEDIA 5060WZ, Japan) taken from the beating heart with 15 frames/s. Thirty consecutive frames with 640 × 480 pixels (pixel size 100 μm) were taken for analysis. Two reference points were assigned in each frame image: one related to a distinctive structure of the tissue, P1, the other one, P2, at the sensor tip (2.3 mm apart from P1). Starting with the first frame, we determined the xy-coordinates of P2 and of P1, and measured the values of the subsequent pairs of P2 and P1. From this data, a sequential set of deflections was calculated representing the distances of P1 to P2 and of P2 to P1. We normalized the deflections to their peak amplitude and determined the linear correlation coefficient as a measure, if and how close the sensor followed the movement of the tissue.

2.3. Experimental preparation

Animals (Guinea pig, mouse) were heparinised and anaesthetised with thiopental sodium (30 mg/kg), both administered intraperitoneally. Hearts were rapidly excised. Animal preparation conformed to the national ethic guidelines. The tissue was placed either in a bath filled with oxygenated Tyrode’s solution (in mM: NaCl 132.1, KCl 5.4, CaCl2 2.5, MgCl2 1.15, NaHCO3 24, NaHPO4 0.42, d-glucose 5.6) flowing through at 36 °C, or the whole heart was mounted on a Langendorff perfusion system. The heart preparation was either beating autonomously or was paced with a stimulus electrode delivering a current of 1 ms pulse width and twice the minimal current strength necessary to excite the tissue.

2.4. Tissue gross-anatomy and micro-structure

During the experiment, the entire heart or the tissue under study with its visible macrostructure, as well as the electrode position, was recorded with a digital camera (Olympus CameDIA 5060WZ, Japan) connected to a PC. Post experimentum, the tissue was fixed in parafomaldehyde–glutaraldehyde and embedded in paraffin. Sections were made parallel to the tissue surface, and stained with Masson’s trichrome, which depicts muscle cells in red and collagen in blue (see Fig. 1b).

2.5. Electrical testing of the sensor

Φ was measured in a bath filled with conductive solution. At its bottom, a circularly formed Ag/AgCl-wire was connected to ground and a stimulus electrode was placed at the centre. Thus, signals (Φ, E) in the bath were generated by AC-interference from the power-line, by local currents from the stimulus electrode connected to a signal generator (FT1, Interstate Electronics Inc., New Jersey), or by local currents arising from active tissue. The first two methods generate a common signal at all four recording electrodes whereas the third method was evaluated by pushing the sensor in steps of 1 mm against the scale and reading the forces. The bending spring constant was, then, computed with a linear correlation of the sampled values.

Displacement of the sensor tip in the x-y-plane during contraction was determined by analysing a digital video sequence (Olympus CamEDIA 5060WZ, Japan) taken from the beating heart with 15 frames/s. Thirty consecutive frames with 640 × 480 pixels (pixel size 100 μm) were taken for analysis. Two reference points were assigned in each frame image: one related to a distinctive structure of the tissue, P1, the other one, P2, at the sensor tip (2.3 mm apart from P1). Starting with the first frame, we determined the xy-coordinates of P2 and of P1, and measured the values of the subsequent pairs of P2 and P1. From this data, a sequential set of deflections was calculated representing the distances of P1 to P2 and of P2 to P1. We normalized the deflections to their peak amplitude and determined the linear correlation coefficient as a measure, if and how close the sensor followed the movement of the tissue.

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measured a propagating biosignal, which produced small differences in waveform and latencies of $\Phi$ at the individual recording sites.

The sensor was connected to a custom designed amplifier (gain factor 100, DC or AC-coupling, 20 kHz 4th order low-pass Bessel filter). Output signals were acquired simultaneously at 100 kHz with 24-bit-A/D-Converter (NI PCI 4472, National Instruments, Texas) controlled by a custom designed program written in LabView 7.0 (National Instruments, Texas).

