Effect of acute atrial fibrillation on phasic coronary blood flow pattern and flow reserve in humans


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Aims To assess the effect of experimentally induced atrial fibrillation on coronary flow in humans.

Methods and Results In 16 patients (10 men, mean age 43 ± 13 years) with normal coronary vessels, baseline and hyperaemic blood pressure and Doppler phasic coronary flow velocity were measured, using a 0.014 inch intra-coronary Doppler flow wire, during sinus rhythm, experimentally induced atrial fibrillation, and right atrial pacing at a similar heart rate to that during atrial fibrillation. Coronary flow velocity integral per minute increased significantly during both right atrial pacing and atrial fibrillation compared to sinus rhythm, but during right atrial pacing the increase was greater (85 ± 43% vs 52 ± 25%, P<0.001). This difference persisted even after correction for the product of heart rate and blood pressure (1.15 ± 0.51 vs 0.97 ± 0.46, respectively, P<0.02). In a further 12 paced patients (seven men, mean age 54 ± 10 years) with complete atrioventricular block the induction of atrial fibrillation (atrial fibrillation with regular RR interval) caused no significant changes in coronary flow velocity variables.

Conclusions Acute atrial fibrillation in humans causes an increase in coronary flow that is, however, insufficient to compensate for the augmented myocardial oxygen demand, mainly because of the irregularity in the ventricular rhythm that exists during atrial fibrillation.


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Key Words: Atrial fibrillation, coronary flow, vasodilation.

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Introduction

Acute atrial fibrillation is characterized by a lack of atrial contraction and an accelerated and irregular cardiac rhythm, conditions that could influence coronary circulation.

Although there are several studies that have investigated the effect of acute atrial fibrillation on coronary flow in animals, there are no data on the effects of atrial fibrillation on humans, mainly because of the fact that the methods used until now for the assessment of coronary flow are difficult or impossible to apply to human subjects[1–6].

Recently developed catheter-tipped Doppler flowmetry, if used in combination with spectral analysis of the Doppler signal, provides an accurate measure of coronary flow dynamics in the cardiac catheterization laboratory[7,8]. This method also has the advantage over previous techniques that it is able to determine the immediate and instantaneous blood flow changes. This could be beneficial in the case of atrial fibrillation.

In this study Doppler flowmetry was used to investigate, for first time, the effects of experimentally induced atrial fibrillation on the phasic coronary blood pattern and flow reserve in humans. To assess the contribution of accelerated heart rate to these effects, we compared the effects of atrial fibrillation with those of right atrial pacing at a similar heart rate.

Furthermore, in order to assess the importance of atrial contraction itself, we estimated the coronary flow changes when atrial fibrillation was induced in a group of patients with dual chamber pacemakers for complete atrioventricular block (atrioventricular sequence vs atrial fibrillation with the same, regular, paced ventricular rate).


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Methods

Patient population

Patients undergoing elective coronary arteriography for routine clinical indications were considered for study if angiography revealed normal coronary arteries and there was no evidence of left ventricular or valvular dysfunction. Exclusion criteria were: a baseline rhythm of atrial fibrillation, atrial flutter or atrial tachycardia; failure to induce atrial fibrillation by pacing; or failure to place a coronary Doppler catheter.

Among the 450 patients screened, 30 patients satisfied all criteria. Of those, 18 unpaced patients (12 men and six women, mean age 45 ± 12 years) made up Group I and the remaining 12 (seven men, five women, mean age 54 ± 10 years), who were paced with dual chamber pacemakers for complete atrioventricular block, made up Group II. All patients gave written, informed consent; the study was approved by the hospital’s Ethics Committee.

Cardiac catheterization and angiography

After sedation with 5 mg diazepam administered orally, patients were brought to the catheterization laboratory in a fasting state. Medications with cardiac or vasoactive properties (i.e. nitrates, calcium channel or β-adrenergic receptor blocking agents and arterial vasodilators) were discontinued at least 48 h before the procedure.

Selective coronary angiography and left ventriculography were carried out by the Judkins technique using a 6-F coronary angiography catheter and the angiograms were immediately analysed visually by two observers to exclude patients with coronary stenosis (≥30%).

All patients received 10 000 IU of intravenous heparin before angiography and 5000 IU hourly during the procedure.

