Dependence of temporal variability of ventricular recovery on myocardial fibrosis. Role of mechanoelectric feedback?

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Received 25 March 1997; accepted 7 August 1997

Abstract

Objective: The study was aimed at establishing the effect of factors involved in the expression of mechanoelectric feedback in the heart, such as R-R interval and connective tissue, on time dependent changes in ventricular recovery, as determined at the body surface by beat to beat variability of QRST integral maps BBV-IM.

Methods: We used 15 normal 6-month-old Wistar rats. In each anesthetized animal, we performed a 3-minute continuous recording of 44 simultaneous chest ECGs. The signals were interactively processed, 1) to determine mean R-R interval and R-R variability throughout the recording period and 2) to compute QRST integral maps from approximately 50 beats belonging to the end of expiration. Then BBV-IM was calculated and expressed as percentage of beats significantly differing from a template. At sacrifice, the amount of myocardial fibrosis was morphometrically evaluated.

Results: R-R interval was 149 ms ± 4, R-R interval variability 0.008 ± 0.001 and BBV-IM 30.7% ± 4.4. Myocardial fibrosis expressed as % volume of left ventricular myocardium, numerical density of fibrotic foci and average cross-sectional area of the foci was 3.0% ± 0.4, 3.8 ± 0.6 and 4.4 μm²/1000 ± 0.1 respectively. BBV-IM was positively correlated to the % volume of fibrosis (r = 0.81, P < 0.0003). Both measurements were positively correlated to R-R interval (BBV-IM: r = 0.83, P < 0.0001; % volume of fibrosis: r = 0.87, P < 0.0001) and negatively correlated to cardiac weights (BBV-IM: r = −0.79, P < 0.0005; % volume of fibrosis: r = −0.75, P < 0.001).

Conclusion: Beat to beat changes in ventricular repolarization attributable to mechanoelectric transduction can be detected at the body surface by means of BBV-IM. © 1998 Elsevier Science B.V.

Keywords: Repolarization; Mechanoelectric feedback; Integral maps; Non-invasive measurements; Myocardial fibrosis; Cycle length; Heart rate variability; Rat, anesthetized

1. Introduction

There is increasing clinical and experimental evidence of a relevant role of mechanoelectric feedback (transduction) in cardiac electrogenesis, in both normal and abnormal conditions [1,2].

In cardiac pathology, the electrical correlates of the feedback process could be involved in the genesis of most rhythm disturbances [3–5]. Conversely, it has been proposed that under normal circumstances mechanoelectric transduction exerts various regulatory actions [3,6]. Importantly, the process could be operative in regional electromechanical interactions across the ventricular wall to maintain spatial and temporal dispersion of action potential duration and repolarization in a normal range. The time dependent changes in recovery dispersion would confer physiological adaptability and favour the prevalence of a stable electrical state.

It is widely held that cardiac mechanoelectric effects detectable by means of extracellular measurements are limited to changes in the recovery process and are hard to detect at the body surface. QRST integral maps, which constitute a three-dimensional and regionally discriminative representation of ventricular repolarization and are largely independent of the activation sequence, can provide non-invasive and detailed information concerning the local

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PII S0008-6363(97)00221-6
dispersion of recovery process [7,8]. Moreover, a procedure for evaluating beat-to-beat variability of QRST integral maps (BBV-IM) has recently been published [9–11]. Thus, the modulatory action of mechanoelectric feedback on cardiac repolarization could be determined at the body surface by analyzing the temporal variability of QRST area maps. This is an important issue in consideration of the potential arrhythmogenic action of stretch-induced effects on the heart and the need for new, non-invasive procedures to approach the problem.

The role of connective tissue as a possible substrate for mechanoelectric feedback has recently been reviewed [12]. Stress-induced changes in electrogensis of myocytes could occur as a result of electrotonic interaction with mechanosensitive fibroblasts via low conductances interconnecting the heterologous cells. This mechanism of active nature would add to passive mechanisms in which the myocardium bordering scarred tissue may be exposed to a greater stretch as compared to the adjacent normal tissue [12,13]. The stretch results in activation of specific or conventional membrane ion channels or changes in net inward current due to variations in intracellular calcium handling [14].

