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SYNCHROMAX PAPERS

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EXO
Soluciones Tecnológicas

SYNCHROMAX
SYNCHROMAX® correlation with invasive electrophysiologic approach and tissue echocardiography for assessing intraventricular asynchrony

SYNCHROMAX® analysis of QRS in patients with conduction disturbances to demonstrate asynchrony

Correlation of electrical synchrony index by noninvasive method (Synchromax®) versus invasive method

Do all pacemakers with leads implanted in the RV apex have electrical asynchrony?

Synchromax®-guided implant and follow-up of a pacemaker lead in the apex of the right ventricle to prevent electrical asynchrony.

Septal stimulation: one way to avoid asynchrony. Noninvasive assessment of electrical synchrony (Synchromax®).

Synchromax® evaluation and optimization of electrical asynchrony index in patients with cardiac resynchronization therapy
SYNCHROMAX® correlation with invasive electrophysiologic approach and tissue echocardiography for assessing intraventricular asynchrony

• Introduction

Currently, a noninvasive way to measure electrical and mechanical asynchrony of the heart is through tissue Doppler echocardiography implemented in last-generation equipment 1-2 for diagnosis and for evaluation of responders to therapy. This entails a huge cash investment in equipment, the addition of another specialist, and a considerable lengthening of the resynchronization device implantation time, trying to assess the more appropriate site of stimulation.

The possibility of determining asynchrony through conventional ECG signal, could simplify the procedure in terms of staff (the same technician can make the connections and measurements), time and equipment. Recently 3, an invasive technique has been reported that provides information on intraventricular asynchrony by measuring the activation of the left ventricle (LV) through a catheter placed in the coronary sinus (CS). This is a very accurate method, with high temporal resolution. Still, this method involves the invasive transcatheter implantation previous to the implant of a cardiac resynchronization device, increasing the number of complications arising from it 4-5.

Mathematically, the heart can be modeled as a large oscillator operating at a fundamental frequency, the sinus node frequency. Attempting to a somewhat more real approach you could say that the right heart and left heart are two oscillators with a single fundamental frequency with a temporal mismatch between them. Moreover, one can say that the left heart can be segmented into several oscillators that according to their location will have different delays (or temporal offsets), although they share the same fundamental frequency. Therefore, one could think of a asynchrony determination that consists of measuring delays between these segments, placing or not this time delays in a normal range.

In this paper we use the method of cross correlation between two signals to determine phase differences between two ECG leads, one of the inferior anterior side and other of lateral side. The choice of lead is based on their anatomical correlate with the regions or segments of the left heart under study. Thus, DII will provide information related to the inferior anterior V5 or V6 on the lateral wall of the left ventricle, which are strategic areas for the study of intraventricular asynchrony.

Then based on the analysis of correlations, the idea of this study is to demonstrate the utility of a noninvasive derivative of digitized ECG for the assessment of electrical asynchrony and its correlation with invasive and echocardiographic methods.

Study objective: To evaluate a new noninvasive method (SYNCHROMAX) based on
correlation analysis, reproducible, easily performed for the diagnosis of intraventricular asynchrony, and its correlation with standard methods used today for this purpose such as tissue echo and invasive mapping.

• Materials and methods

Mathematical analysis:
In order to determine electrical asynchrony noninvasively, we studied the ECG of normal patients scanned and individuals with electrical conduction defects, on which we performed a correlation analysis. To this end, an offline mathematical analysis was created in Matlab 8.0 (The Mathworks, Inc) with Windows platform. The method of analysis consisted in calculating an index of electrical asynchrony (IEA) derived from the cross-correlation between DII and V6, and its frequency spectrum through the Fourier transform. Thus, the index indirectly reflects temporal offsets between different segments of the left ventricle. Before feeding the specific processing module the ECG signals were passed by a general preprocessing step that basically consisted of the detection, sampling, alignment and averaging of QRS complexes, on which the correlation analysis was performed thereafter. The QRS detection algorithm is based on Hilbert Transform 6. The IEA varies between 0 and 1, with larger values meaning increasing asynchrony. That is, a value close to 0 shows normal levels of synchrony while values near 1 show a pathological asynchrony.

Groups:
We analyzed 45 patients, aged between 22 and 76, with an average of 60. Eighteen were female and twenty males. Group A was comprised of 20 normal subjects (control group) with narrow QRS. Patients in this group only 12-lead electrocardiogram was performed. Index normality ranges were determined on the basis of their electrocardiographic studies. The group B was the study group and was formed with the remaining 25 subjects with the following conditions: 1 right bundle branch block (RBBB), one 2:1 AVB, 20 Left bundle branch block (LBBB) with QRS width of 120 msec. and 3 with incomplete LBBB, QRS width less than 120 msec. In these patients, an electrophysiological study (EPS) was performed and all along the studies echocardiography was performed, specifically tissue Doppler imaging (TDI)

Validation by EPS and TDI:
The invasive asynchrony invasive measure consisted in determining the activation latency of the left ventricular free wall in its lateral baseline portion. This was achieved by measuring the deflection time, or the appearance of electrical activity in a multipolar catheter placed in the coronary sinus, evaluating area which was the most delayed with respect to intraventricular septum, as previously described 3. Similarly, asynchrony assessment by TDI measures the latency of electro-mechanical activation of the LV free wall by tissue Doppler ultrasound. In this way, we obtained the activation times of the lateral wall of the LV and the LV posterior wall activation time relative to the intraventricular septum activation time, choosing between them the longest time (higher degree of asynchrony). Both methods were correlated with each other: the invasive (time between surface ECG onset and the latest LV deflection obtained
from the coronary sinus) with tissue Doppler (TDI) assessing the latest LV electromechanical activity, considered the Gold Standard. The new noninvasive method developed by our laboratory was correlated to approval by conventional methods: invasive (EPS) and noninvasive (Gold Standard of TDI).

