Mechanisms of atrial fibrillation

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Chronic left atrial volume and pressure overload in the goat: a new model of sustained atrial fibrillation


Chronic left atrial pressure/volume overload, can induce atrial fibrillation. The role of matrix metalloproteinases in the development of atrial fibrillation

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Background: atrial fibrillation (AF) is associated with important extracellular matrix remodeling which involves atrial fibrosis and atrial dilatation. Angiotensin II mediated pathways and matrix metalloproteinases (MMPs) have been implicated in these processes. The aim of this study was to assess atrial structural remodeling and the expression of the angiotensin receptor subtypes (AT-1 and AT-2), MMPs and their inhibitors (TIMPs) in patients with mitral valve disease with or without AF.

Methods: biopsies from right and left atrial appendages were taken from patients undergoing CABG (n=9, all in sinus rhythm (SR)) or mitral valve surgery (MVS; n=19; 9 with permanent AF and 10 in SR). Left atrial size was assessed by echocardiography and the degree of atrial fibrosis was scored on a scale of 1 to 4. The expression of MMP-1, MMP-4, TIMP-1 and -2 was assessed by northern blotting; TIMP-1 and -2 by immunohistochemistry.

Results: patients with MVS&AF (6.8 ± 0.2 cm) had significantly larger atria compared to patients with MVS&SR (5.8 ± 0.3 cm; p=0.02) and CABG (5.2 ± 0.2; p<0.01). Patients with MVS had significantly more atrial fibrosis than patients undergoing CABG (MVS: 3.2 ± 2, CABG: 2.3 ± 0.3; p<0.01). A significantly lower total amount of MMP-1 was present in patients with mitral valve disease when compared to patients undergoing CABG. However, there was no difference between mitral valve patients in SR or in AF (p=0.95) (relative MMP-1 expression: CABG: 100 ± 7%, MVS&SR: 78 ± 6%, MVS&AF: 78 ± 4%). Pro-MMP-2, MPP-9 and TIMP-2 were also significantly down-regulated in the MVS patients compared to CABG, without a difference between the MVS&SR and MVS&AF groups (pro-MMP-2: CABG: 19 ± 5 optical density (OD), MVS&SR: 3.0 ± 1 OD, MVS&AF: 3.2 ± 1 OD, p=0.01; MMP-9: CABG: 7.5 ± 1 OD, MVS&SR: 2.6 ± 1 OD, MVS&AF: 5.0 ± 1 OD, p=0.01; TIMP-2: CABG: 4.9 ± 1 counts/field, MVS&SR: 2.1 ± 1 counts/field, MVS&AF: 3.7 ± 1 counts/field, p=0.04). Protein expression of AT-1, AT-2, TIMP-1 & -4 did not significantly differ between the 3 groups.

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Effect of chronic amiodarone therapy on the excitability gap during typical human atrial flutter

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Class I antiarrhythmic drugs increase duration of the excitability gap (EG) during typical atrial flutter (AF) whereas intravenous class 3 drugs decrease the EG. The effect of chronic oral amiodarone therapy on the EG is unknown.

Methods: EG was prospectively determined by introducing a premature stimulus and by analyzing the response pattern during typical AF in 30 patients without antiarrhythmic drugs and in 20 patients under chronic oral amiodarone therapy. EG was calculated by the difference between the longest coupling interval leading to resetting and the effective atrial refractory period (EARP). A fully EG was defined by the proportion of EG where the response curve of the return cycles was flat. A partially EG was defined by the portion of EG where the return cycle increases while coupling interval decreases. A resetting response curve was constructed by plotting the duration of the return cycle against the value of the coupling interval.

Results: Cycle length (CL) (222 ± 17 vs 267 ± 20 ms, p<0.0001), EARP (128 ± 16 vs 152 ± 18 ms, p<0.0001) and EG (54 ± 19 vs 70 ± 21 ms, p=0.01) were significantly larger in patients taking amiodarone than in controls. When compared to CL, the relative part of the EARP (57 ± 7 vs 57 ± 6%, p=0.96) and EG (24 ± 7 vs 26 ± 8%, p=0.41) were comparable in both groups. The fully EG was larger in patients under chronic amiodarone therapy than in controls (39 ± 21 vs 26 ± 20 ms, p=0.03). Neither duration of the partially EG (28 ± 15 vs 31 ± 15 ms, p=0.42) nor slope of the ascending portion of the resetting response curve (1.15 ± 0.5 vs 1.13 ± 0.4 ms/ms, p=0.71) differed between the two groups.

Conclusion: EG in patients under chronic amiodarone therapy is significantly larger than in controls, mainly because of a longer fully EG. This observation may be explained by opposite effects on conduction velocity and refractoriness.
Conclusions: re-arrangement of MMP expression is involved in structural atrial remodeling in patients suffering from mitral valve disease. AF in itself however did not lead to an altered expression pattern of MMPs and angiotensin receptor subtypes in this specific population.

479 Role of Bachmann's bundle during chronic atrial fibrillation in patients with mitral valve disease

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Introduction Animal studies have shown that bachmann’s bundle (BB) is essential for development of multiple reentrant circuits perpetuating atrial fibrillation (AF). Mapping of BB in humans has so far not been performed. In this study, high density epicardial mapping of BB was performed to study conduction characteristics of fibrillation waves across BB during chronic AF in humans.