In previous experiments performed on normal adult rats (6–9 months old), we found a temporal variability of QRST integral maps which was ascribed to changes in ventricular repolarization inhomogeneity during successive heart beats [15,16]. Morphological studies in normal rats of different ages (4, 12, 20, 22, 29 months) have revealed small areas of interstitial and replacement fibrosis throughout the left ventricular wall, progressively increasing with aging [17,18]. Thus, normal rats could constitute a suitable model for investigating the effect of connective tissue on beat-to-beat variations of cardiac electrogensis, as measured at the body surface by means of BBV-IM. The absence of large morphofunctional abnormalities usually associated with most heart conditions should facilitate the analysis. On the other hand, several reports have shown a dependence of mechanoelectric feedback on cycle length [19], suggesting that recovery changes of mechanoelectric nature could be modulated by the R-R interval. The effects on cardiac electrical activity resulting from interactions between myocardial fibrosis and R-R interval have not been explored. The present investigation was aimed at analyzing: 1) the correlation between the amount of ventricular myocardial fibrosis and BBV-IM, taken as a measure of temporal variability of the recovery process in the intact animal, attributable to mechanoelectric feedback; 2) the effect of R-R interval on BBV-IM and cardiac structural remodelling.

2. Methods

The experimental protocols were approved by the Veterinary Animal Care and Use Committee of the University of Parma. The investigation conforms with the “Guide for the Care and Use of Laboratory Animals” published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985).

2.1. Animals

We used 15 male 6-month-old Wistar rats weighing 488.2 g ± 35.0 (average value ± standard error; range: 463 g–593 g) randomly selected from a larger population of normal rats chronically instrumented with a telemetry ECG transmitter (Data Sciences, St. Paul, MN; model TA11CTA-F40). The conscious, unrestrained animals were monitored weekly to make sure that cardiac rate and rhythm were normal. Previous studies of our group have shown that the repertoire of behavioural patterns [20] and the amount of myocardial fibrosis (unpublished results) of instrumented rats are comparable to those of control animals without transmitter implantation.

2.2. Map recording and processing

One month after transmitter implantation, a 3-minute continuous recording of 44 simultaneous unipolar chest ECGs was performed with the animal in prone position and anesthetized with droperidol + phentanyline citrate (Leptofen, Farmitalia-Carlo Erba; 0.6 ml/kg, I.M.). The electrodes were regularly distributed on a matrix of 8 columns and 6 rows equally spaced, covering the entire chest surface (Fig. 1A). The analog signals were amplified, sampled at 1 kHz, A/D converted and stored on disk.

From the 3-minute recording, we selected approximately 50 (N) sets of 44 simultaneous ECGs (each set = one beat; Fig. 1B) belonging to the end of expiration. The selection of beats in the same respiratory phase was aimed at minimizing physiological fluctuations in cardiac potentials caused by changes during respiration in either electrical resistance of the conducting medium or cardiothoracic ratio, or in both [21]. The QRST area distribution relating to each beat was computed by algebraically summing in every lead the products of the instantaneous potential values times the sampling interval, throughout QRST (Fig. 1C) [22].

Finally, the ECG obtained from a precordial lead was interactively analyzed for determining R-R interval, R-R variability and rhythm disturbances. R-R variability (indirect evaluation of the autonomic input to the heart) was expressed as the quotient of the standard deviation of the mean R-R interval and the mean R-R interval (coefficient of variance SD_RR/RR) [23].

2.3. Evaluation of BBV-IM

BBV-IM was determined by means of a procedure for statistically comparing multiple ECG signals in map form [9,11]. Briefly, quantitative parameters are obtained which
make it possible to establish whether the differences between two maps relate to the magnitude of the signals (scale parameter), spatial shift (shift parameter) or other factors independent of magnitude and shift (arbitrarily defined shape parameter), according to a computed model of the data. In the present study, we adopted as a model of QRST integral map patterns the potential distribution generated by a fixed dipole placed in the center of a sphere approximating the thorax. The lead-off points on the sphere corresponding to the recording sites on the thorax were distributed asymmetrically with respect to the equator in order to represent the actual distribution of positive and negative QRST integral potential values on the chest (Fig. 1D).

