Autonomic and surgical substrate modulation of atrial fibrillation

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Chapter 4

Disparate response of high-frequency ganglionic plexus stimulation on sinus node function and atrial propagation in patients with atrial fibrillation

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Chapter 4

ABSTRACT

Introduction
In patients with atrial fibrillation (AF), the autonomic nervous system is supposed to play a role in triggering AF; however, little is known of the effect on atrial conduction characteristics. The purpose of this study was to study the effect of ganglionic plexus (GP) stimulation during sinus rhythm on atrial and pulmonary vein conduction in patients during thoracoscopic surgery for AF.

Methods
In 25 patients, the anterior right ganglionic plexus (ARGP) was stimulated (16Hz, at 1, 2, and 5 mA). Epicardial electrograms were recorded using a 48-electrode map from the right pulmonary vein (RPV) or right atrial (RA). Intra-atrial activation time (IAT), local activation time (LAT), and inhomogeneity of conduction (IIC) were determined. ECG parameters (P-P, P-R interval) were measured.

Results
P-P interval was 956 ± 157 ms (range 768–1368 ms), and P-R interval was 203 ± 37 ms (range 136–280 ms). After ARGP stimulation, a short-lasting increase of P-P interval was observed, more prominent at higher output (1 mA = 82 ms, 2 mA = 180 ms, 5 mA = 268 ms, all P < .01 vs baseline). P-R interval remained unchanged. IAT was 34.4 ms (range 5.6–50.3 ms) at the RA and 105.8 ms (range 79.7–163.3 ms) at the RPV. After 1 mA stimulation IAT increased, in patients taking beta-blockers (P = .001), or it decreased, and this change persisted after subsequent stimulation at higher current (1 mA, P = .001; 2 mA, P = .401; 5 mA, P = .593). Similar changes were observed for LAT and IIC.

Conclusions
ARGP stimulation results in a short-lasting, output-dependent decrease in sinus node frequency due to a parasympathetic response. Stimulation of the ARGP induced a prolonged increase or decrease in conduction characteristics in patients with AF, consistent with a persistent differential parasympathetic and/or sympathetic response.
INTRODUCTION

The relation between the autonomic nervous system (ANS) and atrial fibrillation (AF) remains complex and incompletely understood. Parasympathetic and sympathetic nerves cover both atria and ventricle in a complex pattern of subplexus. The ganglionic plexus (GPs), represent conglomerations of autonomic ganglia, located on right and left atrium, predominantly around the pulmonary veins. In many patients, AF is initiated by ectopic firing from the pulmonary veins (PV). These ectopic beats can be initiated by triggered activity after simultaneous activity of both the parasympathetic and sympathetic ANS in animals. However, the effect of the ANS on atrial conduction characteristics in patients with AF, which may be an equally important arrhythmogenic mechanism, is largely unknown. Conduction changes might constitute the substrate in patients with AF induced remodeling of the atria. Similar to the various heterogeneous effects of the ANS on repolarization, a specific differential response may be expected of the parasympathetic or of the sympathetic nervous system on local conduction characteristics. We studied the effect of high frequency anterior right GP (ARGP) stimulation during sinus rhythm on the sinus node and the AV-node and the epicardial atrial conduction times and inhomogeneity of conduction of the atrial or PV myocardium using high resolution multi-electrode mapping in patients undergoing thoracoscopic surgery for AF.

METHODS

Study population
Twenty-five patients with symptomatic paroxysmal (56%) or persistent AF (44%), refractory to anti-arrhythmic drugs, who underwent thoracoscopic surgery for AF and were in sinus rhythm at the time of the surgery, were included in the study. Nine patients (36%) had a previous left atrial catheter ablation for AF. Twenty-four patients (96%) used anti-arrhythmic drugs (15 used beta-blockers including sotalol) and these drugs were continued throughout the admission. Table 1 displays the patient characteristics. This study was approved by the local medical ethics committee and written informed consent was obtained from all patients.