Coronary flow velocity measurements

Immediately following coronary angiography a 0·014 inch (0·036 cm) 15 MHz Doppler guide wire (Flowire, Cardiometrics, Mountain View, California, U.S.A.) was advanced through a coronary catheter engaged in the left main and positioned in the left anterior descending coronary artery (n=10) or left circumflex artery (n=6). Intracoronary nitroglycerin (200 mg) was administered at the start and every 30 min during the procedure to prevent catheter-induced coronary artery spasm and to avoid changes in coronary artery diameters.

Frequency analysis of the Doppler signals was carried out in real time by fast Fourier transform using a velocimeter (Flomap, Cardiometrics, Mountain View, California). Once baseline flow velocity data had been obtained, a bolus injection of 18 µg intracoronary adenosine was given to obtain data during hyperaemia. To confirm that maximal hyperaemia had been achieved, coronary blood flow velocity was recorded during administration of an additional large dose of adenosine (22 µg).

Five minutes after the injection of contrast medium and intracoronary nitroglycerin, phasic coronary flow patterns, along with simultaneous ECG and blood pressure waveforms, were displayed and recorded on videotape. Doppler velocity signals were analysed using a special computer system. The envelope of the flow-velocity signal at rest and at maximal hyperaemia was traced by hand and the systolic and diastolic coronary flow velocity integrals and their sum were measured. The coronary flow velocity integrals per minute, defined as the product of coronary flow velocity integrals and heart rate was then calculated. The averaged values over three to five consecutive beats during sinus rhythm or right atrial pacing and at least 10 beats during atrial fibrillation were used for the quantitative analysis.

Coronary flow reserve was determined as the ratio of the coronary flow velocity integrals/minute after adenosine to the coronary flow velocity integrals/minute at baseline. An index of coronary vascular resistance was calculated as the quotient of mean blood pressure (in mmHg) and coronary flow velocity integrals/minute, expressed in cm³·min⁻¹mmHg⁻¹.

In order to control the changes in coronary flow velocity integrals per minute for changes in metabolic stress an index was calculated as the ratio of the percent change in coronary flow velocity integrals per minute to the percent change in the rate-pressure product during right atrial pacing and atrial fibrillation³⁴.

Experimental protocols

Effect of acute atrial fibrillation and right atrial pacing on haemodynamic and coronary flow velocity variables

For patients in Group I both baseline and hyperaemia pressure and flow measurements were obtained under each of the following conditions: (a) sinus rhythm, (b) atrial fibrillation and (c) right atrial pacing at a rate similar to the average ventricular rate during atrial fibrillation. Each rhythm was maintained for at least 5 min or until all values were stable. Between the atrial fibrillation and right atrial pacing protocols the time necessary for the haemodynamic parameters to return to baseline was allowed (4 min on average).

Induction of atrial fibrillation

Atrial fibrillation was induced by bursts of atrial pacing via a 6F quadripolar electrode, which was positioned in the upper right atrium. If atrial fibrillation did not persist spontaneously for at least 5 min (n=12) repeated electrical stimulation was given to produce stable atrial fibrillation.

Experimental data have shown that the atrial and ventricular rates and the changes in coronary blood flow responses during electrically maintained atrial fibrillation closely mimic those seen during spontaneous atrial fibrillation¹². After the atrial fibrillation
Table 1  Coronary flow velocity variables at rest (R) and hyperaemia (H) during sinus rhythm, atrial fibrillation and atrial tachycardia

