Calcium channel blockers improve exercise capacity and reduce N-terminal Pro-B-type natriuretic peptide levels compared with beta-blockers in patients with permanent atrial fibrillation

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Received 24 February 2013; revised 23 August 2013; accepted 23 September 2013; online publish-ahead-of-print 17 October 2013

Aims
Rate control of atrial fibrillation (AF) has become a main treatment modality, but we need more knowledge regarding the different drugs used for this purpose. In this study, we aimed to compare the effect of four common rate-reducing drugs on exercise capacity and levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with permanent AF.

Methods and results
We included 60 patients (mean age 71 ± 9 years, 18 women) with permanent AF and normal left ventricular function in a randomized, cross-over, investigator-blind study. Diltiazem 360 mg, verapamil 240 mg, metoprolol 100 mg, and carvedilol 25 mg were administered o.d. for 3 weeks. At baseline and on the last day of each treatment period, the patients underwent a maximal cardiopulmonary exercise test and blood samples were obtained at rest and at peak exercise. The exercise capacity (peak VO2) was significantly lower during treatment with metoprolol and carvedilol compared with baseline (no treatment) or treatment with diltiazem and verapamil (P < 0.001 for all). Compared with baseline, treatment with diltiazem and verapamil significantly reduced the NT-proBNP levels both at rest and at peak exercise, whereas treatment with metoprolol and carvedilol increased the levels (P < 0.05 for all).

Conclusion
Rate-reducing treatment with diltiazem or verapamil preserved exercise capacity and reduced levels of NT-proBNP compared with baseline, whereas treatment with metoprolol or carvedilol reduced the exercise capacity and increased levels of NT-proBNP.

Keywords
Atrial fibrillation • Rate control • Exercise capacity • Natriuretic peptides

Introduction
Many patients with permanent atrial fibrillation (AF) experience some degree of impaired exercise capacity.1–3 The exact mechanisms behind the reduced exercise capacity are not clear, but probable contributing factors include rapid ventricular rate, irregular rate, and absence of atrial systole.4

Natriuretic peptide levels are elevated in patients with AF, even when left ventricular systolic function is preserved.5 It has been shown that AF patients with diastolic dysfunction exhibit higher levels of natriuretic peptides than those with normal diastolic function6,7 and that patients with permanent AF tend to have higher levels than patients with paroxysmal AF.8 It has also been shown that AF patients have an increased exercise-induced peptide release compared with healthy control subjects.9,10 In sinus rhythm, both the resting levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the increase in response to exercise are related to age. In young and fit individuals, there may be no significant increase...
in NT-proBNP levels after dynamic exercise, whereas in elderly sedentary individuals, a significant rise in NT-proBNP levels has been found. Elevated levels of natriuretic peptides and/or increased levels in response to exercise have been found to predict occurrence of AF in subjects from the general population, and in post-operative heart surgery patients.

According to current guidelines, beta-blockers or non-dihydropyridine calcium channel blockers alone are the first choice drugs for rate control in AF. Previous studies have shown that treatment with beta-blockers tends to reduce exercise capacity, whereas treatment with calcium blockers may preserve or even improve exercise tolerance. However, few studies have compared beta-blockers and calcium channel blockers with once daily dosage without simultaneous treatment with digitalis, and few women have been included in previous studies.

The aim of this study was to compare exercise capacity and levels of NT-proBNP at rest and during exercise with four different rate-reducing drug treatments, in both men and women with permanent AF.

Methods

Study design and population

The present study was a pre-defined substudy of the RaTTe control in Atrial Fibrillation (RATAF) study, a prospective, randomized, investigator-blinded cross-over study designed to compare four different once daily drug regimens for rate control in permanent AF. The effects on resting and 24-h heart rate have been published previously.