High frequency ganglionic plexus stimulation and activation mapping protocol
The details of the electrophysiological-guided thoracoscopic surgery have been reported earlier. Patients received premedication with midazolam and general anesthesia with either propofol or sevoflurane. Rocuronium was administrated to facilitate endotracheal intubation. Surgery was started on the right side on the beating heart. Before GP ablation,
the area of the ARGP was localized visually and stimulation was performed with a bipolar surgical ablation pen (Isolator® multifunctional pen, Atricure Inc, Cincinnati, OH). A stepwise stimulation protocol (1 ms pulse width, 16 Hz, 1, 2 and 5 mA) was performed to study the effects of low-output stimulation using a stimulation unit (Micropace EPS320 Cardiac Stimulator, Micropace EP Inc., USA) until a vagal response was elicited (increase of R-R interval of >50%) (Figure 1). Stimulation at 10 mA and 25 mA resulted in capture of the atrium and induction of arrhythmias and therefore precluded analysis of sinus rhythm activation (data not shown). No subsequent stimulation was performed on the ARGP after eliciting a vagal response to prevent prolonged asystole. The standard six limb leads of the surface ECG and reference electrograms from a decapolar diagnostic catheter (C. R. Bard Inc, USA) positioned at the left atrial posterior wall, parallel to the coronary sinus, to assess left atrial activation were recorded. Right atrial (RA) lateral free wall (n=13)
or lateral side of the right superior PV myocardial (n=13) unipolar electrograms were recorded with a custom made 48 point electrode grid (6x8 array, interelectrode distance 1 mm) directly before and after HFS using a 256-channel mapping system (BioSemi, 24 bit dynamic range and 1/8192 mV bit step) with a sampling frequency of 2 kHz and 415 Hz lowpass (Figure 2). Simultaneous recording of RA and PV was not possible via the three access ports available during thoracoscopic surgery. A reference surface electrode was positioned from the right side of the chest of the patient. Electrogram analysis was performed offline using a custom-made program based on MATLAB (The MathWorks, Inc., Natick, MA, USA). Sinus rhythm activation was analyzed directly before and after HFS with similar activation patterns as determined by p-wave morphology, the decapolar reference catheter and local activation maps.

Surface ECG parameters
The P-P and P-R interval were measured on lead II of the ECG at 200 mm/sec before and after HFS. Differentiation between sinus rhythm activation, left and right atrial and PV extrasystoles was performed with the activation sequence over the decapolar catheter at the left atrial posterior wall. Sinus rhythm was defined based on normal right to left activation recorded by the catheter and a normal P-wave on the surface ECG. Extra-systoles were defined based on the P-wave morphology and abnormal activation sequence at the posterior wall.
Intra-atrial activation time

Intra-atrial activation time (IAT) was defined as the time between the onset of the atrial activation and the earliest local activation on myocardial electrograms obtained from the 48-electrode grid (48). The onset of atrial activation was defined by the beginning of the P-wave on the surface ECG. Maximal negative dV/dt in the unipolar electrograms defined the moment of local activation under the electrode. The stimulation artifact of the HFS was used as a time reference to align both recordings.

Local activation time

Local activation maps were created from the activation times recorded of the 48 electrodes, and analyzed by two independent observers. The local activation time was determined (LAT), defined as the difference between the first and last local activation on the activation map, representing underlying conduction of the dominant local activation wave front.

Inhomogeneity of conduction

The inhomogeneity index of conduction (IIC) is a quantification of the inhomogeneity of conduction within an activation map. The maximal difference in activation time

Figure 2. – Reference of electrode position during high frequency stimulation. A photograph and schematic view of the RA of the peri-procedural measurements (not to scale). The inlay represents a photograph of the measurements of the RA with the stimulation probe (Stim) and the 48 electrode grid (48). In the schematic the stimulation position, the ARGP, is marked in red and the measurement positions of the 48 electrode grid are marked by the number 48. See text for further details.

compared to activation times recorded at neighboring electrodes on the 48-electrode grid was calculated (phase times) and a phase map was constructed during sinus rhythm directly before or after HFS. Phase maps display the underlying local spatial homogeneity of conduction, in other words, whether there are areas of conduction block and irregular propagation. Histograms were created from the phase times and the median and absolute phase times were determined. From these data the IIC was calculated as a quantification of local spatial inhomogeneity in conduction as the difference between the median and the 95th percentile value of the phase times.12