**Statistics**
The results are expressed as mean ± standard error (X ± SE). For comparisons between pairs of means, Wilcoxon rank-sum test was used. It was considered a significant difference when the value of p <0.01.

• **Results**

**General Considerations**
Asynchrony index (IEAI) varies between 0 and 1, with increasing asynchrony values. That is, a value close to 0 shows normal levels of synchrony while values close to 1 shows a pathological asynchrony. Group A (control group) showed an average IEAI 0.26 ± 0.08 with a QRS width of 91.3 ± 4.8 ms. In pursuit of greater clinical validity in the comparison, group B was subdivided according to conduction pathologies. The subgroup of complete LBBB (QRS> 120 ms) had the highest IEAI (0.78 ± 0.22) with a QRS duration of 155.3 ± 23.2 ms while the subgroup of incomplete LBBB (QRS <120 ms) showed an average IEAI of 0.46 ± 0.24 and a QRS duration of 109.4 ± 7.2 ms. Finally, the RBBB and 2:1 AVB showed low IEAI values, 0.17 and 0.19 respectively. These values suggest an approximate cutoff index of 0.45. Indexes above this value would diagnose asynchrony while those under it would not. There was statistical significance (p <0.01) in the comparison of means between the group of healthy subjects and complete LBBB group. For the remaining subgroups included in group B were the comparison of means could not be performed because the maximum number of these samples was only 3.

Moreover, the values of latest LV free wall segments measured in the CS during the electrophysiological study of patients in group B were as follows: For the complete LBBB (QRS> 120 ms), activity was observed in the CS to 112.9 ± 17 ms whereas those incomplete LBBB (QRS <120 ms) latency of activation of 80.7 ± 5.3 ms was observed in the CS. As expected, activation of the LV free wall viewed from the CS was early, of 49.6 ms and 58.3 ms respectively. Note the marked delay of the LV free wall in those cases with complete LBBB, consistent with a high IEAI and TDI values greater than 60 ms, both of them indicating asynchrony.
Figure 1: Left column, data from a healthy subject with IEAI=0.23. Right column, data from a LBBB patient with IEAI=0.77. A) and E) surface ECG, B) and F) averaged DII and V6 complexes. C) and G) correlation between DII and V6. D) and H) Fourier transform of the correlation signal shown in C) and G), respectively.

Figure 1 provides a graphic comparison of the parameters of IEAI discussed in the preceding paragraphs for a healthy subject and one with complete LBBB. The left column shows from top to bottom: ECG (A), averaged QRS DII and V6 (B), correlation between DII and V6 (C) and frequency spectrum of the signal correlation (D) of a normal subject IEA= 0.23. Consistently, (E, F, G and H) form the analogs for a subject with complete LBBB with QRS> 120 ms and an IDEI of 0.77.

Note the significant temporal mismatch of DII and V6 as highlighted in (F) with respect to the normal mismatch in a healthy subject (B). Note also the difference in width between the correlation signal of a healthy subject (C) and the one with LBBB (G). In this latter case it is also evident the temporal mismatch of the peak of the correlation signal, a characteristic found in most of the LBBB cases analyzed. Finally, observe how the spectral variability of the correlation signal suffers from a LBBB individual (H) to a healthy one (D).

Similarly, the average values of TDI were 69 ± 32 ms delay between intraventricular septum and LV free wall (the worst case between lateral wall and posterior wall was taken) in the subgroup of complete LBBB. For the subgroup of incomplete LBBB with QRS <120 ms a delay of 61.6 ± 26.5 ms was found. Both group A and for the 2:1 AVB of Group B echocardiographic values were not obtained. The RBBB, however, shows a value of normal asynchrony (30 ms). Table 1 summarizes these findings.
<table>
<thead>
<tr>
<th>GROUP</th>
<th>IEAI</th>
<th>CS</th>
<th>QRS</th>
<th>TDI</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>0.26±0.08</td>
<td>NA</td>
<td>91.3±4.8</td>
<td>NA</td>
</tr>
<tr>
<td>B (LBBB; QRS&gt;120ms)</td>
<td>0.78±0.22†</td>
<td>112.9±17</td>
<td>155.3±23.2†</td>
<td>69±32</td>
</tr>
<tr>
<td>B (LBBB; QRS&lt;120ms)</td>
<td>0.46±0.24</td>
<td>80.7±5.3</td>
<td>110.2±6.7</td>
<td>61.6±26.5</td>
</tr>
<tr>
<td>B (RBBB)</td>
<td>0.17</td>
<td>49.6</td>
<td>116</td>
<td>30</td>
</tr>
<tr>
<td>B (AV block 2:1)</td>
<td>0.19</td>
<td>58.3</td>
<td>100.4</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 1: Comparison of the averages found in asynchrony index (IEAI), the values found in the EPS (CS and QRS) and those obtained by tissue Doppler (TDI). † Indicates statistical significance (p <0.01) compared to group A. In the other subgroups the media comparison was not performed because of a low n.

