Exploration of Supraventricular Conduction with respect to Atrial Fibrillation. Methodological Aspects on Selected Techniques

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Modification of Intrinsic AV-Nodal Properties by Magnesium in Combination With Glucose, Insulin, and Potassium (GIK) During Chronic Atrial Fibrillation

M. P. Ingemansson, MD, J. Carlson, MSc, and S. B. Olsson, MD, PhD

Abstract: Objective: To explore the effects of MgSO₄ in combination with glucose, insulin, and potassium (GIK) on intrinsic AV-nodal properties during chronic atrial fibrillation. Methods: The study included two patient groups—(a) control and intervention and (b) intervention—with different infusion times and concentrations of MgSO₄. Ambulatory electrocardiographic recordings were analyzed using modified heart-rate stratified histogram (HRSH) analysis allowing detailed observation of the RR distribution at different average heart rate levels. The two RR-interval populations observed in most patients were characterized by analyzing the relationship between the summits of the peaks of the bimodal histograms. Results: A bimodal RR distribution with a shorter and a longer RR-interval population was observed in 9 of 11 (control), 9 of 11 (intervention) in group (a), and 11 of 13 in group (b) patients. No significant changes in the two RR populations were seen in the control registration (group a). There were, however, indications of a conduction delay in the longer RR intervals in group (a), which received a low concentration of MgSO₄, when control was compared with intervention recordings. In group (b), receiving a high MgSO₄ concentration, a conduction delay was seen in both the shorter and longer RR populations, being most pronounced for the longer RR population. Conclusion: High MgSO₄ levels caused a delay in both the shorter and longer RR intervals. The conduction delay in the longer RR population was most pronounced, indicating that MgSO₄ differently affected the two corresponding AV-nodal pathways. Key words: ambulatory ECG recording, atrial fibrillation, AV node, fast pathway, magnesium, RR interval, slow pathway.
Previous microelectrode studies of AV-nodal conduction have shown that there is a dual AV-nodal input, and the atrionodal input routes represent conduction from the interatrial septum and conduction along the crista terminalis into the AV node, respectively (8).

Although the multiple re-entrant circuits in the fibrillating atrium transmit rapid and irregular depolarizing wavelets to the AV-nodal region, heart-rate stratified histogram (HRSH) analysis from ambulatory electrocardiographic (ECG) recordings reveal an output with a distinct bimodal distribution of RR intervals in most patients (12-14).

On the basis of both invasive (13,15) and noninvasive studies (12,14), it has been suggested that one RR population represents AV-nodal conduction at the anterosuperior perinodal tissue, proximal to the His bundle, and the other, conduction in the posterior AV-nodal approaches, close to the tricuspid annulus.

The transmission of atrial impulses through the nodal region during chronic atrial fibrillation (CAF) is dependent on the conduction velocity and refractory period at the AV node, the main electrophysiologic determinants of the ventricular rate and thereby of the RR-interval distribution during CAF (16). It has been proposed that the two distinct AV-nodal pathways differ in conduction and refractory characteristics and might therefore be affected differently by pharmacological intervention (17).

Based on considerations regarding the pathoelectrophysiology of the fibrillating atrial myocardium (18–22), we have analyzed the effects of MgSO4 and GIK solution on the atrial myocardium during pacing (23) and fibrillation (24). Although these interventions may have beneficial antiarrhythmic properties in addition to their verified effects during sinus rhythm (25,26), detailed information about the effect of MgSO4 and GIK solution on AV-nodal conduction during CAF is lacking. The aim of this study was therefore to evaluate the effects of MgSO4 and glucose, insulin, and potassium (GIK) solution on intrinsic AV-nodal function. For this purpose, we studied their effects on the two RR-interval populations, which can be observed on HRSH analysis in most patients with CAF, and which most likely represent conduction via the dual AV-nodal pathways (12–15).