Each of the N selected beats (template) was compared with all the remaining N-1 beats, separately for scale, shift and shape parameters. For every comparison, the number of beats (n) significantly differing from the template for at least one parameter was determined and expressed as a percentage of N (i.e. \[\frac{n}{N-1} \times 100\]). Finally, the average value of the N percentages was taken as the BBV-IM index of the animal.

2.4. Morphofunctional studies

Three to five days after the map recording, each animal was anesthetized, the right carotid artery was cannulated and the arterial blood pressure was directly measured. Then, in accordance with a procedure previously described [24], the heart was arrested in diastole with 1 ml of cadmium chloride (100 mM, I.V.) and perfused retrogradely through the abdominal aorta with phosphate buffer (pH 7.2) for 3 minutes. Subsequently, the coronary vasculature was perfused and fixed for 15 minutes with a solution containing 2% paraformaldehyde and 2.5% glutaraldehyde. The heart was excised and the weights of the right ventricle and the left ventricle inclusive of the septum were determined. The left ventricle was serially cut into

Fig. 1. A: Schematic drawing illustrating the location of the 44 recording electrodes (black dots) on the ventral and dorsal aspect of the rat thoracic surface. ra = right axilla; sm = sternal midline; la = left axilla; dm = dorsal midline. Letters a to f on the matrix identify a column of electrodes which are mapped on the spherical model of the thorax, illustrated in D (see below). B: ECGs recorded from the 44 chest electrodes during one heart beat, in a representative rat of the study population. The position of the waveforms corresponds to the location of the electrodes on the thorax, shown in A. C: QRST integral map referring to the heart beat reported in B. The dotted line indicates the zero integral level. The symbols + and − indicate the location on the chest of the highest positive and negative integral values respectively, which are reported below the picture, together with the interval (I) between integral lines. D: Spherical model of the thorax with the dipole located at its center. The meridian on which the points a to f are mapped corresponds to the column of electrodes indicated in A with the same letters. The other 7 electrode columns of the thoracic grid are mapped on meridians not reported in the picture equally spaced, at 45°. Note that the electrodes on the meridian are asymmetrically distributed with respect to the equator in order to represent the actual distribution of positive and negative integral values on the chest.
9–10 one-mm-thick slices. From the 2 intermediate rings 5 fragments extending from the endocardium to the epicardium were selected, postfixed in 1% osmium tetroxide, dehydrated in acetone and flat-embedded in Araldite. A one-micrometer thick section, extending to the entire thickness of the wall, was obtained from each tissue block and stained with methylene blue and safranin for quantitative measurements. Ten consecutive fields of each section were morphometrically examined at a magnification of 200 × to determine: 1) the volume fraction of interstitial and replacement fibrosis in the myocardium, 2) the numerical density of fibrotic foci per unit area of myocardium and 3) the average cross-sectional area of the fibrotic foci, at the endocardial, middle and epicardial layers of the left ventricular wall. Since on a qualitative basis no changes were found in the right ventricular myocardium, this ventricle was not subjected to morphometrical analysis.

2.5. Statistical analysis

The normal distribution of variables was checked by means of the Kolmogorov-Smirnov test. Results were expressed as mean ± standard error (s.e.). Additional statistical treatment of the data included one-way analysis of variance (post hoc analysis: Bonferroni test), correlation analysis and stepwise variable selection (Statgraphics, STSC).

3. Results

3.1. Functional measurements

R-R interval during the 3-minute recording was 149 ms ± 4 and the coefficient of variance (SD_{R-R}/R-R) was

<table>
<thead>
<tr>
<th>RATS</th>
<th>Scale</th>
<th>Shape</th>
<th>Scale + Shape</th>
<th>Index</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>15.1</td>
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<td>9.7</td>
<td>46.5</td>
</tr>
<tr>
<td>2</td>
<td>31.0</td>
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<td>10.4</td>
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</tr>
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<td>0.4</td>
<td>28.1</td>
</tr>
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<td>2.1</td>
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<td>1.8</td>
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<tr>
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<tr>
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<td>0.8</td>
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</tr>
<tr>
<td>Mean</td>
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<td>30.7</td>
</tr>
<tr>
<td>s.e.</td>
<td>2.6</td>
<td>1.8</td>
<td>1.8</td>
<td>4.4</td>
</tr>
</tbody>
</table>

For each animal, the number of beats (mean of N comparisons in % value, see also text) differing from the template for scale, shape or both parameters is reported in columns 2–4. The last column refers to the number of beats differing from the template for at least one of the parameters (BBV-IM index of the animal).