**EPS and TDI validation**

We found a good correlation between the method described and the value of activation of the latest LV segments obtained through the coronary sinus at electrophysiologic study (r = 0.83). Consistently, we obtained a good correlation with data from Doppler tissue imaging (r = 0.71). Figure 2 shows these correlations. In this validation the BAV group A and group B 2:1BAV is ignored due to lack of echocardiographic data, which is considered the Gold Standard for measuring asynchrony.

![Figure 2: Relationship between activation of the LV free wall measured by the method of the CS in an EPS and the value of asynchrony index derived from the cross-correlation of DII and V6 leads.](image)

On the other hand, Figure 3 shows an example where you can see the consistency between the results obtained by echocardiography and electrophysiology, both in turn consistent with the IEA obtained, all for the same subject under study.
Figure 3: Example of a dyssynchronous patient with an index of 0.71. Above: Echo study showing a asynchrony of 75 ms (right: interventricular septum; left: lateral wall). Below: electrophysiological study in the CS showing a latency of activation of LV free wall of 120 ms.

Here are the studies of TDI for the interventricular septum and posterior wall (upper panel, from left to right), for a difference between them of 75 ms, clear diagnosis of asynchrony. Consistently, the EPS shows a latency of activation of LV free wall of 120 ms, a value that indicates a delay of the LV free wall. Finally, the IEA obtained for this patient was 0.71, closing the diagnosis of asynchrony by the three methods. Note that the simultaneity of the three methods are only carried out to validate the IEA obtained from surface ECG, and that the correlation values presented in this paper suggest its use in individual cases both in the therapy indications as the assessment during and post devices implant.

• Discussion

The study of electrical asynchrony is one of the most important paradigms in the study of heart failure. Having more knowledge and methods for evaluation could allow us to finding more effective treatments. The study of heart tissue Doppler gives us the opportunity to assess different areas of electromechanical mismatch both inter-and intraventricular. However, the use of this method for assessing which patients are responders to resynchronization therapy, is now under discussion. Recently invasive methods both with navigation systems, such as transcatheter direct electrical mapping are being used for the same purpose. These methods are
based on the fact that the therapy is intended to modify electrical properties with the potential hemodynamic change, being of interest in our research group to approach and measure eminently electrical electrophysiological situations in these patients. Electrocardiography allows us to quickly assess the possible extent of asynchrony by either native left bundle branch block (LBBB) or harmful stimulation to the tip of the right ventricle in patients who have a need to be stimulated with standard pacing 8. The association of poor ejection fraction and this pacemaker “novo LBBB” cause severe short-term clinical deterioration. While these cases can be solved by avoiding the injurious stimulation in the RV apex, choosing more physiological alternative sites like septal, hisian or para-hisian, it is true that they exhibit some degree of QRS widening9. In ventricular asynchrony there is in an obvious primary electrical problem and its treatment is also based on electrical stimulation principles and as such our team developed a method of diagnostic evaluation, preoperative and intraoperative monitoring of patients responders or not, based in purely electrical principles. We developed a simple noninvasive method that allows us not only to diagnose asynchrony in situ in patients with LBBB and heart failure, but also those cases of asynchrony caused by conventional pacing. This benefit is enhanced for two reasons: (1) the possibility of performing the assessment intra procedure both in conventional RV-LV resynchronization therapy and in alternative pacing sites (in search of a more physiological stimulation trying to avoid that asynchrony). (2) the reproducibility of the method and the possibility of use in patient monitoring, as well as a new objective technique for acute optimal therapy selection. The basis of this method is the analysis of multiple electrocardiographic variables that make up an electrical asynchrony index (IEAI) with mathematical averaging of QRS and analysis of their interrelationships, in an area of DII and V6, inferior and lateral LV. In the control group this index is close to 0.2 and in those patients with marked asynchrony its values are greater than 0.7 (see Figure 1) The correlation of this method proved satisfactory when compared with traditional methods that have obvious shortcomings when being used. Future research with groups selected according to different degrees of asynchrony will be evaluated to support this idea. No doubt the advantages of not harming the patient, the reproducibility, the simplicity of the method and its low cost, make this an everyday tool for the diagnosis and treatment of ventricular asynchrony.

• Conclusions

There is good correlation between the IEAI and the activation time of LV lateral wall measured through a catheter in the coronary sinus at baseline, which gives the method a good diagnostic capacity. There is good correlation between asynchrony data measured with tissue Doppler and this index IEAI, validating this method with the Gold Standard. Therefore, the device becomes a tool capable of replacing the catheter into the coronary sinus or tissue Doppler to measure time between ventricular segments, either for diagnostic purposes, for implants or processes to determine improvements in clinical follow-up treatment. Because it does not require dedicated equipment for that purpose, the method provides qualitative benefits from the economic point of view and simplification of procedures on echocardiography or invasive studies.
**SYNCHROMAX® analysis of QRS in patients with conduction disturbances to demonstrate asynchrony**

*Introduction*

It is known that the left bundle branch block (LBBB) causes electrical and eventually mechanical asynchrony, this being used as an indication for pacemaker implantation. Other conduction disturbances (without being LBBB) can also generate asynchrony with similar characteristics. The purpose of this study is to assess the degree of electrical asynchrony by means of a noninvasive method, with the determination of an index and characteristic curves representing a group of patients with different types of conduction disturbances.