<table>
<thead>
<tr>
<th></th>
<th>Sinus rhythm</th>
<th>Atrial fibrillation</th>
<th>Atrial tachycardia</th>
</tr>
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<tbody>
<tr>
<td>CFVI/min</td>
<td>R 787 ± 370</td>
<td>1208 ± 541*</td>
<td>1466 ± 694**†</td>
</tr>
<tr>
<td></td>
<td>H 2935 ± 1253</td>
<td>2610 ± 1428*</td>
<td>3308 ± 2040†</td>
</tr>
<tr>
<td></td>
<td>R 144 ± 56</td>
<td>235 ± 107*</td>
<td>257 ± 111*</td>
</tr>
<tr>
<td>Systolic CFVI/min</td>
<td>H 622 ± 228</td>
<td>685 ± 392</td>
<td>706 ± 330</td>
</tr>
<tr>
<td></td>
<td>R 643 ± 329</td>
<td>944 ± 485*</td>
<td>1089 ± 648*†</td>
</tr>
<tr>
<td>Diastolic CFVI/min</td>
<td>H 2313 ± 1136</td>
<td>2054 ± 1280*</td>
<td>2611 ± 1800†</td>
</tr>
<tr>
<td></td>
<td>R 0·14 ± 0·04</td>
<td>0·09 ± 0·038*</td>
<td>0·08 ± 0·039†</td>
</tr>
<tr>
<td>CVR index</td>
<td>H 0·03 ± 0·02</td>
<td>0·05 ± 0·025*</td>
<td>0·03 ± 0·02†</td>
</tr>
<tr>
<td></td>
<td>3·7 ± 0·9</td>
<td>2·15 ± 0·5*</td>
<td>2·39 ± 0·5*†</td>
</tr>
</tbody>
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*Significant difference compared to sinus rhythm.
Significant difference compared to atrial fibrillation.
CFVI = coronary flow velocity integral in cm; CVR = coronary vascular resistance; CFR = coronary flow reserve.

measurements were completed the patients were left to return to sinus rhythm. If this did not occur spontaneously within 5 min chemical cardioversion was applied and the patient was excluded from the study.

Effect of atrial contraction on haemodynamic and coronary flow velocity variables
All the patients in Group II were initially paced with an atroventricular sequential pacing rhythm at a rate close to the mean heart rate during atrial fibrillation in Group I (115 beats . min⁻¹). Then atrial fibrillation was induced and sustained according to the protocol described above and the pacing mode was changed to VVI. Rest and hyperaemic pressure and flow measurements were obtained during each of the above conditions, in accordance with the protocol. The left anterior descending artery was used for measurements in seven patients and the left circumflex artery in five.

Statistical analysis
Continuous data are summarized as mean ± SD. Repeated measures analysis of variance with two within factors was used to examine differences in coronary flow velocity integrals per minute, coronary vascular resistance (and various other measures) among the three states (sinus rhythm, atrial fibrillation, right atrial pacing) and the two phases (rest, hyperaemia). Post-hoc tests with Bonferroni adjustment were performed to pinpoint differences. Resting and hyperaemic percent changes (Δ) of coronary flow velocity integrals per minute etc, from sinus rhythm to atrial fibrillation and from sinus rhythm to right atrial pacing were compared with the paired t-test. The effect of Aheart rate and Δblood pressure on Δcoronary flow velocity integrals per minute was examined with simple linear regression. The dependence of the current, preceding and pre-preceding RR on coronary flow velocity integrals was assessed on a per patient basis, by means of a step-wise linear regression model. The level of statistical significance was set at 5%.

Results
Two patients from Group I did not spontaneously revert to sinus rhythm from atrial fibrillation and were excluded from the study. They were given amiodarone intravenously and sinus rhythm was restored after 3 and 4 h, respectively. The 16 remaining patients completed the protocol successfully and without complications (10 men, mean age 43 ± 13). The mean heart rate increased significantly during atrial fibrillation compared to sinus rhythm (from 69 ± 12 to 117 ± 22 beats . min⁻¹, P<0·001). The mean blood pressure decreased significantly during atrial fibrillation (from 95 ± 23 to 90 ± 16 mmHg, P<0·01), while it increased non-significantly during right atrial pacing (to 98 ± 16 mmHg). The product of mean blood pressure and heart rate (rate–pressure product) increased during both atrial fibrillation and right atrial pacing, but more so during right atrial pacing (76·1 ± 20% vs 63·5 ± 16·3%, P<0·001) and thus the rate–pressure product during right atrial pacing was significantly greater than during atrial fibrillation (11 556 ± 3479 vs 10 732 ± 3159 beats . min⁻¹ × mmHg, P<0·01).