**Methods**

**Patient Groups and Interventions**

Two patient groups, (a) and (b), were included in the study (Fig. 1). Both control and intervention recordings were performed in group (a), whereas only intervention recordings were performed in group (b). Group (a) consisted of 9 men and 2 women, average age 64 ± 11 years. In group (b), there were 10 men and 3 women, average age 68 ± 8 years. There were no significant differences in age and gender between the two groups. All patients included had CAF with duration of more than 3 months. In group (a), pharmacological treatment had been unsuccessful in terminating the arrhythmia, and DC conversion had not been attempted. In group (b), both pharmacological treatment and DC conversion had been unsuccessful in terminating the arrhythmia. The same exclusion criteria were
used in both groups: diabetes mellitus, hyperthyroidism, renal or hepatic diseases, infections, or severe electrolyte disturbances. All antiarrhythmic treatment, including digoxin, was withdrawn at least 5 $T_{1/2}$ before participation in the study.

No infusates were given during the control registration in group (a). The intervention in the same group was performed 1 to 5 days later and consisted of a 24-hour infusion with 2,000 mL glucose (100 g/L$^{-1}$), MgSO$_4$ (100 mmol/L$^{-1}$), 40 IU/L$^{-1}$ of Actrapid, and K$^+$ supplement (80 mmol/L$^{-1}$), if S-K was below 4.0 mmol/L$^{-1}$ at the start. In group (b), a higher dose of MgSO$_4$ and a shorter infusion time was used. Three hours after start of the recording, a bolus infusion of 0.15 mmol/kg/hr of MgSO$_4$ was given over 10 minutes in 250 mL glucose (50 g/L$^{-1}$). The MgSO$_4$ and GIK maintenance infusion was started after 4 hours of recording and was given over 8 hours. It consisted of 1,000 mL glucose (100 g/L$^{-1}$), MgSO$_4$ (0.1 mmol/kg$^{-1}$/hr$^{-1}$), Actrapid 20 IU/L$^{-1}$, and K$^+$ supplement (40 mmol/L$^{-1}$), if S-K was below 4.0 mmol/L$^{-1}$ at the start. The MgSO$_4$ and GIK solutions were administered via a peripheral vein.

The investigation conforms to the principles outlined in the Declaration of Helsinki (BMJ 1964;ii:177). The study was approved by the Ethical Committee of the Medical Faculty, Lund University, Sweden, approval numbers LU 134-94, LU 15-96.

**ECG Recording and Analysis**

The ECG recordings were performed using a model 423 Dynacord Holter cassette recorder. The electrode configuration consisted of two V leads, consistent with typical, 2-channel Holter recording (423 Dynacord; Del Mar Avionics, Irvine, CA), as well as a modified lead III on the third channel. Soft, flexible electrodes were used. In group (a), ECG recordings were performed over 24 hours and the whole periods of control and intervention recordings were compared to each other. In addition, the first 7 hours (0–7) of the recording in the control registrations were compared with the last 7 hours (17–24). In group (b), the recordings were continued for 12 hours and the first 4 hours (0–4) of recording were compared with the last 4 hours (8–12) (Fig. 1).

The ECG was analyzed with a model 263 StrataScan Holter analysis system with a resolution of 15 to 16 ms, and it was also carefully analyzed by visual inspection, to make sure that only AF with narrow QRS complexes was included. Afterward, the lengths of all RR intervals were saved onto a 5½-inch floppy disc and analyzed on a computer running a specially developed MATLAB®-based program. The methodologic aspects of the RR-interval pooling procedure have been described elsewhere (14), but the following modifications were made. The entire series of RR-intervals was divided into sequences of 20 individual RR intervals as follows, 1–20, 2–21, 3–22 . . . (Fig. 2). Each sequence was then pooled into different heart-rate levels, according to its average heart rate (eg, 45–50, 50–55, 55–60 beats per minute [bpm], etc.). Histograms were constructed of the individual RR-interval values at each heart-rate level. Each histogram had a width of 15 to 16 ms, corresponding to the resolution of the StrataScan system.

Each histogram was analyzed by the computer with regard to the number of distinct populations of RR intervals (peaks). Each point at which the slope of the histogram changed from positive to negative was considered a peak. If the distance between 2 peaks was less than 3 bars (<50 ms), this was considered a ripple in the histogram, and a smoothing procedure was used in which the value for each bar was recalculated as the average between its original value and that of one bar on each side. The smoothing procedure was repeated until no peaks were closer to each other than 50 ms. The remaining peaks were considered to belong to different RR-interval populations. The peak locations of the RR-interval populations were estimated by fitting a second-degree polynomial to the highest bar and the 2 adjacent bars on each side. The highest and second-highest peaks were classified as dominant and nondominant, respectively. The quotient of and distance between the peak locations of the longer and shorter RR population were calculated as the peak value ratio (PVR) and peak gap [PG(ms)], respectively (Fig. 2). At lower heart-rate levels, the peak corresponding to the longer RR-interval population [PV(s)] is dominant. As the heart-rate increases, the peak of the shorter RR-interval population [PV(f)] will increase and become dominant. The heart-rate level at which a change in peak dominance was seen was called the peak dominant change (PDC). PVR, PG, PV(f), and PV(s) were calculated at the PDC.