The offset voltage and amplification factor of each amplifier was precisely determined in advance to compensate for inter-individual differences of $\Phi$ caused by amplifiers. Bipolar recordings $\Delta \Phi$ were computed from the dataset of four signals $\Phi_{i-1}, \Phi_{i}, \Phi_{i+1}, \Phi_{i+2}$. $\Delta \Phi = \Phi_{i} - \Phi_{i+1}$, assigned to electrode 1, and $\Delta \Phi = \Phi_{i+1} - \Phi_{i+2}$, electrode 3.

2.5.1. AC-interference and noise

Without tissue and no stimulus, we examined the signal $\Phi_{ACpp}$ produced by the interference of power lines and its representation in the bipolar recording $\Delta \Phi_{ACpp}$. After compensation of these components, we measured the peak-to-peak noise level $\Phi_{pp}$ and computed the rms-noise, $\Phi_{rms}$.

2.5.2. Stimulus response

Signals of sinusoidal (50 Hz/20 mV), rectangular (2 Hz/20 mV) and of triangular shape (1 kHz/20 mV) were delivered by the stimulus electrode. The sinusoidal signal was chosen to examine the system behaviour at the power-line frequency. The rectangular waveform allowed us to check the system with both very slow signals (plateau phase of the rectangle) and very fast events (the slope of the rectangular signal). The triangular signal was used, then, to test the system feature to monitor different DD was studied: $\Phi_{ACpp}$ of these components, we measured the peak-to-peak noise level $\Phi_{pp}$ and computed the rms-noise, $\Phi_{rms}$. An overview of the measurement results is shown in Table 1. Power line induced AC-interference $\Phi_{ACpp}$ at the four electrodes varied between 0.296 and 0.316 mV. $\Phi_{pp}$ was between 24 and 28 $\mu$V, whereas difference signals $\Delta \Phi$ (not given in the table) showed even decreased noise levels of 12–13 $\mu$V. Recordings of 50 Hz sinus signals yielded in good matching of the individual responses (IEMR of 34–38 dB). The response to rectangular pulses showed that during the plateau phase IEMR was excellent (63–66 dB), and that during the fast edge of pulse switching, the system can follow slow rates >500 V/s. Despite noticeable variations, the need to follow slopes of >200 V/s was met.

3. Results

The fabricated sensor is depicted at different magnification stages showing the entire device plus connector or details up to the nanostructure of the electrode surface (Fig. 3b).

3.1. Mechanical characteristics

The mass of the sensor (electrodes plus substrate) was 9.1 mg. The bending force–elongation relationship was strongly linear from 0 to 10 mm ($n = 10$, $r^2 = 0.98$), resulting in 6.33 N/m. A swing at the tip of 5 mm at 5 Hz corresponds to a peak acceleration of 2.69 m/s$^2$. Regarding only the distal third of the sensor, which primarily experienced motion and represented roughly a tenth of the total mass, the peak inertial force $F_1$ was estimated applying Newton’s second law, and resulted in 2.45 mN. When placing the sensor on tissue, a feed of 2 mm after reaching the surface produced a bias force of 13 mN. A swing of 2 mm caused by contraction, then, resulted in an total bearing strength $F_B$ of 13–26 mN. Tensile forces in the heart examined experimentally (Lunkenheimer et al., 2004) let us estimate contraction forces $F_3$ in the range of 0.1–0.2 N. The correct ranking of $F_3 > F_B > F_1$, a condition to prevent undesired mechanical impact on the 3-movement, is met with 200 > 26 > 13 mN. Displacement analysis in the x-y-plane resulted in an amplitude of 1.53 mm at $P_1$ and 1.02 mm at $P_3$. The sequences of elongations $S_y$ and $S_x$ correlated with $S_y = 1.34 S_x$ ($n = 30$, $r^2 = 0.81$). Since the standard deviation was 130 $\mu$m and the image pixel size corresponded to 100 $\mu$m, no notable displacement could be detected with our system.