Table 2

<table>
<thead>
<tr>
<th>Cardiac weights</th>
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<tbody>
<tr>
<td>Weights</td>
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<tr>
<td>HW mg</td>
</tr>
<tr>
<td>LVW mg</td>
</tr>
<tr>
<td>RVW mg</td>
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<tr>
<td>HW/BW mg/g</td>
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<tr>
<td>LVW/BW mg/g</td>
</tr>
<tr>
<td>RVW/BW mg/g</td>
</tr>
</tbody>
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BW = body weight, HW = heart weight, LVW = left ventricular weight, RVW = right ventricular weight.

0.008 ± 0.001. QRST area maps showed a significant variability among beats. The average BBV-IM index was 30.7% ± 4.4. Differences depended exclusively on scale and shape parameters. For each animal, the number of beats differing from the template as to scale, shape or both parameters is reported in Table 1, in % value.

Diastolic blood pressure was 78 mmHg ± 2.6 and systolic pressure 112 mmHg ± 4.1.

3.2. Gross cardiac characteristics and morphological changes

The weights of whole heart (HW), right ventricle (RVV) and left ventricle (LVV) are reported in Table 2, together with their corresponding ratios to body weight (BW): HW/BW, RVV/BW and LVV/BW.

The morphometric analysis of the left ventricular wall revealed a small amount of interstitial and replacement fibrosis. The volume fraction of myocardial fibrosis, the numerical density of fibrotic foci per unit area of tissue and the average cross sectional area of the foci for the three layers of the left ventricular wall are reported in Table 3. No significant difference was found between structural alterations at the epicardium, mid-myocardium and endocardium (P = 0.1–0.3). On the entire wall, the volume fraction of fibrosis was 3.03% ± 0.39, the numerical density of fibrotic foci per unit area 3.79 n/mm² ± 0.65 and the cross sectional area of the foci 4.41 μm²/1000 ± 0.12.

Owing to the homogeneous distribution of the damage in the three layers of the left ventricular wall, only morphometric variables relating to the entire wall were used for subsequent statistical analysis.

Table 3

<table>
<thead>
<tr>
<th>Amount of myocardial fibrosis</th>
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<tr>
<td>Volume fraction (%)</td>
</tr>
<tr>
<td>Epimyocardium</td>
</tr>
<tr>
<td>Midmyocardium</td>
</tr>
<tr>
<td>Endomyocardium</td>
</tr>
</tbody>
</table>

Data are presented as means ± s.e.
3.3. Functional-structural correlations

The correlation matrix of all the variables showed that the volume fraction of myocardial fibrosis was positively correlated to the numerical density of fibrotic foci \((r = 0.94, P < 0.00001)\) and to the cross-sectional area of the foci \((r = 0.59, P < 0.02)\). In addition, by submitting the three morphometric variables to stepwise variable selections in which the dependent variables were BBV-IM index, R-R interval, \(SD_{RR}/RR\) and LVW/BW respectively, the volume fraction of fibrosis resulted as being the only significant variable and was then used for correlation to the functional variables.

Morphometric data exhibited a very high positive corre-

![Fig. 2](image_url)

**Fig. 2.** Linear correlation between: a) % volume of myocardial fibrosis in the entire left ventricular wall and BBV-IM index; b) BBV-IM index and left ventricular weight/body weight ratio (LVW/BW); c) % volume of fibrosis and LVW/BW.