Statistical analysis
Data are presented as mean ± standard deviation for normally distributed continuous variables or median and range for non-normal distribution. Categorical variables are presented in numbers with percentages. Differences were determined with an independent Student T-test for normally distributed data or a Mann-Whitney U-test for not-normally distributed data. A p value of <0.05 was considered significant. Paired testing was used to assess changes before and after stimulation. Increasing output reduced the amount of observations and therefore no repeated ANOVA was used. To correct for multiple testing a Bonferroni correction was used at p<0.017. Correlation was assessed in normally distributed data with the Pearson Rho or Spearmans Rho for non-parametric data. Statistical analyses were performed with SPSS, version 20 (Chicago, IL, USA).

RESULTS
Surface ECG parameters
After HFS the P-P interval prolonged, more prominent at higher output (absolute change vs baseline 1 mA n=25, p=0.001, 2 mA p=0.002, 5 mA p=0.002, persistence of change, pre 1 mA vs pre 2 mA p=0.248, pre 1 mA vs pre 5 mA p=0.232) (Figure 3A). Successful atrial recordings decreased with increasing output of HFS (1 mA n=25, 2 mA n=20, 5 mA n=12) because induction of atrial arrhythmias. An age-associated increased response to GP stimulation was observed on P-P interval prolongation (p=0.025, ρ=0.448). PR interval was unchanged after HFS of the ARGP (Figure 3B), irrespective of HFS output (1 mA p=0.131, 2 mA p=0.931, 5 mA p=1.000).

Response to high frequency stimulation
Nineteen patients showed ectopic beats. No accurate differentiation was possible between RA and RPV ectopy based on timing intervals and activation maps. No prolonged ectopic firing was observed after cessation of HFS and ectopy never induced AF. Six patients showed no ectopy during or after HFS at low output stimulation (<5 mA). In
14 patients AF (n=11) or atrial tachycardia (n=3) was induced during HFS. Four of these patients showed no vagal response to HFS. Three patients had no vagal response or any arrhythmia after HFS. The absence of a vagal response was not associated with type of AF or prior catheter ablations for AF. In the 8 remaining patients a vagal response occurred at low output (<5 mA) and HFS was not continued at higher output.

**Figure 3.** – Influence of high frequency stimulation on P-P interval and P-R interval. Panel (A) mean changes in P-P interval ± SEM before and after HFS (vertical dotted lines, 1-5 mA). Panel (B) mean changes in P-R interval.

*HFS: high frequency stimulation, SEM: standard error of the mean.*
### Table 2. Conduction parameters before and after stimulation of the anterior right ganglionic plexus

<table>
<thead>
<tr>
<th></th>
<th>1mA</th>
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<th>2mA</th>
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<th>5mA</th>
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<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
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<tr>
<td>RA n=7</td>
<td>34.4 (5.6-50.3)</td>
<td>35.3 (4.3-59.5)</td>
<td>38 (33.5-61.7)</td>
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<td>14.2</td>
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<td>2.2 (1-6.6)</td>
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<td>2.6 (1.8-7.2)</td>
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<td>PV n=6</td>
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<td>112.7 (67.2-186.3)</td>
<td>88 (71.7-156.7)</td>
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<td>120.5 (70.9-170.1)</td>
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<td>12.4 (7.3-27.3)</td>
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<td>70.7 (36.9-186.6)</td>
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<td>12.7 (7.3-27.3)</td>
<td>10 (7.8-16.1)</td>
<td>10.7 (7.3-13.2)</td>
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<td>2.4 (1.5-7.2)</td>
<td>2.5 (1.5-2.6)</td>
<td>2.3 (1.5-3.3)</td>
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Median and ranges of the values of the parameters measured before and after high frequency stimulation of the GP. 