*Materials and methods*

Electrical asynchrony was analyzed by QRS spectral phase analysis (Synchromax) to obtain an index and characteristic types of curves in 154 patients, conforming 5 groups. In Group 1 there are 54 patients without conduction disturbances. Group 2: 50 patients with right bundle branch block (RBBB). Group 3 consisted of 23 patients with LBBB. Group 4 includes fourteen patients with RBBB and left axis deviation -45°, anterior hemi-block (LAHB). Group 5 is conformed with 13 patients with LAHB. Sample recording was made by conventional method and asynchrony indexes were identified in each group of patients observing any different morphologies of curves, to determine the curves 1 and 2 as synchronous, 3, 4, 5 and 9 as an intermediate; 6, 7, 8 and 10 as asynchronous (see Figure 1). We assessed the statistical significance of the results to see if there was difference between them by the Student test and Chi square.
Synchrony index and the various possible types of curves found in the assessment of synchrony by this method. Index values above 0.7 were considered as dyssynchrony. Those indexes below 0.4 were considered as synchronous. There is an intermediate gray zone, with indexes in the range of 0.4 to 0.7. References: RBBB: right bundle branch block. LAHB: left anterior hemiblock. CRT: cardiac resynchronization therapy. PM: pacemaker.

- Results

Group 1: average index 0.26 (+/- 0.23), with curves Type 1 (33p), type 3 (18p) and type 9 (3p). The group 2 had a index of 0.33 (+/- 0.28), curve type 3 (29p), Type 1 (13p), type 9 (5p) and type 10 (3p). Group 3, with a index of 0.85 (+/- 0.24), with type curves 6 (15p), type 9 (5p) and type 3 (3p). Group 4 had a index of 0.85 (+/- 0.27) with type curves 10 (5p), type 9 (6p) and type 6 (3p). Group 5 had a index of 0.79 (+/- 0.24), with type curves 9 (6p), type 10 (6p) and type 6 (1p). Significant difference exists between normal and RBB, compared to other conduction disturbances, and the LBB, RBB with LAHB and LAHB only, behaved as dyssynchronous, with no difference between them (see Figure 2-7).

![Figure 2. Examples of noninvasive electrical synchrony measurement (Synchromax) in different types of conduction disturbances. The group of patients without conduction disturbance as well as the group of patients with right bundle branch block, showed a synchronous average index, with no significant difference between these two groups. Patients with left bundle branch block, right bundle branch block and those with left anterior hemiblock alone, had average dyssynchronous indexes, with statistically significant difference compared to the first two groups. RBBB: right bundle branch block, LBBB: left bundle branch block; LAHB: left anterior hemiblock. * P = ns, ** p <0.005.](image-url)
Figure 3. Patient in group 1, no conduction disturbance. Curve 1, index=0.1281.

Figure 4. Patient in group 2, with right bundle branch block. Curve 3, index=0.2241.
Figure 6. Patient in group 4, with right bundle branch block and left anterior hemiblock. Curve 10, index=0.9836.
• Conclusions.

Patients with normal QRS or RBBB either have no electrical asynchrony or it may be minimal. The left anterior hemiblock with or without associated right bundle branch and left bundle branch block have a marked asynchrony. These indexes may be useful for evaluating potential candidates for cardiac resynchronization therapy.
Correlation of electrical synchrony index by noninvasive method (Synchromax®) versus invasive method.

The Apex of RV pacing usually produces electrical asynchrony. In previous studies electrical asynchrony has been evaluated measuring through electrophysiological studies (EPS) the interval between QRS onset and LV deflection in coronary sinus, at different stimulation sites. Our group developed a non-invasive system based on spectral analysis of the QRS for determining the electrical synchrony (Synchromax). The aim of this study is to compare the QRS width and the time QRS onset to VI with different stimulation sites, versus the index of noninvasive electrical asynchrony (Synchromax).

• Materials and methods

Electrophysiological studies were evaluated in 26 patients with a mean age of 47.57 years (range 22 to 83 years), 30.76% female and 69.24% male, all with QRS width less than 120 msec at baseline ECG, 9 patients with incomplete left bundle branch block and 17 patients with normal ECG. ECG was performed at baseline, at parahisian septal stimulation and at apex pacing. Indexes and synchrony curves were obtained by Synchromax (see Figure 1), by measurement of QRS and by the QRS-distal CS time (see Figure 2).

<table>
<thead>
<tr>
<th>TYPES OF CURVES</th>
<th>GROUP</th>
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<tbody>
<tr>
<td></td>
<td>SYNCHRONOUS</td>
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<tr>
<td>I.E.D.I.</td>
<td>0 - 0.4</td>
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<tr>
<td>BASELINE RHYTHM</td>
<td>1: NARROW QRS</td>
</tr>
<tr>
<td>PACEMAKER</td>
<td>2: SEPTAL STIMULATION</td>
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</table>

Figure 1. Synchromax: index of synchrony and the various possible types of curves found in the assessment of synchrony by this method. Indexes above 0.7 are considered dyssynchronic. Indexes below 0.4 are considered synchronous. There is an intermediate gray zone, with rates in the range of 0.4 to 0.7. References: RBBB: right bundle branch block. LAHB: left anterior hemiblock. CRT: cardiac resynchronization therapy. PM: pacemaker.
Figure 2. Invasive method to measure electrical synchrony. Through a multipolar catheter positioned in the coronary sinus, measuring the time from the onset of QRS to ventricular electrogram deflection recorded in the distal electrode of the catheter (distal time QRS-CS). Note that this time during sinus rhythm in a patient with narrow QRS, is short, being the ventricular deflection in the final portion of the QRS, but during pacing in the apex of RV, this time is extended, leaving the ventricular deflection after the QRS; however, parahisian septal stimulation, has actions similar to those of the baseline rhythm.