3.2. Electrical testing of the sensor

An overview of the measurement results is shown in Table 1. Power line induced AC-interference $\Phi_{ACpp}$ at the four electrodes varied between 0.296 and 0.316 mV. $\Phi_{pp}$ was between 24 and 28 $\mu$V, whereas difference signals $\Delta \Phi$ (not given in the table) showed even decreased noise levels of 12–13 $\mu$V.
Table 1

<table>
<thead>
<tr>
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<th>CH1</th>
<th>CH2</th>
<th>CH3</th>
<th>CH4</th>
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<td><strong>A. Noise and AC-interference</strong></td>
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<tr>
<td>Φ_{ACpp} (mV)</td>
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<td>0.316</td>
<td>0.296</td>
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<tr>
<td>ΔΦ_{ACpp} (mV)</td>
<td>4.1</td>
<td>4.1</td>
<td>13.7</td>
<td>4.1</td>
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<tr>
<td>( ΔΦ/Δt) _{ACpp} (ΔV/s)</td>
<td>0.049</td>
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<tr>
<td>Φ_{Acref} (μV)</td>
<td>27</td>
<td>28</td>
<td>24</td>
<td>28</td>
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<tr>
<td>Φ_{nref} (μV)</td>
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<td>92</td>
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<td><strong>B. Sinusoidal signal 50 Hz</strong></td>
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<td>Φ_{pp} (mV)</td>
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<td>16.29</td>
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<td>ΔΦ_{pp} (μV)</td>
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<td>356</td>
<td>205</td>
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<td>IEMR (dB)</td>
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<td><strong>C. Square signal 2 Hz</strong></td>
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<td>Φ_{pp} (μV)</td>
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<td>IEMR (dB)</td>
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<td>65.6</td>
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<td><strong>D. Triangular signal 1 kHz</strong></td>
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\( Φ\) and \( ΔΦ\) as function of DD

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<tr>
<th>DD (μm)</th>
<th>500</th>
<th>200</th>
<th>100</th>
<th>70</th>
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<th>20μm</th>
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<td>15.5</td>
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<td>6.48</td>
<td>4.73</td>
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<tr>
<td>Φ_{npp} (μV)</td>
<td>79</td>
<td>41</td>
<td>41</td>
<td>41</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>SNR (dB)</td>
<td>45.9</td>
<td>51.6</td>
<td>48.6</td>
<td>46.0</td>
<td>41.2</td>
<td>37.9</td>
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</tbody>
</table>

θ. With DD = 70 μm (like in use with our floating sensor), the value of SNR of ΔΦ, and therefore of \( E\), can still be kept above an acceptable value of 41 dB, like theoretically predicted (Plank and Hofer, 2003). \( Φ\), its derivative \( dΦ/dt\), and a magnified section of \( Φ\), depicting the noise are shown in Fig. 4b. We obtained a \( Φ_{pp}\) of 16 mV, \( Φ_{npp}\) of 46 μV and a \( dΦ/dt\) of −49 V/s. SNR, then, was 51 dB. The time course of the orthogonal components \( E_x\) and \( E_y\) and the vector representation \( E\) taken from a Guinea pig heart are displayed in Fig. 5. \( Φ\) shows a typical biphasic waveform of a 10 mV amplitude with small irregularities in the onset and end phase of the signal indicating discontinuities of conduction. The \( x\)- and \( y\)-components of \( E\) differ in amplitude resulting from directional effects. \( E\) with a peak value in magnitude of 22 V/m describes a loop with morphology similar to the predicted one (Fig. 2). We could not detect any displacement of the sensor tip during contraction of the beating heart.
4. Discussion