GP: ganglionic plexus, IAT: intra-atrial activation time, IIC: inhomogeneity index of conduction, LAT: local activation time, PV: pulmonary vein, RA: right atrium
**Intra-atrial activation time**

Electrograms with only remote activity (n=8) because of insufficient contact due to heart movement (n=4) precluding the detection of an activation front, were excluded. IAT was 34.4 ms (range 5.6-50.3 ms, n=7) at baseline for the RA and 105.8 ms (range 79.7-163.3 ms, n=6) for the RPV myocardium (difference p=0.001, Table 2). No significant differences in patients with paroxysmal or persistent AF were observed in IAT. At HFS with 1 mA, IAT increased or decreased and changes persisted after stimulation at higher output, with no return to baseline (absolute change vs baseline, 1 mA p=0.001, 2 mA p=0.401, 5 mA p=0.593, persistence of change, pre 1 mA vs pre 2 mA p=0.012, pre 1 mA vs pre 5 mA p=0.109). IAT increased in and decreased in 4 patients, independent of the mapping site (Figure 4). In patients using beta-blockers including sotalol IAT solely increased (p=0.001). The mean change of IAT in these patients was significant (p=0.028) and non-significant in patients without beta-blockers (p=0.499) (Figure 4). Other antiarrhythmic drugs did not influence IAT change (not shown). All patients with a previous PVI had beta-blockers and an increased IAT (p=0.049).

**Local activation time**

Figure 5 and 6 show activation maps recorded from RA and RPV myocardium before and after HFS. The pattern before and after stimulation is similar. At baseline, maximum LAT was slightly longer on the right atrium (median 12.2 ms, range 8.3-16.6 ms), but not significantly different from the RPV (median 11.2 ms, range 5.9-20.5 ms, p=0.836, Table 2). LAT was not significant different in patients with paroxysmal or persistent AF. After 1 mA stimulation LAT mainly increased, two patients had a decrease of LAT, both measured on the RA, and this change persisted after subsequent 2 and 5 mA HFS, with no return to baseline (absolute change pre-post, 1 mA p=0.003, 2 mA p=0.040, 5 mA p=0.180, persistence of change, pre 1mA vs pre 2 mA p=0.018, pre 1 mA vs pre 5 mA p=0.180, Figure 4). The changes in LAT did not correlate with the changes in IAT (p=0.851, ρ=0.058).

**Index of inhomogeneity of conduction**

Phase maps and corresponding histograms changed after 1 mA HFS (Figure 5 and 6). Median IIC was 2.2 (range 1.0-6.9) in the RA and 2.0 (range 1.2-4.9) in the RPV myocardium before stimulation (difference p=0.366, Table 2). IIC changed significantly after 1 mA stimulation and this change persisted at higher output, with no return to baseline (absolute change pre-post, 1 mA p=0.005, 2 mA p=0.518 5 mA p=0.655, persistence of change, pre 1 mA vs pre 2 mA p=0.018, pre 1 mA vs pre 5 mA p=0.109, Figure 4). Four patients showed decreased IIC, either on the RA or PV (Figure 4). In the other nine patients IIC increased. Changes in IIC did not correlate with changes in IAT (p=0.588, ρ=0.166) or LAT (p=0.184, ρ=0.393).
Figure 4. – Influence of high frequency stimulation on conduction parameters. Initial response to HFS (at 1 mA) on the IAT (A, B, C), LAT (D) and IIC (E). Gray dotted lines: changes of individual patients in milliseconds. The red line: median absolute normalized IAT (A). Patients on beta-blockers (B) and patients without beta-blockers (C) (p=0.001). The orange line reflects the median changes in IAT. (D) Changes in LAT. (E) Changes in IIC.

HFS: high frequency stimulation, IAT: intra-atrial activation time, IIC: inhomogeneity index of conduction, LAT: local activation time.
DISCUSSION

We observed a disparate response after HFS of the ARGP on the sinus node and atrial or PV myocardium in patients with AF. The decrease in sinus node frequency is commensurate with the output intensity of HFS, is short-lasting and quickly normalizes after cessation of stimulation. AV nodal conduction is unchanged following ARGP stimulation. After low-output HFS activation times either increase or decrease depending on the presence of beta-blocking drugs; both IAT and LAT are affected and activation times are increased in the majority of patients. However, the change in LAT and IIC do not cor-

Figure 5. – Activation and phase maps maps of sinus rhythm beats before and after high frequency stimulation of the right atrium. Activation maps and phase maps of the RA immediately before and after HFS. Left: activation maps. Numbers represent activation times in ms (isochrones 2 ms) from the first activation on the surface ECG (IAT). Below the activation map: unipolar electrograms at two different positions showing dv/dt max (red dot). Right: phase maps of the activation data. Numbers represent the phase times. The phase map displays conduction slowing or block of the local activation map. Below the phase maps: histograms and values for the median, absolute and IIC. HFS: high frequency stimulation, IAT: intra-atrial activation time, RA: right atrium.
relate with nor are proportional to the change in IAT. These HFS effects on the ARGP on conduction properties are both observed in the RA and the RPV myocardium. Contrary to changes induced by HFS in sinus rhythm frequency, changes in IAT and LAT persist during subsequent stimulation attempts.