Effect of atrial fibrillation and right atrial pacing on coronary flow velocity integrals/minute (Table 1)
Coronary flow velocity integrals per minute increased significantly during both atrial fibrillation and right atrial pacing compared to sinus rhythm (P<0·001 for both). The increase, however, was greater during right atrial
pacing than atrial fibrillation (percent changes from sinus rhythm values 85 ± 43 vs 52 ± 25, respectively, \(P<0.001\)). The increase in diastolic coronary flow velocity integrals per minute compared to sinus rhythm was significantly greater during right atrial pacing than atrial fibrillation (percent increase 86 ± 44 vs 49 ± 23, \(P<0.001\)), whereas for the systolic coronary flow velocity integrals per minute the increase did not differ significantly (84 ± 65 vs 65 ± 51, \(P=\text{ns}\)).

The magnitude of percent increases in coronary flow velocity integrals per minute during right atrial pacing had a significant positive correlation with the magnitude of percent changes in heart rate (r=0.558, \(P=0.02\)), while the magnitude of percent increases in coronary flow velocity integrals per minute during atrial fibrillation had no such correlation (r=0.083, \(P=\text{ns}\)). The magnitude of the percent increase in coronary flow velocity integrals per minute did not correlate significantly with the magnitude of percent changes in blood pressure during either right atrial pacing or atrial fibrillation (r=0.07 and r=0.198, \(P=\text{ns}\), respectively) (Fig. 1).

The difference in coronary flow velocity integrals per minute between right atrial pacing and atrial fibrillation was significant even after control for changes in metabolic stress: the ratio of the percent change in coronary flow velocity integrals per minute to the percent change in the rate–pressure product was greater during right atrial pacing than during atrial fibrillation (1.15 ± 0.51 vs 0.87 ± 0.46, \(P<0.02\)).

The coronary vascular resistance index decreased significantly during both right atrial pacing and atrial fibrillation compared to sinus rhythm, but the decrease was greater during right atrial pacing (−41 ± 15% vs −35.7 ± 11% \(P<0.04\)) and thus this index had a lower mean value during right atrial pacing than during atrial fibrillation (\(P<0.01\)).

**Figure 1** Scatter-plots of percent changes in coronary flow velocity integral per minute (ΔCFVI/minute) from sinus rhythm to atrial fibrillation (upper) and paced atrial tachycardia (lower), with percent changes in heart rate (ΔHR) and blood pressure (ΔBP). There was a significant positive correlation only between ΔCFVI/minute and ΔHR (r=0.558, \(P=0.02\)).
Maximal coronary response to adenosine

The coronary flow velocity integrals per minute increased significantly under adenosine, during sinus rhythm and during both atrial fibrillation and right atrial pacing (P<0.01 for all). At maximal hyperaemia the highest coronary flow velocity integrals per minute was seen during right atrial pacing, even though this was not significantly greater than during sinus rhythm, while during atrial fibrillation the coronary flow velocity integrals per minute only reached levels considerably lower than in both other conditions (P<0.01 for both). Coronary flow reserve measured during atrial fibrillation was significantly lower than during right atrial pacing (P<0.01) and was lower than during sinus rhythm under both rhythms (P<0.001 for both).

The coronary vascular resistance index was reduced significantly by adenosine both during sinus rhythm and during atrial fibrillation and right atrial pacing (P<0.01 for all). However, the decrease during sinus rhythm was greater than during right atrial pacing and atrial fibrillation (−73 ± 8%, −54 ± 13%, −47 ± 10%, respectively, P<0.01 for both), while the decrease during right atrial pacing was marginally greater than during atrial fibrillation (P=0.059). As a result, at maximal hyperaemia the coronary vascular resistance index during right atrial pacing reached the same levels as during sinus rhythm, whereas the coronary vascular resistance index during atrial fibrillation was considerably higher (P<0.01).

Beat-to-beat relation between coronary flow velocity integrals and RR interval in atrial fibrillation

In all patients there was beat-to-beat variability for both RR interval and coronary flow velocity integrals. Significant correlations of varying strength (r from 0.44 to 0.94) between current RR and coronary flow velocity integrals were observed in all patients (Fig. 2). Preceding RR interval was a significant independent covariate in only two of the patients, while pre-preceding RR interval did not contribute significantly to the overall correlation in any of the patients.