![Fig. 3](image_url)

**Fig. 3.** Linear correlation between R-R interval and: a) BBV-IM index; b) % volume of myocardial fibrosis; c) LVW/BW. In Fig. 3b, the empty circle indicated by the arrow refers to two animals which had approximately the same values for coordinates \(x = 139.9\) ms, \(y = 1.24\%; x_1 = 139.8\) ms, \(y_1 = 1.26\%\). Two similar correlations were found between R-R interval on one side and BBV-IM index and the amount of myocardial fibrosis on the other (Fig. 3a,b). In addition, BBV-IM, morphometric measurements and R-R interval were inversely correlated to LVW/BW (Fig. 2b,c and Fig. 3c). Finally, \(SD_{RR}/RR\) showed no correlation to any of the other measurements.

3.4. Comparison with data from conscious animals.

R-R interval and \(SD_{RR}/RR\) relating to a 15-minute telemetry ECG recording \((R-R_{tel} and SD_{RR}/RR_{tel})\) in
conscious animals were significantly higher than in anesthetized animals (172 ± 7 ms vs. 147 ± 5 ms and 0.073 ± 0.01 vs. 0.009 ± 0.001 respectively; P < 0.005).

R-R was positively correlated to BBV-IM index and % volume of myocardial fibrosis (r = 0.63, P < 0.02; r = 0.67, P < 0.03, respectively).

4. Discussion

We showed that in normal anesthetized rats the temporal variability of ventricular repolarization as measured at the body surface by means of BBV-IM is positively correlated to the amount of fibrosis of the left ventricular wall. In addition, BBV-IM and the morphometric measurements of myocardial damage are positively correlated to R-R interval. Finally, SDRR/RR is independent of BBV-IM and myocardial damage. As a whole, the data suggest close interaction among modulation of the recovery process, amount of ventricular connective tissue and heart rate.

The morphometric measurements concerning the numerical density of fibrotic foci per unit area of ventricular myocardium and the cross-sectional area of the fibrotic foci indicated that myocardial damage consisted of limited regions of interstitial and replacement fibrosis homogeneously distributed in the entire thickness of the ventricular wall. On the other hand, the finding that significant functional correlates of the damage were dependent on the volume fraction of ventricular fibrosis suggested that in hearts with scattered, small size structural alterations the total amount of connective tissue is the main factor responsible for the changes with time in the recovery process.

The assessment of beat to beat variability of ventricular repolarization by means of QRST integral maps enabled us to detect definite time-dependent changes in the surface distribution of heart potentials, which could be attributed to a regulatory action of contraction-excitation feedback. Our data support this hypothesis both by implying a mechanoelectric nature of BBV-IM and by excluding its dependence on other mechanisms.

The close relationship between BBV-IM and the amount of fibrosis of the left ventricular wall suggests a role of connective tissue in the temporal variability of ventricular repolarization and constitutes a relevant finding in favour of the involvement of mechanoelectric feedback in the genesis of BBV-IM. This interpretation is in agreement with published data showing that both cellular and extracellular components of fibrotic tissue are important factors responsible for mechanoelectric transduction by active and/or passive mechanisms, as summarized in the Introduction section [12–14].

A component of fibrotic nature in the events which could generate BBV-IM is also indicated by the observation that the LVW/BW ratio is negatively correlated to both BBV-IM and the amount of structural remodelling. Indeed, it has been reported that during normal life rats exhibit a progressive loss of contractile myocardium [17,18,25]. In the absence of a pronounced reactive response, the cardiac myocyte death and the associated development of interstitial and replacement fibrosis lead to a decrease in heart weight [18,25].

Final evidence of a possible dependence of the temporal variability of QRST area maps on mechanoelectric mechanisms is provided by the highly positive correlation between R-R interval and BBV-IM. This finding is consistent with previous results [19] revealing a positive relationship between cycle length and mechanoelectric transduction in isolated and in situ mammalian hearts.