In short, we included patients with permanent AF, >18 years of age, without heart failure (clinical or radiological signs of congestive heart failure and/or reduced ejection fraction) or ischaemic heart disease. Patients who were treated with rate-reducing drugs at the time of inclusion had a 2-week wash-out period before baseline evaluations were performed. The patients on digitalis were instructed to discontinue this drug, and did not start the wash-out period until digitalis was undetectable in serum. After baseline evaluations, the participants received all of the following drug regimens for at least 3 weeks in a randomized cross-over design: (i) metoprolol slow-release tablets 100 mg o.d. (AstraZeneca), (ii) diltiazem sustained release capsules 360 mg o.d. (Pfizer), (iii) verapamil modified release tablets 240 mg o.d. (Abbott), and (iv) carvedilol immediate release tablets 25 mg o.d (Roche/HEXAL). All study drugs were taken in the morning, shortly after getting up. There was no wash-out period between treatments, but each treatment regimen started with 3 days on half dosage of the drug to allow for wash-out of the previous treatment. The investigator was blinded with regard to study drug sequence, whereas for practical reasons the participants were aware of the drug assigned. Compliance with the drug regimen was assessed by pill count after each drug period. Before starting the first treatment, and on the last day of each of the four treatment periods, the patients underwent a maximal exercise test with respiratory gas analysis and blood sampling for analysis of NT-proBNP levels.

The RATAF study was approved by the Regional Ethics Committee and the Norwegian Medicines Agency, and was registered at www.clinicaltrials.gov (NCT00313157). In accordance with the Helsinki Declaration, each patient signed informed consent before any study-related procedures were performed.

Examinations

At baseline, all the participants were assessed by physical examination and routine blood tests. Echocardiographic measurements were averaged over five cardiac cycles, if possible in a phase with close to normal heart rate and relatively regular RR intervals. Pulmonary function was assessed by spirometry and diffusing capacity.

The cardio pulmonary exercise tests were performed on a bicycle ergometer (Ergoline 800, Bitz, Germany) in accordance with ACC/AHA guidelines. The expected peak oxygen uptake (VO2) was calculated for each patient based on age, gender, and weight. A protocol was then chosen for each patient with the aim of achieving exercise duration of 8–12 min. All protocols included a 4 min warm-up phase with low load pedalling before the work load was increased in a ramp fashion by 10, 20, or 30 W every minute depending on the assigned protocol. Oxygen consumption, carbon dioxide production, and respiratory exchange ratios were measured continuously during exercise by an automated gas exchange system (Vmax Spectra, SensorMedics, CA, USA). Patients were encouraged to maintain a pedalling rate of at least 60/min and continue until exhaustion. The patients’ subjective perception of exertion was evaluated using the Borg 6–20 point scale. The tests were terminated when the patients could not continue due to dyspnoea, fatigue, or pain, or for safety reasons in case of fall in systolic blood pressure, sustained heart rate > 240 b.p.m. or ventricular arrhythmias. After completion of the test, there was a 15 min recovery phase consisting of 5 min sitting on the bicycle followed by 10 min relaxing in the supine position. All exercise tests were performed between 09.00 and 13.00 on regular weekdays, and preferably at the same time of the day for each patient. Each patient was tested with the same protocol every time. A physician and a technician blinded to the patients’ treatment were present during all tests.

Venous blood samples for the measurement of NT-proBNP levels were obtained after 30 min of rest in the supine position for pre-test concentrations, at peak exercise, and 15 min after exercise termination. Blood samples were stored on ice until they were centrifuged for 15 min at 2000 g at 4°C, and serum was then frozen at −70°C. The samples were later analysed in one batch using the Elecsys proBNP sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Basel, Switzerland). The calculated coefficient of variation was 2.3–2.5% depending on NT-proBNP levels.

Statistical analyses

The sample size for the overall RATAF study was based on assessment of the primary outcome (ventricular rate) to obtain power of 80% with type 1 error of 5%. Assessment of adequate sample size for our secondary outcomes, peak VO2, and levels of NT-proBNP, reported in this study was based on the same assumptions for power and significance level. Average standard deviations (SD) were 3.38 mL/kg/min for peak VO2 and 370 pg/mL for levels of NT-proBNP. In the de facto power analysis, we supposed that a difference in peak VO2 of 2 mL/kg/min (≈10%) and a difference in NT-proBNP levels of 150 pg/mL (≈15%), would be clinically relevant. We are not aware of any published data on clinically relevant differences in peak VO2 or NT-proBNP levels in AF patients. In chronic heart failure patients, changes in peak VO2 as small as 6% have been found to be associated with differences in outcomes (time to all-cause mortality or all-cause hospitalization). For NT-proBNP levels in this population, we do not have data on the clinical importance of changes. However, in stable heart failure patients the week-to-week variation has been found to be small, 8% and we therefore supposed that a 15% change would be of interest. Adequate sample size based on paired sample t-test was then estimated to 24 and 49 pairs for peak VO2 and levels of NT-proBNP, respectively.