**Effects of ganglionic plexus stimulation on the sinus node and AV-node**

Innervation of the sinus node is complex and its function is influenced by the effects of the cardiac GPs acting in concert with local interconnections and modulated by input from the extrinsic ANS.\textsuperscript{2,13,14} Earlier studies have shown that ablation of the ARGP attenuates the vagal response of the sinus node.\textsuperscript{13,14} Older patients showed an augmented response in the increase of the P-P interval, probably due to a decreased rate response to sympathetic neurotransmitters in the ageing heart.\textsuperscript{15} Additionally, the sinus node is more sensitive for and has a faster response to vagal activity, than the AV-node.\textsuperscript{16} In our

\begin{figure}[h]
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\caption{Activation and phase maps of sinus rhythm beats before and after high frequency stimulation of the right pulmonary vein. Legend as figure 5, but for the RPV myocardium. \textit{RPV: right pulmonary vein.}}
\end{figure}
study low-output HFS of the ARGP had no substantial response on the AV-node. At higher output however, there was capture of the atrium, and arrhythmia induction. Rapid atrial pacing can provoke a transient AV-block, activate the extrinsic ANS through reflex pathways via afferent nerves or through remote capture influence the atrial neural network and subsequently induce an AV-block.\textsuperscript{13,14}

**Ganglionic plexus stimulation and conduction properties of atrial and pulmonary vein myocardium**

Our observations demonstrate that GP stimulation goes beyond triggering AF, but also directly affects atrial conduction properties in patients with AF. Its exact influence on conduction in AF patients is unknown and data from animal models are conflicting. Stimulation of the parasympathetic system appears to decrease conduction velocity and the sympathetic system appears to increase conduction velocity, whereas in other studies there is little effect of ANS neurotransmitters on conduction.\textsuperscript{16–18} Whilst the exact mechanism cannot be ascertained in these human measurements, a role of ANS-mediated changes on conduction properties is supported by the patients on beta-adrenergic blocking agents who showed an increase in IAT, absent in patients without beta-blocking drugs. Therefore, whilst HFS of the GP triggers both branches of the ANS, a predominant parasympathetic response is observed. Additionally, other neurotransmitters, released by GP stimulation might change conduction characteristics.\textsuperscript{19} However, due to the nature of stimulation, afferent nerves could be stimulated and we could not exclude that a predominantly primary sympathetic response results in a reflex parasympathetic activation and vice versa. The change in LAT likely represents the effect of local small parasympathetic or sympathetic fibers, whilst the change IAT reflects the global atrial ANS response.\textsuperscript{20–23} From our study, it appears that RA and RPV myocardium have similar local responses to ARGP stimulation. Most of activation time changes persisted during subsequent stimulation attempts, whereas sinus rate rapidly normalized. Prolonged GP activation is not essential for the prolonged effects of the small nerve fibers on the atrial and RPV myocardium.\textsuperscript{20,21} This implicates a functional separation between GP and small nerve fibers probably related to the reuptake speed of neurotransmitters. Alternatively, short-duration stimuli can alter network function in the longer-term and may induce a form of neural memory.\textsuperscript{22} Otherwise, change in sinus node exit might influence IAT.\textsuperscript{18} However, (local) atrial activation and P-wave morphology remained unchanged. Only sinus complexes were included in our analysis. Furthermore, on the RA, closer to the sinus node, IAT changed ±4 ms and the RPV, farther from the sinus node, IAT changed ±14 ms. Hence, IAT increased proportionally to the distance to the first activation during sinus rhythm. Additionally, if IAT was influenced by a change in sinus node exit, changes in conduction properties were still observed locally in the RA and RPV, with an unchanged activation pattern. Thirdly, heart rate affects atrial conduction.\textsuperscript{23} However, decrease in
rate was ±3 beats per minute at 1 mA. More pronounced decreases in heart rate occurred at higher output stimulation but did not correspond to local conduction characteristics changes (p=0.529, ρ=0.192). In contrast, LAT either increased or decreased. Additionally, the change in sinus node rate was short-lasting, whilst the effects on conduction properties persisted.