The correlation between R-R interval and myocardial fibrosis suggests that cardiac cycle length is associated with differing cardiac connective tissue content. We are not aware of any study aimed at analyzing the role of R-R interval in the genesis of ventricular fibrosis in normal hearts. On the other hand, several reports have shown an increase in collagen synthesis in response to cardiac tissue stretch, suggesting a regulation of collagen expression via mechanical stimulation [26]. It is tempting to speculate that the increased diastolic filling associated with low heart rate may result in larger cyclic stretches of the cells within the ventricular wall and a correspondingly larger synthesis of connective tissue in bradycardiac animals, as compared to those with higher heart rates. Interestingly, in hearts of senescent rats, which typically exhibit bradycardia, a large amount of fibrotic tissue is a constant feature [17]. Finally, in failing hearts, an abnormal load typically induces enlargement of the ventricular chamber volume with increased diastolic wall stress, accompanied by areas of myocardial fibrosis [27].

As an alternative, the structural damage could be mediated by neurohumoral factors. Among these, transient increases in circulating catecholamines following sympathetic activation could be the most likely candidate in normal subjects [28]. It has been recently suggested that in vivo norepinephrine may modulate events such as release of growth factors or hormones that ultimately result in increased collagen gene expression and myocardial fibrosis [29]. Thus, the different degree of fibrosis in the various animals of this study could be attributed to differences in autonomic cardiac regulation. By considering SDRR/RR as a reliable index of the sympathetic input to the heart, one would expect the amount of fibrotic tissue to be negatively correlated to SDRR/RR. However, we found that SDRR/RR did not exhibit any correlation to morphometric measurements. These data indicate that, in normal animals, any involvement of the sympathetic tone in the genesis of ventricular fibrosis is hard to detect by indirect measurements. Similar conclusions may also apply to the lack of correlation between BBV-IM and SDRR/RR.

Finally, it is well known that the cardiac potential distribution at the body surface is affected by the blood volume of the ventricular cavity (Brody effect) [30,31].
Great volume changes result in marked potential changes while small ones are associated with negligible potential changes. Thus, high R-R variability, which determines substantial variations in ventricular diastolic filling, should be associated with high values of BBV-IM. Conversely, no positive correlation was observed between SD_{RR}/RR and BBV-IM, as previously mentioned. Therefore, an exhaustive explanation for BBV-IM cannot be provided on the purely physical basis implied by the Brody effect.

5. Study limitations

The main limitation of the study regards the use of anesthetics, which can interfere in the autonomic control of the heart and affect measurements such as R-R interval and R-R variability [32]. Although anesthesia actually decreased the values of both parameters, the correlations between R-R and SD_{RR} on one side and BBV-IM index, \% volume of myocardial fibrosis and LVW/BW on the other were largely comparable to those obtained when R-R and SD_{RR}/RR were used (anesthetized animals). The sole differences regarded: 1) the correlation between R-R_{tel} and LVW/BW, whose statistical significance was only borderline (P < 0.08 in conscious animals vs. P < 0.03 in anesthetized animals) and 2) the lower values of r coefficients in correlations between R-R_{tel} on one side and BBV-IM and myocardial fibrosis on the other (r = 0.63 vs. 0.83 and 0.67 vs. 0.87, respectively). These differences could be at least partially explained by considering that physical activity can affect heart rate and heart rate variability [33], resulting in a larger dispersion of the data. Thus, the findings suggest that information collected in anesthetized animals can be reasonably transferred to conscious animals.

An additional limitation is related to the possible effect of myocardial damage of the right ventricle on temporal variability of cardiac repolarization. However, the fibrosis in the right ventricular myocardium in these animals was negligible, implying a very limited influence of the right ventricle on BBV-IM.

6. Conclusions

We showed that in the normal heart the temporal variability of ventricular repolarization as measured at the body surface by means of BBV-IM is related to the amount of ventricular fibrosis. Although our findings regarded young adult rats with limited structural alterations, an increase in BBV-IM should be expected in the presence of more extensive myocardial damage.

The data support the hypothesis that BBV-IM is an expression of mechanoelectric events mediated by the connective tissue and could be used for the non-invasive measurement of cardiac electrical perturbations of mechanical origin.

The study has potential clinical relevance in consideration of the increasing attention devoted to mechanolectric transduction as a possible arrhythmogenic mechanism.

Acknowledgements

This work was supported by grants from the Italian Ministry of University and Scientific and Technological Research (MURST) and the Italian National Research Council (CNR).

References