• Results

In the baseline rhythm, the average index was 0.208 (+/- 0.19) with a 91.08 msec QRS (+/- 17.44) and QRS-CS time of 46.17 msec (+/- 14.58), presenting 100% of synchronous curves (80% and 20% curve 1 curve 3). Parahisian septal stimulation index was 0.25 (+/- 0.156), with a QRS of 116.66 msec (+/- 15.27) and a QRS-CS time of 58.57 msec (+/- 6.9), with 100% of synchronous curves (curve 2). The RV apex stimulation index obtained was 0.737 (+/- 0.30), with a QRS of 142.60 msec (+/- 23.54) and a QRS-CS time of 91.73 msec (+/- 18.74). No significant differences were observed between baseline rhythm and septal parahisian. Statistically significant difference was found between them and the RV apex pacing in the 3 variables analyzed (see Figures 3-8). Patients with RV pacing showed a peak of 40.9% intermediate curves (curve 5 with an average index of 0.45) and 60.1% dyssynchronous curves (curve 8 with a index of 0.96), with difference between the indexes of the two curves (p<0.005) and no differences in the width of the QRS.
Figure 3. Electrical synchrony indexes with noninvasive method (Synchromax), baseline rhythm, septal pacing and RV apex pacing * P = ns, ** p <0.005.

Figure 4. Measurement of QRS width during baseline rhythm with septal stimulation and RV apex pacing * P = ns, ** p <0.005.

Figure 5. Measurement of electrical synchrony through invasive method (interval between the onset of QRS and the ventricular deflection in the distal tip of a catheter inserted into the coronary sinus). Comparison of measurements during baseline rhythm and those with septal pacing and RV apex pacing * P = ns, ** p <0.005.
Figure 6. Synchromax data from patients with narrow baseline QRS. Curve 1, index=0.1281.

Figure 7. Synchromax data from patient with parahisian septal stimulation. Curve 2, index=0.1135.
Figure 8. Synchrony curves from patient with RV apex pacing. Curve 8, index=1.

- **Conclusions**

There is good correlation of electrical synchrony measurements using noninvasive versus invasive methods, which can be useful to noninvasively evaluate electrical asynchrony with different types of ventricular pacing.
Do all pacemakers with leads implanted in the RV apex have electrical asynchrony?

The right ventricular pacing generates changes in interventricular synchrony that evolves with higher rate of long-term heart failure. The aim of this study is the noninvasive evaluation of electrical asynchrony in patients implanted with pacemaker leads radiology-guided to right ventricular apex, with the purpose of determining characteristic curves and indexes, comparing them with the QRS duration.

• Material and Methods

We retrospectively studied 150 patients aged between 19 and 101 years (mean 66 years) with DDD pacemakers conventionally implanted in the right ventricular apex. We analyzed noninvasively electrical asynchrony by the Synchromax II ® method validated with tissue Doppler echocardiography in previous research. We determined the electrical asynchrony index and the correlation curves (Fig. 1).

<table>
<thead>
<tr>
<th>GROUP</th>
<th>SYNCHRONOUS</th>
<th>INTERMEDIATE</th>
<th>DYSSYNCHRONOUS</th>
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<td>I.E.D.I.</td>
<td>0 - 0.4</td>
<td>0.41 – 0.70</td>
<td>0.71 – 1</td>
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<td>BASELINE RHYTHM</td>
<td>NARROW QRS</td>
<td>NORMAL +/- RBBB</td>
<td>LABH +/- RBBB</td>
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<td>CONVENTIONAL C.R.T.</td>
<td>OPTIMIZED C.R.T.</td>
<td>NON OPTIMIZED C.R.T.</td>
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<tr>
<td>PACemaker</td>
<td>SEPTAL STIMULATION</td>
<td>PACemaker IN RV APEX</td>
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</table>

Figure 1: Different Synchromax II curves obtained at different electrocardiographic patterns with their respective electrical asynchrony index. They were classified into three groups, namely: intrinsic rhythm, cardiac resynchronization therapy (CRT) or pacemaker. Three synchrony categories were established, according to each curve and index.
Previously validated asynchrony indexes were found in a range from 0 to 0.4 (synchronous), 0.4 to 0.7 (slightly dyssynchronous) and above 0.7 (dyssynchronous). Curve 5 was assessed as synchronous (Figure 2) while Curve 8 as dyssynchronous for pacemaker patients (Figure 3).

Figure 2: Example of pacing in right ventricular apex, with curve type 5. Note that the curves are negative and close together. The index is 0.44, determining the absence of electrical asynchrony by Synchromax II method.
Figure 3: Example of pacing in right ventricular apex, with curve type 8. Note the mismatch of the curves with an electrical synchrony index of 1, electrical asynchrony determined by the method of Synchromax II.

• **Results**

It was found that 51% of the patients studied were type 5 curve showing no electrical asynchrony. The remaining 49% showed curve type 8 with electrical asynchrony (Figure 1).
Figure 1 shows the distribution of patients with curve 5 (synchronous) and curve 8 (dyssynchronous). Almost 50% of patients tested had electrical asynchrony.