Atrial and pulmonary vein ectopy and arrhythmias
No accurate differentiation between RA ectopy and RPV ectopy based on timing intervals and activation maps was possible. Therefore, we cannot demonstrate that extrasystoles or prolonged triggered firing originated from the PV, as observed in other studies.14 This could relate to continued anti-arrhythmic drug use of our patients or general anesthesia. Secondly, although higher output stimulation possibly increases the likelihood of PV ectopy, atrial myocardial capture during HFS may have suppressed PV ectopy.

Clinical implications
Patients in this study had symptomatic AF and remodeled atria, including electrical, structural but also autonomic remodeling.24 This autonomic remodeling includes a sympathetic hyperinnervation and might lead to a hyperactive state of the ANS.25 Disparate local effects of the ANS on the atrial neural network can introduce a heterogeneous change in conduction and influence the arrhythmogenic substrate for re-entry, particularly in the presence of fibrosis.8 Focal ablation of GPs might prevent trigger formation, but complete atrial denervation is difficult, due to the extensive neural network.2 Incomplete denervation however, might increase the heterogeneous effects on conduction of the atrium and subsequently the arrhythmogenic substrate.26 A prolongation of the R-R interval by >50% is a commonly used criteria of response HFS used for periprocedural testing of the GPs.27 The short-lasting HFS changes on the sinus node do not reflect the persistent ANS influence on the atrial myocardium as the >50% R-R prolongation of occurs mainly at higher output. Furthermore, due to the interrelation of the intrinsic cardiac ANS, ablation of the right GPs might reduce or eliminate any HFS response of the left GPs.13,14 The clinical limitation of this functional parameter of GP identification was confirmed by the finding that functional ablation of GPs results in a lower success rate in comparison with anatomical ablation of GPs.28

Limitations
Thoracoscopic surgery for AF was performed under general anesthesia. However, many studies on the function of the ANS have been performed under general anesthesia.6,13,14 Nevertheless, the response to HFS is likely more pronounced in awake patients. Medication was not discontinued before surgery, therefore all measurements might be influenced. However, in our study design, every patient was his own control. Nine
patients had a previous catheter ablation for AF, which might have damaged the endocardial innervation of the atrium. Still, all these patients had a sinus node response to GP stimulation, reflecting (restored) atrial innervation, or at least an intact pathway between ARGP and sinus node. Furthermore, if PVI had affected the nerve fibers near the PV, the RA would presumably still remain unaffected. No significant differences were observed in IAT and LAT in patients with or without an earlier catheter ablation. At high output ARGP stimulation, arrhythmias were induced. Therefore, at higher output stimulation few measurements and no data from the other GPs were available for analysis. Additionally, an effect on the inferior right GP could not be excluded as the ARGP was tested first. Right GP and PV ablation was performed before left GP testing, its effects on left GP function could not be excluded. Indeed, a vagal response of left GP stimulation was infrequent (data not shown), presumably due to disconnection of left and right GPs. However, the effects of the ANS on the atrial neural network and atrial conduction characteristics are likely similar in the other GPs, but may be contained to different regions of the atrium.20

CONCLUSIONS

In patients with AF, the sinus-node responses with a short-lasting progressive decrease in frequency at increasing output of ARGP stimulation, most likely due to a short lasting parasympathetic response. Atrial and pulmonary vein myocardial conduction times and inhomogeneity of conduction are changed by HFS, presumably mediated by either a parasympathetic or sympathetic response. Patients with beta-blocking drugs predominantly showed an increase of IAT. These changes persist during subsequent stimulation attempts. Our study supports the notion that GP ablation may contribute to decrease the arrhythmogenic substrate for AF not only by prevention of triggered activity, but by modulation of atrial conduction.
REFERENCES

Chapter 4