**Statistical Evaluation**

Data are expressed as medians (tables), means and standard deviations (SD) from the mean (text + tables). Friedman’s Test for repeated measurements was used for statistical evaluation of the whole group. Wilcoxon’s signed rank test was used
Modification of Intrinsic AV-Nodal Properties During Atrial Fibrillation • Ingemansson et al.

Table 1. Peak Indices for the Control Group, Comparing the First Seven Hours (0–7) with the Last Seven Hours (17–24)

<table>
<thead>
<tr>
<th>Case</th>
<th>PDC (HR level)</th>
<th>PG (ms) at PDC</th>
<th>PVR at PDC</th>
<th>PV(f) (ms) at PDC</th>
<th>PV(s) (ms) at PDC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–7 hr</td>
<td>17–24 hr</td>
<td>0–7 hr</td>
<td>17–24 hr</td>
<td>0–7 hr</td>
</tr>
<tr>
<td>1</td>
<td>MV</td>
<td>120</td>
<td>MV</td>
<td>184</td>
<td>MV</td>
</tr>
<tr>
<td>2</td>
<td>105</td>
<td>100</td>
<td>245</td>
<td>246</td>
<td>1.65</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>95</td>
<td>257</td>
<td>261</td>
<td>1.61</td>
</tr>
<tr>
<td>4</td>
<td>115</td>
<td>120</td>
<td>157</td>
<td>138</td>
<td>1.36</td>
</tr>
<tr>
<td>5</td>
<td>105</td>
<td>100</td>
<td>179</td>
<td>193</td>
<td>1.41</td>
</tr>
<tr>
<td>6</td>
<td>125</td>
<td>115</td>
<td>100</td>
<td>159</td>
<td>1.26</td>
</tr>
<tr>
<td>7</td>
<td>UM</td>
<td>UM</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>8</td>
<td>115</td>
<td>120</td>
<td>137</td>
<td>100</td>
<td>1.39</td>
</tr>
<tr>
<td>9</td>
<td>110</td>
<td>105</td>
<td>166</td>
<td>135</td>
<td>1.38</td>
</tr>
<tr>
<td>10</td>
<td>110</td>
<td>115</td>
<td>86</td>
<td>165</td>
<td>1.19</td>
</tr>
<tr>
<td>11</td>
<td>UM</td>
<td>UM</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>110</td>
<td>115</td>
<td>157</td>
<td>159</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>111 (8)</td>
<td>110 (10)</td>
<td>122 (93)</td>
<td>146 (85)</td>
<td>1.33 (0.2)</td>
</tr>
</tbody>
</table>

HR, heart rate; h, hours; ms, milliseconds; MV, missing value; NS, nonsignificant; PV(f), peak value of the shorter RR-interval population; PV(s), peak value of the longer RR-interval population; PDC, peak dominant change; PG, peak gap; PVR, peak value ratio; SD, standard deviation; UM, unimodal.

as a post hoc test to evaluate the significance of changes within the groups. P values were considered significant if P < .05 (*).

Results

HRSH Analysis

In the control registrations in group (a), peaks representing the shorter and longer RR-interval populations [PV(f) and PV(s)] could be distinguished in 9 of 11 patients in the whole 24-hour registration and in both shorter registrations (0–7 hr and 17–24 hr) (Tables 1 and 2). There was a shift in dominance between the two RR-interval populations, and consequently PDC, PG, PVR, PV(f), and PV(s) could be estimated in all these nine patients. The PDC location in the first patient (Table 1) could not be determined in the 0–7-hour registration, because heart-rate variability was low. However, the heart-rate variability increased, and the PDC location could be determined in the 17– to 24-hour registration. The remaining two patients had a unimodal RR-interval distribution and PDC could not be calculated. Based on earlier observations (2), these were regarded as 2 superimposed RR populations, and PG and PVR were therefore given the values 0 and 1, respectively. The change in dominance occurred at average heart-rate levels ranging from 100 to 125 (0–7 hr) and from 95 to 120 bpm (17–24 hr) for the shorter registration periods, and from 100 to 130 for the whole 24-hour registration. No significant changes were seen in PDC location, PG, PVR, PV(f), and PV(s) when comparison was made between the first 7-hour registration (0–7 hr) and the last 7-hour registration (17–24 hr) (Table 1).