The average index in patients with curve 5 was 0.5 (IEAI 0.45 to 0.55). In patients with curve 8 average index was 0.96 (IEAI 0.93 to 0.99). The comparison between the curves based on QRS duration showed that the average QRS width for curve 5 was 163 msec (SD 14.49) and for those with curve 8 it was 173.97 msec (SD 20.68) with a statistically significance using two-sample t test (p = 0.0032).

**Conclusions**

Patients with pacemakers implanted into the apex have electrical asynchrony measured with Synchronax II® with nearly 50% of them with an associated asynchrony index of 0.96, as measured by the same method. Longer QRS duration was evident in patients with electrical asynchrony, although in both groups the QRS duration was greater than 120 msec.
Synchromax®-guided implant and follow-up of a pacemaker lead in the apex of the right ventricle to prevent electrical asynchrony.

The right ventricular pacing generates changes in interventricular synchrony leading to a higher rate of long-term heart failure. The aim of this study is to evaluate the possibility of avoiding electric asynchrony using Synchromax II ® method when implanting pacemaker leads in the right ventricular apex; and the use of same method for the subsequent monitoring of asynchrony indexes and curves.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>TYPES OF CURVES</th>
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</thead>
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<tr>
<td>I.E.D.I.</td>
<td>SYNCHRONOUS</td>
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<td></td>
<td>0 - 0,4</td>
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**Figure 1:** Different Synchromax II curves obtained at different electrocardiographic patterns with their respective electrical asynchrony index. The curves were classified into three groups, namely: intrinsic rhythm, cardiac resynchronization therapy and pacemaker. Three synchrony categories were established according to different curves and indexes.

- **Material and Methods**

Thirty patients were prospectively studied, 60% were male, aged between 42 and 87 years (median 66 years). The implants were guided by Synchromax II ® in radiological areas like apex of the right ventricle to assess sites that do not cause electrical asynchrony with normal thresholds. Electrical asynchrony was noninvasively analyzed by Synchromax II ® method validated with tissue Doppler echocardiography in previous research. We determined the electrical asynchrony index and electrical correlation curves. Asynchrony indexes were...
previously validated in a range from 0 to 0.4 (synchronous), 0.4 to 0.7 (slightly dyssynchronous) and more than 0.7 (dyssynchronous). Curve 5 was assessed as synchronous and Curve 8 as dyssynchrinetic in pacemaker patients.

Figure 2: Example of pacing in right ventricular apex, with curve type 5. Note that the curves are negative and close together. The index is 0.44, determining the absence of electrical asynchrony by Synchromax II method.
Figure 3: Example of pacing in right ventricular apex, with curve type 8. Note the mismatch of the curves with an electrical synchrony index of 1, electrical asynchrony determined by the method of Synchromax II.

- Results

Curve 5 showing no electrical asynchrony was found in 90.9% of patients studied. The remaining 9.1% showed curve type 8 with electrical asynchrony related to technical difficulties in catheter manipulation. The average index in patients with curve 5 was 0.52 (IEAI 0.46 to 0.58). In patients with curve type 8 was 0.92 (IEAI 0.77 to 1.07), statistically significant differences using two-sample T-test (p = 0.0007).
Examples of curves obtained during implant guided Synchromax II of the patients studied, in order to avoid electrical asynchrony during pacing. Negative curves correspond to implant the right ventricular apex, the positive ones to septal implants. Only one patient had a curve 8 (dyssynchronous), related to technical difficulties during implantation.

An average of three attempts was made to obtain curves type 3 (± 2) The procedure time was 45 ± 10 minutes, finding no significant changes to the standard implant methods. The follow-up between 3-6 months showed the preservation of the curve type 5 and asynchrony index in 100% of cases.
Figure: Example of a patient prior to permanent pacemaker implantation for sinus node disease. It is noted that it presents a curve type 1 (synchronous) and an index of 0.13. This indicates that the patient is not electrically dyssynchronous.

The same patient as above. It is noted that after pacemaker implantation in a conventional manner a curve is obtained with an index type 5, IEAI = 0.44 (not dyssynchronous). This shows that with the implant guided Synchromax II electrical asynchrony during pacing can be avoided.

• Conclusions

Pacemaker implantation in right ventricular apex guided by Synchromax II ® allows to locate an area free of electrical asynchrony in 90% of cases using 3 attempts on average, with no changes in normal procedure times. The 6 month follow up shows the continuity of electrical synchrony in all cases.
**Septal stimulation: one way to avoid asynchrony. Noninvasive assessment of electrical synchrony (Synchromax®).**

### Introduction

Permanent cardiac pacing in right ventricular apex causes asynchrony with deterioration of left ventricular function by creating left bundle branch block, especially in patients with narrow QRS. Alternative pacing places, as parahisian septal zone, has been proposed as a way to avoid asynchrony. Our group developed a non-invasive system based on spectral analysis of the QRS for determining electrical synchrony (Synchromax). The aim of this study was to evaluate pre and post-operative electrical synchrony in cases of septal parahisian implant of patients undergoing permanent cardiac pacing.