Effect of acute atrial fibrillation on haemodynamic and coronary flow variables in paced patients with complete atrioventricular block

In patients of Group II there was no significant reduction in blood pressure (from 101 ± 12 to 97 ± 11 mmHg), coronary flow velocity integrals per minute (from 1091 ± 333 to 888 ± 307 cm·min⁻¹) or coronary vascular resistance index (0.12 ± 0.02 vs 0.12 ± 0.03) after the induction of atrial fibrillation.

Adenosine caused a significant increase in coronary flow velocity integrals per minute, during both atrioventricular pacing rhythm and atrial fibrillation (P<0.01 for both), reaching similar maximum levels in both cases.
animal studies[1–6] whose findings have been conflicting. Fibrillation on coronary flow have been experimental
precisely, the induction of atrial fibrillation in our patients also applies to conscious humans. More pre-
absolute values. Changes in coronary flow resistance, rather than
mediators of this vasoconstriction[3–6]. Coronary alpha adrenoreceptors have been identified as
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An activation of the sympathetic nervous system and coronary alpha adrenoreceptors have been identified as mediators of this vasoconstriction[3–6].

Effect of acute atrial fibrillation on coronary circulation in humans
In this study, coronary flow dynamics were assessed by analysis of the phasic coronary flow velocity pattern obtained with catheter-tipped Doppler flowmetry and fast Fourier spectral analysis of Doppler signals. In that case, volumetric flow rate corresponds to the product of total flow velocity integral times heart rate times cross-sectional area at the site of the Doppler crystal. However, since we could not measure the cross-sectional area precisely, we concentrated on the changes, rather than the absolute values of coronary flow, keeping the vessel diameter constant using intracoronary nitro-
glycerin. Previous studies have proved that in this way the diameter of epicardial vessels remains constant even under the maximal coronary flow induced by adenosine[12,13]. For the same reason, we focused on changes in coronary flow resistance, rather than absolute values.
Our results showed that the conclusion regarding animals also applies to conscious humans. More precisely, the induction of atrial fibrillation in our patients caused an increase in coronary flow, but this increase was less than that caused by right atrial pacing at the same mean heart rate. Of course, at first glance this difference could be explained by the fact that the increase in myocardial oxygen demand, as indicated by the rate–pressure product, is smaller during atrial fibrillation than during atrial fibrillation. However, the fact that the difference in percentage increase in coronary flow between atrial fibrillation and right atrial pacing remains even after correction for the rate–pressure product suggests that there are some other factors which prevent the coronary flow from increasing as much during acute atrial fibrillation as it does during right atrial pacing. Moreover, the fact that the increase in coronary flow following the induction of atrial fibrillation is independent of the changes in heart rate and blood pressure suggests that, in humans as in animals, this increase is not proportional to the augmented myocardial oxygen demand, further reinforcing the above hypothesis.

In addition, our study showed that the induction of atrial fibrillation in humans, as in animals, causes a reduction in coronary flow reserve, more than could be explained by the increase in heart rate, while there is also a reduction in coronary vascular resistance. The latter finding suggests initially that the coronary vessels dilate in response to the accelerated heart rate and to the increase in metabolic demand that occurs in atrial fibrillation.
However, there are two factors suggesting that during acute atrial fibrillation in humans, as in animals, there is some degree of coronary vasoconstriction in addition to vasodilation: first, the reduction in coronary vascular resistance is smaller during acute atrial fibrillation than during right atrial pacing at a similar heart rate; and second, at maximal dilation by adenosine when metabolic regulation is blunted, the coronary vascular resistance is greater during atrial fibrillation than during either sinus rhythm or right atrial pacing.
Our study also provides new data concerning the effect of acute atrial fibrillation on the coronary circulation. More precisely, it demonstrates that there is a beat-to-beat variability in coronary flow during atrial fibrillation and shows that during acute atrial fibrillation it is mainly the diastolic coronary flow that is affected.

Effect of irregularity of ventricular rhythm on coronary flow
The most important new finding of this study is that the main factor that impedes the increase in coronary flow and causes the exaggerated reduction in coronary flow reserve during acute atrial fibrillation is the irregularity of the ventricular rhythm. Our results indicate that the loss of atrial contraction alone, as seen following the induction of atrial fibrillation in patients with complete atrioventricular block under pacing (induction of atrial fibrillation with regular paced ventricular rhythm and a heart rate similar to that of the earlier atrioventricular
sequential pacing rhythm), has only a small effect on coronary flow and tends to increase the coronary flow reserve.