Methods Epicardial mapping studies of BB were performed in pts (n=10, age 58±7 yrs) with chronic AF during cardiac surgery for mitral valve disease with a template containing 60 unipolar electrodes (inter-electrode distance 1.5 mm). Ten seconds of AF were recorded from the middle (MBB), right (RBB) and left site of BB (LBB). Isochronal maps were off-line constructed. For each mapping site, AF cycle length (ACFL), conduction velocity (CV) and the incidence of conduction block (CV < 7.5 cm/s) was determined. Fibrillation potentials were classified according to the degree of fractionation.

Results 398±12039 fibrillation potentials and 197±56 fibrillation mapsets were analysed. In most pts, multiple waves separated by arcs of conduction block were observed. In 3 pts, only single waves propagating at high CV were present. There were no preferential conduction directions. Electrophysiological variables are summarized in Table 1. CV was slower and conduction block occurred more frequently at MBB compared to RBB and LBB (CV: MBB:29±18cm/s vs RBB:46±30cm/s, LBB:52±20cm/s, p<0.02, conduction block: MBB:20±10% vs RBB:5±3%, LBB:7±2%, p<0.01).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean±SD</th>
<th>Minimum</th>
<th>Maximum</th>
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<tr>
<td>ACFL (ms)</td>
<td>193±25</td>
<td>143</td>
<td>252</td>
</tr>
<tr>
<td>CV (cm/s)</td>
<td>49±21</td>
<td>21</td>
<td>71</td>
</tr>
<tr>
<td>Conduction block (%)</td>
<td>11±8</td>
<td>0.48</td>
<td>23</td>
</tr>
<tr>
<td>Degree of fractionation (%)</td>
<td>31±17</td>
<td>4</td>
<td>51</td>
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</table>

Conclusion There is a large inter-individual variation in activation patterns across BB during chronic AF in MVD patients. The results of this study suggest that BB is 1) a crucial pathway of conduction for fibrillation waves propagating from the right to the left atria or vice versa, or 2) a perpetuator of chronic AF.

480 RR intervals have an individually specific pattern in atrial fibrillation

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Ventricular rhythm in atrial fibrillation is irregular. Current data are conflicting on the randomness of the RR intervals. We investigated the RR intervals to determine whether any individually specific parameters of ventricular response can be proven. A method to differentiate one patient’s data from others’ was developed and validated.

245 records of 100 RR interval length from 20 patients with atrial fibrillation were examined. 343 statistical parameters were calculated in each sample, which described the mean, distribution, variability and randomness of the RR intervals. Differentiation of samples was accomplished with the following method: a sample was chosen from a patient, thereafter a set of 5 samples, which contained 1 sample from the same patient and 4 samples from other patients. Our method to find the corresponding sample used iteration to find the most effective combination of individually specific statistical parameters of RR intervals for differentiation. To determine the success ratio, all calculations were repeated 6 times to diminish the effect of random sample selection. Theoretically, the chance to find the correct sample was 20%, if the selection is random. Our algorithm showed a 71.7±0.36% success ratio to identify the correct sample. To validate the method, it was tested using random numbers instead of the RR intervals. Here it showed a 23.6±0.35% success ratio: even if the consecutive numbers are random, specific parameters can be found with a sensitive method in arbitrary determined sets of samples of limited length. The sensitivity of the method was demonstrated using chi square distributed random numbers (degree of freedom 6 – it was chosen to have a distribution similar to RR intervals in atrial fibrillation, which are usually skewed to the right), where each set of 100 numbers had the same average as the original patients’ data. The algorithm showed a 45.2±14.0% success ratio to identify the correct sample: it is efficient to find individually specific parameters for differentiation, if they exist.

This study showed that there are individually specific statistical parameters of RR intervals in atrial fibrillation and these can be used to differentiate the patients’ samples from each other. The developed iterative method of differentiation can be used to demonstrate differences or similarities in various groups of data.

481 Posterior wall of left atrium and pulmonary veins refractory period is related to atrial fibrillation inducibility in pigs

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Introduction: the ectopic activity from inside of pulmonary veins (PVs) has demonstrated to cause paroxysmal atrial fibrillation (AF) episodes in some patients. However, the exact role played by PVs and by the posterior wall of left atrium in maintaining the AF is unknown.

Methods: we assessed the relation between the refractory period (RP) in the lateral wall of the right atrium (RA), the lateral wall of the left atrium, the posterior wall of left atrium (PLA) and the PVs and the AF inducibility in a pig experimental model. We evaluated the inducibility of atrial fibrillation by means of programmed pacing before and after administration of high doses of intravenous methacholine in 20 pigs with median sternotomy.

Results: AF was induced in 17 out of 20 pigs. All refractory periods were related to AF inducibility, with a proportionally inverse relation in the univariate analysis; for a shorter refractory period a higher AF inducibility was demonstrated. In the multivaried analysis only PLA and PPVV refractory periods were related to inducibility. We also assessed the relation between local cycle length AF and RP, a good correlation only existed in lateral RA (Pearson correlation coefficient 0.97).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Non inducible</th>
<th>Inducible</th>
<th>P</th>
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<tbody>
<tr>
<td>RA RP</td>
<td>167±13</td>
<td>144±11</td>
<td>0.53</td>
</tr>
<tr>
<td>LA RP</td>
<td>136±7</td>
<td>107±8</td>
<td>0.4</td>
</tr>
<tr>
<td>PLA RP</td>
<td>170±26</td>
<td>86±27</td>
<td>0.011</td>
</tr>
<tr>
<td>PVs RP</td>
<td>170±11</td>
<td>92±6</td>
<td>0.021</td>
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Conclusions: in a pig experimental model, AF inducibility is related to refractory periods both in pulmonary veins as well as in posterior left atrium wall.