Following intervention with MgSO₄ and GIK infusion in group (a), (low MgSO₄ concentration),
shorter and longer RR-interval populations could be distinguished in 9 of 11 patients (Table 2). The remaining two patients had a unimodal RR-interval distribution, and the PDC could not be calculated. Once again, the PG and PVR were given the values 0 and 1, respectively, in these 2 cases. The PDC occurred at average heart-rate levels ranging from 70 to 130. No significant change was seen in PDC location when comparing the control and the intervention recordings in group (a), although the mean value decreased from 113 bpm (control) to 104 bpm (intervention) ($P = .05$) (Table 2). The PV(f) and PVR at the PDC were unaffected, whereas the PG and PV(s) showed a significant increase, from 132 to 146 ms ($P < .05$) and from 574 to 633 ms ($P < .05$), respectively.

In group (b) (high MgSO4 concentration), shorter and longer RR-interval populations could be distinguished in both shorter registration periods (0-4 hr and 8-12 hr) in 11 of 13 patients (Table 3). The remaining two patients had a unimodal RR-interval distribution in at least one of the registrations and the PDC could not be calculated. As before, the PG and PVR were given the values 0 and 1, respectively. In the 11 patients in whom both RR-interval populations could be discerned, the PDC occurred

### Table 2. Peak Indices for Group (a) (Control + Intervention), Comparing Recordings of the Whole 24-Hour Control Period With the 24-Hour Intervention Period in Group (a)

<table>
<thead>
<tr>
<th>Case</th>
<th>PDC (HR level)</th>
<th>PG (ms) at PDC</th>
<th>PVR at PDC</th>
<th>PV(f) (ms) at PDC</th>
<th>PV(s) (ms) at PDC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Interv</td>
<td>Control</td>
<td>Interv</td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td>120</td>
<td>70</td>
<td>169</td>
<td>187</td>
<td>1.43</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>95</td>
<td>245</td>
<td>273</td>
<td>1.63</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>95</td>
<td>258</td>
<td>253</td>
<td>1.61</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>110</td>
<td>153</td>
<td>136</td>
<td>1.37</td>
</tr>
<tr>
<td>5</td>
<td>105</td>
<td>110</td>
<td>175</td>
<td>197</td>
<td>1.40</td>
</tr>
<tr>
<td>6</td>
<td>130</td>
<td>102</td>
<td>116</td>
<td>112</td>
<td>1.27</td>
</tr>
<tr>
<td>7</td>
<td>UM</td>
<td>UM</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>8</td>
<td>115</td>
<td>105</td>
<td>140</td>
<td>173</td>
<td>1.36</td>
</tr>
<tr>
<td>9</td>
<td>115</td>
<td>110</td>
<td>117</td>
<td>156</td>
<td>1.28</td>
</tr>
<tr>
<td>10</td>
<td>110</td>
<td>110</td>
<td>87</td>
<td>111</td>
<td>1.19</td>
</tr>
<tr>
<td>11</td>
<td>UM</td>
<td>UM</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Median</td>
<td>115</td>
<td>110</td>
<td>147</td>
<td>156</td>
<td>1.36</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>113 (10)</td>
<td>104 (16)</td>
<td>132 (84)</td>
<td>146 (88)</td>
<td>1.32 (0.2)</td>
</tr>
</tbody>
</table>