Optical techniques using fluorescent dyes (Efimov et al., 2004), as well as improved and refined electrical potential mapping systems (Kim et al., 2004; Malkin and Pendley, 2000; Mastroットaro et al., 1992) with various spatio-temporal resolutions and numbers of recording sites, are widely used to study the excitation spread on the surface of entire isolated hearts or within cardiac tissue probes. Both methods offer different advantages and constraints. In optical methods, the advantages include detecting depolarization as well as repolarization, preventing any mechanical lesion or interference, and flexibility in determining recording spots by optics. These are opposed to constraints like a rather modest SNR, toxicity and photo bleaching effect of dyes, and possible interference with normal function by commonly used electro-mechanic uncoupling substances making long-lasting experiments difficult or impossible. Electrical methods stand out by their excellent SNR and accurate determination LAT from \( \frac{d \Phi}{dt} \) (4.1 \( \mu \)V) and in \( \frac{d \Phi}{dt} \) (0.049 V/s) are negligible compared to corresponding values of cardiac signals (5 mV, 80 V/s). A larger factor affecting the quality of signal recording and analysis is noise from the electrodes and SNR. Some authors specify SNR with the more favourable ratios of \( \Phi \text{rms} \) instead of \( \Phi \text{pp} \). In this view, the largest bio-signal we observed (~30 mV) related to the lowest noise level we measured (15 \( \mu \)Vrms) would result in SNR of 2000. The inter-individual differences of electrode noise, despite a perfect structural match ensured by microfabrication, may be caused by variability of the electrochemical chloriding procedure. With increasing frequency, components of the signal \( \Phi \) matching the electrode characteristic degrades as can be seen when comparing variations of \( \Phi \text{pp} \) at 50 and 2 Hz, and \( \frac{d \Phi}{dt} \text{edge} \) and \( \frac{d \Phi}{dt} \text{app} \) in Table 1. This can be explained by differences of electrode resistance and capacitance between the leads. The triangular test signal of 1 kHz was applied to mimic signal slopes of depolarisation. Noticeable variations of 25.8–29.5 V/s were observed. To examine whether these errors in \( \frac{d \Phi}{dt} \text{app} \) would affect the determination of LAT, we computed \( \frac{d \Phi}{dt} \) of the rectangular test signal, determined LAT of the edge phase of \( \Phi \) (a needle-like representation in \( \frac{d \Phi}{dt} \) and could not detect any differences of LAT between the recording channels.

There have been earlier attempts to represent the propagating depolarisation wave by vector loops from two orthogonal bipolar electrograms (Kadish et al., 1986). However, the large electrode spacing of 2 mm did not allow capture of \( \Phi \). Later, from recordings with a five-element electrode array (DD 65 \( \mu \)m) sewed on the epicardium, \( \Theta \) and the membrane current were computed (Witkowski et al., 1993). Our device differs from this application in several aspects: (1) it is a non-contact application barely affecting the cardiac near field; (2) the sensor is not fixed but manoeuvrable to any site; (3) high-performance data acquisition available now allows substantially improved accuracy of analysis.

Conduction velocity \( \Theta \) like taken from epicardial mappings reflects only the component of \( \Theta \) on the surface; propagation occurring in the depth is disregarded. When activation propagates from the endocardium to the epicardium, conduction may be oriented oblique or even perpendicular to the surface of the heart. At those sites depolarization may occur simultaneously at all four recording sites and lead to an “apparently” infinite value of \( \Theta \). In thin tissue (e.g. in the right auricle), or in excitation spread caused by epicardial pacing, conduction runs parallel to the surface and \( \Theta \) reflects the true local conduction velocity. For appropriate interpretation of \( \Theta \) and \( \Theta \), one has to regard this.

5. Conclusions

This technique makes it possible to record \( \Phi \) at a given recording site, to monitor local conduction on a beat-to-beat basis, and, furthermore reveals details of local conduction hidden using conventional mapping systems. \( \Phi \) and its beat-to-beat analysis taken from a site of critical conduction (like bifurcation of conduction
structures in the atrium) or in the presence of critical function (acidosis, hypoxia, high frequency pacing) may open a completely new microscopic view on arrhythmia.

The method can be extended to in vivo applications during animal surgery. Measured intra-cardially with a catheter could be used for improving diagnostic tools. During animal experiments, procedures like those applied in human cardiac surgery could help to predict the potential diagnostic and therapeutic power of this technique. The new knowledge about microconduction in the heart, detectable by this method might become important in clinical applications in the future. As mentioned in Section 1, the prevalence of microstructure-related cardiac arrhythmias will increase with the increased life expectancy. Hence, minimal-invasive diagnostic tools to detect the status of cardiac microstructure might gain in importance. The method described in this work might contribute to the progress in this field.

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