### Materials and methods

Thirty-two patients (pts) were included, with narrow QRS in ECG, without intraventricular conduction disturbances and pacemaker implant indication (see Table 1). Ages were between 27 and 72 years. One pt had congenital AV block (AVB), 22 pts had severe sinus bradycardia, sick sinus syndrome (SSS), 2 pts had SSS associated with 1st degree AVB, 4 pts with atrial fibrillation (AF) with low ventricular response, 1 pt with AV node ablation chronic AF and heart failure, and 2 pts with septal implanted ICD. Active fixation catheters were used in 3 pts only, and deflectable leads with sheaths in all other 29 pts. The implants were monitored by ECG (see Figure 1). The thresholds obtained in the implant were less than 1 volt and R wave measurements were greater than 5 mV. Electrical synchrony assessment was performed non-invasively with Synchromax II using conventional techniques before implantation and after 6 months of implant with septal pacing. Timing curves and indexes were evaluated pre-and post-implant.

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Patients</th>
</tr>
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<tbody>
<tr>
<td>Congenital AV block</td>
<td>1*</td>
</tr>
<tr>
<td>Sick Sinus Syndrome, symptomatical from bradycardia</td>
<td>22</td>
</tr>
<tr>
<td>Sick Sinus Syndrome + 1st degree AV block</td>
<td>2</td>
</tr>
<tr>
<td>Atrial Fibrillation with low ventricular response</td>
<td>4</td>
</tr>
<tr>
<td>Chronic Atrial Fibrillation. AV node ablation</td>
<td>1*</td>
</tr>
<tr>
<td>Sick Sinus Syndrome . Ischemic cardiomyopathy with VT induction.</td>
<td>2*</td>
</tr>
</tbody>
</table>

Table 1. Patients who underwent permanent septal pacing. * Patients with three-chamber pacemakers implanted, with a lead in atrium, an interventricular septum lead (parahisian
pacing) and the third lead in right ventricular apex (the latter pacing lead acts as backup in case of septal catheter instability, right ventricular apex pacing being programmed 80 msec after parahisian pacing pulse)

• Results

Patients were followed-up for 6 to 40 months. The average chronic threshold was 1.4 volt +/− 1.0 volts, with an R wave average of 5 mV +/− 2 mV. The time of implantation with conventional catheters was 30 min +/− 10 min, and 18 min +/− 11 min with special catheters with deflectable sheath. Complications: 2 lead displacements, with effective relocation. With regard to electrical synchrony index (see Figure 2) before implantation we had a mean of 0.35 (+/− 0.36) with 86% of synchronous curves (curves 1.3 and 9). At 6 months post-implant, with septal stimulation synchrony index average was 0.31 (+/− 0.30) with 93% of synchronous curves (curves 2 and 3) (p = ns) (see Figures 3 and 4)

Figure 1. Electrocardiographic monitoring during implantation of the adequate parahisian pacing. Note in the frontal plane ECG (ampliIEA image) The paced QRS (1st beat) has an electrical axis similar to baseline QRS (2nd beat) and a slightly wider QRS, with an initial slowing following the pacing spike (delta wave as if it were a Wolf Parkinson White ECG). This initial slowing has been attributed to initial depolarization of the parahisian septal myocardium, previous to His activation.
Figure 2. Synchronax: index of synchrony and the various possible types of curves found in the assessment of synchrony by this method. Index values above 0.7 are considered dyssynchronous. Those index values under 0.4 are synchronous cases. There is an intermediate gray zone, with rates in the range of 0.4 to 0.7. References: RBBB: right bundle branch block. LAHB: left anterior hemiblock. CRT: cardiac resynchronization therapy. PM: pacemaker.
Figure 3. Synchromax analysis of electrical synchrony in a patient with septal parahisian permanent cardiac pacing. In A, we observe the patient's baseline rhythm, with a curve type 1 and an index of 0.0590. In B, with septal stimulation, the curve is still synchronous (Type 2) with an index also synchronous (0.3957).
Figure 4. Electrical synchrony index before implantation (baseline ECG) and 6-month follow-up of patients with implanted parahisian septal pacemaker (p = ns).

- **Conclusions**

Long-term lead stability, pacing and sensing thresholds were adequate. Acute and chronic Synchromax evaluation of electrical synchrony showed that permanent septal parahisian cardiac pacing does not cause electrical dyssynchronization.
Synchromax® evaluation and optimization of electrical asynchrony index in patients with cardiac resynchronization therapy.

Cardiac resynchronization therapy is designed to achieve simultaneous contraction of the septum and LV lateral wall to avoid the deleterious effects of LBBB in patients with heart failure. At present there is not a "gold standard" method for CRT optimization. We present a noninvasive method for assessing cardiac electrical synchrony, validated by electrophysiological study and tissue Doppler. The clinical application of this system in cardiac resynchronization allows a quick and noninvasive method to select the optimal interventricular interval. The electrical response is immediate. The aim of this study was the noninvasive evaluation and CRT optimization in patients with indication of cardiac resynchronization therapy, determining characteristic curves and indexes allowing optimal setting of the interventricular pacing interval.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>TYPES OF CURVES</th>
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<tbody>
<tr>
<td></td>
<td>SYNCHRONOUS</td>
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<tr>
<td></td>
<td>INTERMEDIATE</td>
</tr>
<tr>
<td></td>
<td>DYSSYNCHRONOUS</td>
</tr>
<tr>
<td>I.E.D.I.</td>
<td>0 - 0,4</td>
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<tr>
<td>BASELINE</td>
<td>0,41 – 0,70</td>
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<tr>
<td>RHYTHM</td>
<td>0,71 – 1</td>
</tr>
<tr>
<td>CONVENTIONAL</td>
<td></td>
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<tr>
<td>C.R.T.</td>
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<td>PACEMAKER</td>
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Figure 1: Different Synchronax II curves obtained at different electrocardiographic patterns with their respective electrical asynchrony indexes. The curves were classified into three groups, namely: intrinsic rhythm, cardiac resynchronization therapy (CRT), or pacemaker. Three synchrony categories were established, depending on each curve and index.
• Material and Methods