$P$ value $P = .05$ $P < .05$ NS NS $P < .05$

HR, heart rate; interv, intervention; ms, milliseconds; NS, nonsignificant; PV(f), peak value of the shorter RR-interval population; PV(s), peak value of the longer RR-interval population; PDC, peak dominant change; PG, peak gap; PVR, peak value ratio; SD, standard deviation; UM, unimodal.
at average heart-rate levels ranging from 85 to 110 (0–4 hr) and from 65 to 115 bpm (8–12 hr). The heart-rate level at which the PDC was located decreased from 97 (0–4 hr) to 90 bpm (8–12 hr) ($P < .05$) (Table 3). The PG and PVR increased from 143 ms to 178 ms ($P < .05$) and from 1.30 to 1.40 ($P < .05$), respectively. At the PDC, both the PV(f) and PV(s) were significantly increased, from 459 to 513 ms ($P < .01$) and from 628 to 706 ms ($P < .01$), respectively. The difference in conduction delay between PV(f) (459 to 513) and PV(s) (628 to 706) was 24 ms ($P < .05$).

**Blood and Urine Parameters**

In the intervention study in group (a), S-Mg increased from 0.94 to 2.18 mmol/L$^{-1}$ ($P < .01$), and in group (b), from 0.92 to 2.39 mmol/L$^{-1}$ ($P < .01$). Blood and urine parameters are shown in Table 4.

**Discussion**

**Evidence That the Two RR-Interval Populations Represent a Dual AV-Nodal Conduction System During CAF**

A characteristic and highly reproducible RR-interval distribution, with two separate RR-interval populations, is evidenced when HRSH analysis is performed during CAF (12,14). The distribution of RR intervals is estimated at well-defined average heart-rate levels (ie, at a distinct balance between the vagal and the sympathetic nervous discharge). Provided that the RR distribution can be studied over a wide range of average heart-rate levels, the bimodal RR distribution can be found in a majority of patients, consistent with the frequency of dual pathway physiology found in invasive studies (27). That the bimodal RR distribution represents the dual pathway is strongly supported by the fact that interference with conduction along the posterior nodal input via catheter ablation markedly changes the RR distribution pattern (15). In some cases, a third RR population is found at lower heart-rate levels and has been defined as a nodal escape rhythm (12). The two separate RR populations, made up of shorter and longer RR-intervals at heart rate levels above 70 bpm, thus suggest AV-nodal conduction via dual AV-nodal pathways.

The longitudinal dissociation of a slow and a fast pathway within the AV node is well established (1–2,28). Supported by mapping and catheter ablation studies (28–30), it has been proposed that the slow pathway can be attributed to cells with characteristics for slow conduction (17), surrounding the tricuspid annulus in the posterior approaches to the AV node, whereas the fast pathway has been targeted at the anterosuperior perinodal tissue, proximal to the His bundle (31).

It is obvious from RR-interval analysis that a decreased average ventricular rate is achieved by more abundant use of RR intervals within the long RR population, together with a successive and parallel prolongation of all RR intervals of both RR populations, known as rate dependence of peaks (Fig. 3) (14). The successive and parallel changes of all RR intervals could reflect successive changes in

![Table 4. Statistical Evaluation of Peak Indices](image-url)

<table>
<thead>
<tr>
<th>No. of RR Intervals</th>
<th>PDC</th>
<th>PG</th>
<th>PVR</th>
<th>PV(f)</th>
<th>PV(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CV (%)</td>
<td>r</td>
<td>CV (%)</td>
<td>r</td>
<td>CV (%)</td>
</tr>
<tr>
<td>240</td>
<td>3.0 (1.9)</td>
<td>0.98</td>
<td>20.9 (27.3)</td>
<td>0.98</td>
<td>4.8 (3.2)</td>
</tr>
<tr>
<td>500</td>
<td>2.4 (1.1)</td>
<td>0.98</td>
<td>14.1 (10.1)</td>
<td>0.96</td>
<td>4.1 (3.1)</td>
</tr>
<tr>
<td>1,000</td>
<td>2.0 (1.3)</td>
<td>0.98</td>
<td>13.6 (8.8)</td>
<td>0.99</td>
<td>4.2 (3.0)</td>
</tr>
<tr>
<td>5,000</td>
<td>0.8 (1.4)</td>
<td>0.99</td>
<td>6.8 (4.9)</td>
<td>1.0</td>
<td>2.1 (1.5)</td>
</tr>
<tr>
<td>20º (24 hr)</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>20º (24 hr)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Coefficients of variance (CV) in percentage, presented as means and standard deviations from the mean (mean (SD)), and correlation (r) between peak indices. Data are derived from histograms constructed using 240, 500, 1,000, 5,000, and all RR intervals, obtained with the pooling procedures of 20º (ie, one-by-one step movement) and 20º (ie, 20-by-20 RR-interval movement) in 8 patients chosen from the control group. The CV was calculated from 3 different analyses, where 240, 500, 1,000, and 5,000 RR intervals were randomly chosen over the whole 24-hour registration period. The correlation between peak indices was calculated for the whole 24-hour interval with the 20º pooling procedure and the whole 24 hr with the 20º pooling procedure, and from the mean value of 3 different analyses of 240, 500, 1,000, and 5,000 RR intervals randomly chosen over the whole 24-hour registration. This method of heart-rate stratified histogram analysis is a modification of the method used until now. As evidenced by the correlation values, with the new 20º pooling procedure, 240 RR Intervals were considered sufficient for estimation of peak indices. PDC, peak dominant change; PG, peak gap; PVR, peak value ratio; PV(f), peak value of the shorter RR-interval population; PV(s), peak value of the longer RR-interval population.
Modification of Intrinsic AV-Nodal Properties During Atrial Fibrillation