The mechanism through which an irregular ventricular rhythm exercises these ‘negative’ effects is still unclear. Previous studies have shown that an irregular sequence of RR intervals alone may have deleterious haemodynamic consequences\cite{10,11}. However, given that, according to our results, the changes in coronary flow caused by atrial fibrillation are not correlated with changes in blood pressure, the possibility that these haemodynamic consequences affect coronary flow, at least directly, seems remote. Rather, the fact that the loss of atrial contraction does not affect the coronary vascular resistance suggests that the irregular rhythm is solely responsible for the coronary vasoconstriction that acts in opposition to dilation during acute atrial fibrillation, thus impeding coronary flow and reducing coronary flow reserve. However, the precise mechanism through which this irregularity leads to coronary vasoconstriction in humans remains to be investigated.

Of course, we cannot rule out the possibility that the rhythm irregularity also acts directly to inhibit coronary flow. According to our results, the beat-to-beat coronary flow is mainly correlated with the current RR interval. However, it is possible that the effect of short RR intervals may be entirely negated by the increase in coronary flow that accompanies longer RR intervals and thus the coronary flow per minute may be less than during atrial tachycardia at the same heart rate. Furthermore, short RR intervals could be followed by systoles that generate insufficient pressure to open the aortic valve. In this case there is a significant inhibition of coronary inflow and a reduction in coronary flow, regardless of the subsequent RR interval (see Fig. 3). Frequent such systoles may have a significant negative effect on the coronary flow per minute. The fact that, in at least two patients, the preceding RR interval appeared to affect the beat-to-beat flow may be related with this hypothesis.

**Study limitations**

According to our results, coronary flow does not correlate with changes in blood pressure. It is possible, however, that coronary flow and coronary flow reserve might be altered significantly by changes in blood pressure of greater magnitude, particularly if these changes were to exceed the bounds of coronary autoregulation. Such a fluctuation in blood pressure in humans, however, would be extreme.

We used atrial pacing to assess the effects of increases in heart rate. However, it is important to note that this method is not physiological because, in most instances, increases in heart rate occur with other dynamic changes...
in mean aortic pressure, left ventricular systolic and diastolic function and loading conditions.

Our results were observed during an acute haemodynamic study and may not apply to more long-term conditions in which adaptive mechanisms may reduce these effects. Also, our patients had good left ventricular function and thus we do not know whether our findings apply to patients with more severely impaired left ventricular systolic or diastolic function.

Clinical implications — Conclusions

This study provides certain new data that may prove useful, both for the understanding of the clinical consequences of atrial fibrillation in humans and for its treatment. The fact that during acute atrial fibrillation the coronary flow does not increase in proportion to the needs of the myocardium, especially in view of the severe reduction in coronary flow reserve, may have deleterious consequences in patients with coronary artery disease, causing or worsening myocardial ischaemia to a greater degree than would an elevated heart rate alone.

Even in patients without epicardial stenoses in the coronary vessels, the induction of atrial fibrillation could have implications for the development of subendocardial ischaemia, especially if coronary flow and coronary flow reserve are already compromised, and could thus contribute to chronic left ventricular dysfunction. The fact that atrial fibrillation mainly influences diastolic coronary flow is a further exacerbating factor, given that perfusion of the subendocardium occurs during diastole.

As far as the treatment of atrial fibrillation is concerned, the finding that it is mainly the irregularity of the ventricular rhythm that is responsible for these negative effects on the coronary circulation may have practical significance. On this basis, it is possible that regularization of ventricular rhythm using the ablate-and-pace strategy could be appropriate therapy for patients with paroxysmal atrial fibrillation, especially if they have coronary artery disease. Previous studies, showing that in those patients this treatment leads to an improvement in the quality of life and exercise capacity, support such an approach. Furthermore, if our findings were shown to apply also in the case of longer periods of atrial fibrillation, this would reinforce the view that catheter ablation of the atrioventricular junction and implantation of a rate–response pacemaker represents a more appropriate therapeutic modeling in persistent atrial fibrillation than treatment targeting rate control.

References