Thirty patients (pts) were retrospectively studied, 80% of which were male, aged between 28 and 86 years (mean 60 years), 27 patients had dilated cardiomyopathy and left bundle branch block, and the others had complete AV block with narrow QRS, and received cardiac resynchronization therapy with conventional lead in right ventricular apex. The left heart lead was placed in the coronary sinus in 27 pts; in the three pts with complete AVB the lead was placed in septal position. Electrical asynchrony was noninvasively analyzed by Synchromax II® method validated with tissue Doppler echocardiography in previous research. We determined the electrical asynchrony index and electrical correlation curves. Asynchrony indexes were previously validated in a range from 0 to 0.4 (synchronous), 0.4 to 0.7 (slightly dyssynchronous) and above 0.7 (dyssynchronous). Curve 4 was assessed as synchronous and curve 7 as dysynchronous. We evaluated the interventricular pacing interval in all patients and optimized it in relation to the best rate and synchrony curve obtained by Synchromax II®.

Figure 2 Example of a patient with resynchronization therapy with curve type 7, with an interventricular pacing interval of 0 msec. Note that the curves are separated from each other. The index is 1, determining electrical asynchrony by the method of Synchromax II®.
Figure 3 Example of a patient with resynchronization therapy optimized with Synchromax II with curve type 4, with interventricular pacing interval (LV-RV) of 40 msec. Note that the curves are close together. The index is 0.52, determining the absence of electrical asynchrony by Synchromax® method.

• Results

In these patients the baseline QRS averaged 163.2 msec (SD = 27.8) After optimizing the interventricular intervals the best QRS intervals achieved averaged 143.6 msec (SD = 21.58) with an average reduction of 19.6 msec, with a statistically significant difference (p = 0.0001) with T test for paired samples. The average baseline was 0.70 (SD = 0.36), while the average best index obtained after the electrical resynchronization was 0.31 (SD = 0.14), with an average difference of -0.39, the difference being statistically significant (p = 0.0001).
Figure 4 Example of patient with electrical resynchronization therapy where optimization of electrical synchrony was performed with Synchromax II. You can see the different curves and indexes to different interventricular pacing intervals. Note that the optimal curve with the best index is found when you pace the right ventricle earlier than the left ventricle at an interval of 20 msec.

Figure 5 Example of patient with electrical resynchronization therapy where optimization of electrical synchrony was performed with Synchromax II. You can see the different curves and indexes to different interventricular pacing intervals. Note that the optimal curve with the best index is found when only the left ventricle is paced. It is important to note that this patient has a left ventricular lead implanted in the interventricular septum.
84.7% of patients had a curve 7 with a baseline interventricular pacing interval of 0 msec. After electrical optimization, a curve type 4 was obtained in 93.3% of the cases. Optimized interventricular times equal to 0 msec were found in 6.7% of cases.

Figure 6 Graphic showing the interventricular pacing interval where optimal curve and index were found to prevent electric asynchrony in patients with cardiac resynchronization therapy. Note that only two pts were optimized with an interventricular pacing interval of 0 msec (programmed “by default”). It can be also seen that two pts had optimal results when their left ventricle was the only chamber paced. In these latter cases, the left ventricular pacing lead was implanted in the interventricular septum.

• Conclusions

Electrical optimization of the interventricular times by this method is very simple, fast and inexpensive. It achieves a significant reduction in QRS duration, with improved electrical synchrony indexes and curves. The observed distribution of optimal interventricular intervals in electrical resynchronization suggests that this value is variable and dependent on each patient. Therefore leaving device in “nominal” parameters is not optimal in most cases.
Use of the blood pressure bar for AV interval adjustment: examples.

Case 1

Mode VDD. AV delay 100 msec

Mode VDD. AV delay 150 msec

Mode VDD. AV delay 200 msec
Mode DDD. AV delay 50 msec

Mode DDD. AV delay 100 msec

Mode DDD. AV delay 150 msec

Mode DDD. AV delay 200 msec
Graph showing that for both pacing modes the optimal AV delay is 150 msec

**Case 2**

Mode VDD. AV delay 50 msec

Mode VDD. AV delay 100 msec
Mode VDD. AV delay 150 msec

Mode DDD. AV delay 50 msec

Mode DDD. AV delay 100 msec

Mode DDD. AV delay 150 msec
Mode DDD. AV delay 200 msec

Graph showing that the best AV delay for VDD is 100 msec, and for DDD it is 200 msec. Usually the difference is around 50 msec

**Case 3**

Mode VDD. AV delay 100 msec
Mode VDD. AV delay 150 msec

Mode VDD. AV delay 200 msec

Mode DDD. AV delay 50 msec

Mode DDD. AV delay 100 msec
Graph showing that the best VDD AV delay is paradoxically longer than best DDD AV delay interval. This can be explained because the atrial lead was implanted in the atrial septum and the intra atrial interval is shorter when pacing than when sensing.