Table 5. Blood and Urine Parameters in Groups (a) and (b)

<table>
<thead>
<tr>
<th>Parameter Measured</th>
<th>Group (a)</th>
<th>Group (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Inf</td>
<td>12-Hour Inf</td>
</tr>
<tr>
<td>MgSO4 (mmol L⁻¹)</td>
<td>0.94 (0.02)</td>
<td>1.85 (0.06)**</td>
</tr>
<tr>
<td>Potassium (mEq L⁻¹)</td>
<td>4.08 (0.11)</td>
<td>4.09 (0.07)</td>
</tr>
<tr>
<td>Calcium (mmol L⁻¹)</td>
<td>2.34 (0.02)</td>
<td>2.17 (0.02)**</td>
</tr>
<tr>
<td>Sodium (mmol L⁻¹)</td>
<td>141 (0.75)</td>
<td>140 (0.65)*</td>
</tr>
<tr>
<td>Glucose (mEq L⁻¹)</td>
<td>5.28 (0.47)</td>
<td>4.22 (0.36)</td>
</tr>
<tr>
<td>U-Mg (mmol L⁻¹)</td>
<td>2.14 (0.22)</td>
<td>21.1 (1.57)</td>
</tr>
</tbody>
</table>

inf, infusion.

Conduction and refractory properties within the AV node. The two AV-nodal conduction pathways differ in electrophysiologic characteristics (1-2), the fast pathway being characterized by a longer refractory period and a shorter conduction time, compared with the slow pathway. In the above-mentioned studies (1-2), atrial stimulation was used and the effects of regular or single interpolated stimuli explored. During AF, however, the number of atrial impulses exceeds by far the ventricular response. Fast pathway ablation produces no appropriate decrease in heart rate during AF and has no influence on the global AV-nodal effective refractory period (32), whereas slow pathway ablation decreases the heart rate in AF during rest and autonomic blockade and does not influence the heart rate during exercise and sympathetic stimulation (29). It remains to be verified to what extent the conduction velocity and refractoriness of the different pathways contribute to the specific behavior of the AV-nodal pathways during AF.

Methodological Modification of the HRSH

The newly developed find-peak function made it possible to calculate the histogram peak indices with great precision (Figs. 2, 3). In the method previously used, peak indices were estimated by visual inspection and by manual measurement, and the mean heart rate used for the pooling procedure was calculated from consecutive sequences of 64 RR intervals (14). In this work, sequences of 20 RR intervals were extracted by one step movement (20°), using intervals 1–20, 2–21, 3–22, and so on. The number of analyzed 20-interval sequences in a 24-hour registration thus increased from approximately 125 thousand/20 to 2.5 million/20, with an unchanged number of individual RR intervals. The coefficient of variance and correlation for the new 20° pooling procedure are illustrated in Table 5. The modified method allowed a more detailed analysis and made it possible to analyze shorter time intervals.