Categorical variables are given as frequencies (%) and continuous variables are given as means ± SD for normally distributed variables, whereas median and ranges are given for variables not normally distributed. A two-sided P-value of <0.05 was considered statistically
significant. Bivariate correlations were assessed using Pearson’s correlation coefficients, with logarithmic transformation of variables not normally distributed. The different treatment regimens (included baseline with no drug intervention) were compared using a linear mixed model for repeated measurements with a random intercept for each patient. Possible carry-over effects were assessed with an interaction term between treatment regimens and time periods. If this interaction term was not statistically significant, it was removed from the final statistical model. P-values from multiple comparisons between the treatments were Bonferroni adjusted. All data management and analysis were performed using the SPSS 18.0 software (SPSS, IL, USA).

Results

Randomization took place from May 2006 to June 2010. In total, 80 patients with permanent AF were included in the study, of which 60 patients (42 men and 18 women) completed all four treatment periods and performed five cardio pulmonary exercise tests (including baseline with no rate-reducing drug). The overall compliance with the study drugs was 97.4% as measured by pill count after each treatment period. There were no carry-over effects between treatments and the interaction term between treatment regimens and time periods was thus omitted in all linear mixed models. Figure 1 shows a flow chart of the inclusion process. Baseline characteristics are presented in Table 1.

As previously reported, the mean resting ventricular rates (± SD) were baseline (no treatment) 95 ± 15 b.p.m., diltiazem 77 ± 13 b.p.m., verapamil 82 ± 16 b.p.m., metoprolol 81 ± 15 b.p.m., and carvedilol 78 ± 11 b.p.m. (P < 0.001 for all treatments compared with baseline, P = 0.041 for the difference between diltiazem and verapamil). At baseline, with no rate-reducing drug, 51 (85%) of the patients had a resting ventricular rate <110 b.p.m. The mean resting systolic blood pressure was 141 (± 18) mmHg at baseline and decreased with all treatments (P ≤ 0.01 for all), but there were no significant differences between the drugs.

Exercise capacity

The median duration of all the exercise tests was 8 min and 28 s. The median Borg score at peak exercise was 19 (15–20). Only one (0.3%) of the 300 exercise tests performed were terminated before reaching Borg 17 and thus classified as submaximal. Median respiratory quotient was 1.17 (0.7–1.4), also indicating maximal effort.

The mean ventricular heart rate (± SD) at maximum exercise was 190 ± 26 b.p.m. at baseline (no treatment), 158 ± 28 b.p.m. during treatment with diltiazem, 158 ± 29 b.p.m. on verapamil, 162 ± 29 b.p.m. on metoprolol, and 148 ± 30 b.p.m. on carvedilol. All

**Figure 1** Flow chart. Flow chart of the study. n, number of patients; SR, sinus rhythm.
treatments reduced peak heart rate compared with baseline ($P < 0.001$ for all). Treatment with carvedilol resulted in a lower peak heart rate than treatment with the calcium inhibitors ($P < 0.001$ for both). At peak exercise, the mean systolic BP was unchanged by treatment with the calcium channel blockers and decreased by the beta-blockers ($P \leq 0.001$ for both).

Peak VO$_2$ (mL/kg/min) at baseline was correlated to age ($r = -0.42$, $P = 0.001$), male gender ($r = 0.53$, $P < 0.001$), forced expiratory volume in one second (FEV$_1$) ($r = 0.59$, $P < 0.001$) and diffusion capacity of the lung for carbon monoxide (DLCO) ($r = 0.34$, $P = 0.008$). Through all treatment periods, peak VO$_2$ was correlated to peak heart rate during the exercise tests ($r = 0.49$, $P < 0.001$).