Effects of MgSO4 and GIK Infusion on the Short and Long RR Populations During CAF

The protocols for groups (a) and (b) were designed to allow the study of short-term effects. However, it was not possible to analyze the effects of MgSO4 alone in group (b), since the heart-rate variability was too low to provide a sufficient range of average heart-rate levels during the 1-hour study period. Therefore, the RR populations in group (b) were estimated at a lower S-Mg concentration (0–4 hr) and compared with those obtained with MgSO4 and GIK infusion at a higher S-Mg concentration (8–12 hr), as indicated by the blood parameters (Table 4).

We have recently shown that parenteral adminis-
tration of MgSO₄ and GIK solution increases atrial cycle length and decreases heart rate during CAF (24). In this study, the same amount of infusates affected the RR histogram contour by delaying both the shorter and the longer RR populations [group (b)]. The delay in conduction for the longer RR intervals was, however, more pronounced than the delay in conduction for the shorter RR population, as indicated by the difference in conduction delay between PV(f) and PV(s) (24 ms [mean], P < .05) and the increased PG and PVR in group (b). There were indications of a similar change in group (a) (low MgSO₄ concentration), but only the changes in PG and PV(s) were significant. Because the only difference between the infusates in groups (a) and (b) was a higher MgSO₄ concentration in group (b), the conduction delay seems to be caused by MgSO₄ alone.

Explanations on the Cellular Level for the Conduction Delay in the Two RR-Interval Populations

The MgSO₄ and GIK solution affect at least two different populations of AV-nodal cells (33). The combination of a fast inward current, I_{Na}, and a transient outward current, I_{to}, has been found in 93% of cells with an AN-like structure but in only 24% of cells with an N- or NH-like action potential configuration (33). The myocytes in the AN region seem to be more atriumlike and of fast response type, whereas myocytes in deeper AV-nodal layers (ie, N- or NH-cells) seem to have slow response characteristics.

The two AV-nodal conduction pathways have different electrophysiological characteristics (1-2). This may correspond to different distribution of the different cell populations (17). The fast pathway may have a higher density of myocytes of the fast response type, whereas the slow conduction pathway has a higher density of the slow response type. MgSO₄ is a known calcium entry blocker and will decrease the conduction velocity in cells with slow conduction properties (34). However, MgSO₄ is also known to decrease potassium conductance, which will increase refractoriness in cells with fast conduction properties (35-36).

There are at least two possible explanations on the cellular level for the MgSO₄ effect: (1) the population of longer RR intervals corresponds to the slow pathway and the delay in conduction is caused by a calcium entry blockade that is more pronounced than the increased refractoriness in cells with fast conduction properties, or (2) the population of longer RR intervals corresponds to the fast pathway and the delay in conduction is caused by an increased refractoriness that is more pronounced than the calcium entry blockade in cells with slow conduction properties.

Alternative Interpretations for the Observed Conduction Delay in the Two RR Populations

Although the findings of this study can thus be explained by a more marked effect of MgSO₄ on one of the AV-nodal pathways, other mechanisms cannot be excluded. Others and we have shown that intra-atrial conduction during AF is a nonrandom phenomenon, indicating the possibility of a systematic relationship between the timing of fibrillatory impulses reaching the AV-node from the different atrial inputs (37,38). Although there is no report available concerning the interrelationship between time and direction of atrial excitation at different perinodal positions, another plausible interpretation of the MgSO₄ effects could be systematic changes in the RR distribution, reflecting a change in timing between the excitation of fibrillatory wavelets at the different atrial inputs (ie, the crista terminalis and interatrial septum) (8). Thus, an increase in the atrial fibrillatory cycle length may change the intra-atrial pattern of conduction, resulting in different timing between the excitation of different pathways and thereby in a reshaping of the RR histogram contour (24). This mechanism occurs, for instance, when the global atrial conduction is affected by surgical incision far away from the AV node (13). This alternative explanation of our findings is, however, contradicted by the preliminary report that slow pathway ablation may change a bimodal RR distribution to a unimodal one (15).

Conclusion

Conduction in both the shorter and longer RR populations was delayed by the intervention that had a high MgSO₄ concentration. The conduction delay in the longer RR intervals was more pronounced than for the shorter RR intervals. Therefore, we conclude that MgSO₄ differently affected the two AV-nodal conduction pathways. A possible interpretation of the results is that the fast and the slow pathways consist of cells with different ion channel densities.
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