The mean peak oxygen uptake (peak VO$_2$) was significantly lower during treatment with metoprolol and carvedilol, compared with baseline or treatment with diltiazem and verapamil ($P < 0.001$ for all). Results are given in Table 2 and Figure 2. Results presented as change from baseline are available in Supplementary material online, Table S3.

### N-terminal pro-B-type natriuretic peptide levels

At baseline (no treatment), NT-proBNP levels both at rest and at peak exercise were correlated to patients age ($r = 0.41$, $P = 0.001$ and $r = 0.37$, $P = 0.004$, respectively) and inversely correlated to...
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NT-proBNP levels both at rest ( \( r = -0.01, P = 0.31 \)) and at peak exercise ( \( r = -0.01, P = 0.011 \)) compared with baseline, whereas treatment with metoprolol and carvedilol increased the levels (metoprolol: \( P < 0.001 \) both for rest and exercise, carvedilol: \( P = 0.009 \) and \( P = 0.024 \), respectively). Values are given in Table 2 and Figure 3.

There was a significant increase in NT-proBNP levels from rest to peak exercise, 220 (± 146) ng/mL at baseline, 152 (± 91) ng/mL on diltiazem, 166 (± 113) ng/mL on verapamil, 298 (± 184) ng/mL on metoprolol, and 235 (± 139) ng/mL on carvedilol. Diltiazem and verapamil reduced the increase in NT-proBNP levels in response to exercise, compared with baseline ( \( P = 0.001, P = 0.008 \)), whereas the increase was augmented by metoprolol ( \( P < 0.001 \) and unchanged by carvedilol. Women had numerically less increase than men both at baseline and through all treatments, but the difference was not significant.

Resting and peak NT-proBNP levels were inversely correlated to peak heart rate during the exercise tests ( \( r = -0.31 \) and \( r = -0.33, P = 0.01 \), respectively).

Treatment with diltiazem and verapamil significantly reduced the NT-proBNP levels both at rest ( \( P < 0.001 \) and \( P = 0.048 \)) and at peak exercise ( \( P < 0.001 \) and \( P = 0.011 \)) compared with baseline, whereas treatment with metoprolol and carvedilol increased the levels (metoprolol: \( P < 0.001 \) both for rest and exercise, carvedilol: \( P = 0.009 \) and \( P = 0.024 \), respectively). Values are given in Table 2 and Figure 3.

Table 2  Peak oxygen uptake and NT-ProBNP levels at rest and peak exercise

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Peak VO₂ (mL/kg/min)</th>
<th>NT-proBNP at rest (pg/mL)</th>
<th>NT-proBNP at peak exercise (pg/mL)</th>
<th>Increase in NT-proBNP in response to exercise (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>23.1 ± 5.9</td>
<td>1039 ± 636</td>
<td>1262 ± 759</td>
<td>220 ± 146</td>
</tr>
<tr>
<td>(no treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>23.7 ± 6.4</td>
<td>831 ± 528*</td>
<td>985 ± 597♭</td>
<td>152 ± 91♭</td>
</tr>
<tr>
<td>Verapamil</td>
<td>23.1 ± 6.5</td>
<td>897 ± 517♭</td>
<td>1063 ± 602♭</td>
<td>166 ± 113♭</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>21.1 ± 6.5*</td>
<td>1332 ± 815*</td>
<td>1634 ± 962*</td>
<td>298 ± 184*</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>20.0 ± 5.5*</td>
<td>1205 ± 742†</td>
<td>1440 ± 832♭</td>
<td>235 ± 139♭</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD. VO₂ = Peak oxygen uptake during exercise test. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

* \( P < 0.001 \) compared with baseline and treatment with diltiazem or verapamil.
♭ \( P < 0.05 \) compared with baseline and treatment with diltiazem or verapamil.
§ \( P < 0.001 \) compared with baseline and treatment with metoprolol or carvedilol.
† \( P < 0.05 \) compared with baseline and treatment with metoprolol or carvedilol.

The 20 patients that were excluded from the analysis due to premature discontinuation had similar baseline characteristics as those who completed the study, except for prior metoprolol use (Table 1). Four of these 20 patients were withdrawn from the study before initiating the first study drug (two patients developed symptoms of heart failure during the wash-out period before the baseline visit, one patient had normalization of heart rate and one patient had an episode of ventricular tachycardia during the baseline exercise test). Four patients were withdrawn during the course of the study due to unrelated events (death from intracerebral haemorrhage, ischaemic stroke, renal failure due to concomitant antibiotic treatment, and spontaneous conversion to sinus rhythm). Twelve patients discontinued prematurely due to adverse effects of one of the study drugs (seven on metoprolol, three on carvedilol, and two on diltiazem). Details on completed study drug periods, study drugs not tolerated and related adverse effects are presented in Supplementary material online, Table S4.
The main results were consistent if the 16 patients with partial data were included in the analysis, except that the difference between NT-proBNP levels at baseline and during treatment with carvedilol was no longer statistically significant (Supplementary material online, Table S5).

**Discussion**

In this randomized, investigator-blinded cross-over study of four different drugs for rate control in permanent AF, exercise capacity was reduced by treatment with metoprolol and carvedilol compared with no treatment, whereas treatment with diltiazem and verapamil did not influence exercise capacity. NT-proBNP levels both at rest and at peak exercise decreased during treatment with diltiazem and verapamil and increased during treatment with metoprolol and carvedilol. Overall, there was an inverse relationship between peak VO₂ and levels of NT-proBNP both at rest and at peak exercise.

To our knowledge, this is the first study to compare the effect of beta-blockers and calcium channel blockers on exercise capacity and NT-proBNP levels in permanent AF. Both of the calcium channel blockers preserved exercise capacity and reduced NT-proBNP levels, whereas the beta-blockers reduced exercise capacity and increased NT-proBNP levels. Beta-blockers are often used as first line treatment for rate control in AF patients; however, in this study, calcium channel blockers had similar effects on heart rate during exercise, without the negative impact on exercise capacity.

Many earlier studies have investigated the effect of beta-blocker and calcium channel blocker treatment on exercise capacity. Most studies have shown that calcium channel blockers preserved or even improved exercise capacity, whereas treatment with beta-blockers affected exercise capacity negatively. However, the mechanisms behind the adverse effect of beta-blockers on exercise tolerance are unknown. We believe that the inverse relationship between exercise capacity and NT-proBNP levels found in this study may reflect some of the underlying mechanisms behind this phenomenon. Earlier studies have suggested that even in AF patients without systolic heart failure, the levels of natriuretic peptides may reflect the left ventricular filling pressure. The increase in left ventricular filling rate in diastole during exercise depends on the ability of the left ventricle to relax rapidly and completely. It has been postulated that beta-blockers may interfere with the relaxation process, as they exert not only negative inotropic and chronotropic effects, but also a negative lusitropic effect. Both for normal subjects and for patients with systolic heart failure, beta-adrenergic receptor stimulation has been shown to accelerate left ventricular isovolumic relaxation. Furthermore, one might speculate if AF patients are more vulnerable to adverse effects of beta-blockers given the absence of atrial contraction and disturbed diastolic filling of the ventricles.

In heart failure patients, a transient increase in NT-proBNP levels has been demonstrated after initiation of beta-blockers. However, in the long term, most studies show a decline in the levels of natriuretic peptides. In the Carvedilol Or Metoprolol European Trial (COMET), NT-proBNP levels in patients with heart failure declined both during treatment with carvedilol and metoprolol during >2-year follow-up. Whether the increased NT-proBNP levels demonstrated on beta-blocker treatment in our study are transient or permanent, remains unknown. Longer treatment periods and repeated exercise tests could have shed light on this; however, the study time frame would then have to be extended significantly and the comparisons between treatment periods might therefore be less valid. We are not aware of any studies on the effect of beta-blocker treatment on NT-proBNP levels in subjects in sinus rhythm without heart failure; however, in this situation NT-proBNP levels are usually much lower without treatment.

In this study, we observed reduced levels of NT-proBNP during treatment with the calcium channel blockers. In elderly people with diastolic dysfunction in sinus rhythm, treatment with verapamil decreases the isovolumic relaxation time and thus improves the diastolic function. The effect of the different drugs on NT-proBNP...
levels may also reflect effects on the atria. In heart failure, the predominant source of NT-proBNP is the left ventricle, whereas in AF patients without heart failure the atria may be the most important source. Verapamil has been found to have a protective effect against atrial stunning after conversion from AF to sinus rhythm, and it might be that calcium channel blockers also exhibit similar favourable effects in the atria during AF. Although there are several mechanisms for release of natriuretic peptides, myocardial stretch is the most common mechanism. Hence, differences in atrial wall stretch may explain the differences in NT-proBNP levels between treatments. Unfortunately, we did not perform repeat measurements of atrial dimensions after each treatment period in this study. However, NT-proBNP secretion may be sensitive to changes in atrial wall stretch too small to be recognized by transthoracic echocardiography. It is possible that beta-blockers adversely affect left ventricular function leading to increased left atrial pressure and dilatation, and that this increase in atrial pressure is transferred retrogradely to the pulmonary veins.

At the time our study was planned, guidelines recommended strict rate control aiming at a resting heart rate between 60 and 80 b.p.m. Taking into account the results of the RACE II study, the 2010 ESC guidelines recommend a lenient rate control with a target resting heart rate of 110 b.p.m. or less, for most AF patients. However, a stricter rate control strategy is recommended when symptoms persist or tachycardiomyopathy occurs despite lenient rate control. Although a large proportion of the patients in our study had a baseline heart rate <110 b.p.m., most patients had symptoms that were reduced by calcium channel blockers, but not by beta-blockers; 93–100% of the patients fulfilled the criteria for the lenient rate control when on study drugs, whereas 48–58% fulfilled the criteria for the strict rate control. In the RACE II study, most patients received beta-blockers; only 5–6% received calcium channel blockers as the only rate-reducing drug. Whether more frequent use of calcium channel blockers in the RACE II study would have affected the outcomes with regard to symptoms and quality of life remains unknown.

We emphasize that patients with heart failure and ischaemic heart disease were not included in the study; therefore, our results may not be valid for such patients. Beta-blockers have well-documented beneficial effects in heart failure and ischaemic heart disease and are thus the first choice of drugs in these conditions. Also, the results of this study should not be extrapolated to patients with paroxysmal or persistent AF, where treatment with verapamil may provoke AF and beta-blockers may prevent AF recurrence.

The main clinical implication of our findings is that calcium channel blockers should probably be considered more often for rate control in patients with permanent AF without heart failure or ischaemic heart disease.

Limitations
The sample size of our study is limited, and 20 patients (25%) did not complete the study. The different drugs used in this study are not equivalent in dosages or duration of action, and approved dosages and drug formulations may vary between countries. Larger, long-term studies are needed to confirm our findings, and determine whether they are consistent over time.

Conclusion
In this study of patients with permanent AF, the calcium channel blockers preserved exercise capacity with a reduction in serum NT-proBNP levels, whereas the beta-blockers reduced exercise capacity and increased the levels of NT-proBNP.

Supplementary material
Supplementary material is available at European Heart Journal online.

Funding
This work was supported by the South-Eastern Norway Regional Health Authority and by the Medical Research Foundation, Bærum Hospital, Norway. Roche diagnostics, Oslo, Norway provided most of the NT-proBNP assays free of charge.

Conflict of interest: K.G.: board membership—Sanofi-aventis; payment for lectures including service on speakers bureaus—AstraZeneca, Meda, MSD, Nycomed. A.T.: board membership—Bayer, Bristol Myers Squibb, MSD, Sanofi-aventis; consultancy—Bayer, Boehringer Ingelheim, Sanofi-aventis; payment for lectures including service on speakers bureaus—Nycomed, Pfizer; payment for development of educational presentations—Nycomed.

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