Acute Effect of Atrial Fibrillation on Circulating Natriuretic Peptides: The Influence of Heart Rate, Rhythm Irregularity, and Left Atrial Pressure Overload

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Plasma natriuretic peptides (NPs) are increased in patients with atrial fibrillation (AF) compared with the patients with sinus rhythm. This study investigated whether this phenomenon is intrinsic to heart rhythm irregularity and independent of the heart rate and left atrial pressure (LAP) overload. We investigated 46 patients (age: 59 ± 10 years, male gender: 77%) with non-valvular paroxysmal AF who were scheduled for catheter ablation and had documented stable sinus rhythm for at least 18 hours before the procedure. All patients underwent direct measurement of right atrial pressure and LAP, simultaneously with assessment of plasma B-type NP, N-terminal pro-brain NP, and mid-regional pro-atrial NP. The baseline measurement was followed by induction of AF by rapid atrial pacing in the first 24 patients and by regular pacing from the coronary sinus at 100/min (corresponding to the mean heart rate during induced AF) in the latter 22 patients. Hemodynamic assessment and blood sampling were repeated after 20 min of the ongoing AF or fast regular paging. The baseline characteristics and hemodynamic measurements were comparable between study groups; however, patients in the regular atrial pacing group had a higher body mass index and a larger left atrial diameter compared with the induced AF group. Plasma levels of all 3 NPs increased significantly during induced AF but not during fast regular pacing, and the increase of NPs was independent of right atrial pressure and LAP. Baseline concentrations of NPs and heart rhythm irregularity were the only independent predictors of increased NPs. **(Am J Cardiol 2023;208:156−163)**

Keywords: arrhythmia, atrial fibrillation, hemodynamics, natriuretic peptides

Cardiac natriuretic peptides (NPs) are well-established diagnostic and prognostic biomarkers of heart failure (HF).[1,2] The main stimulus for NPs release is believed to be myocardial wall stretch (either atrial or ventricular) because of the pressure or volume overload.[3,4] However, studies demonstrated increased NP concentrations also in patients with atrial fibrillation (AF) compared with those with sinus rhythm (SR), even in the absence of overt HF.[5−7] It is still unclear whether this phenomenon is related to the gross hemodynamic alterations caused by AF or by intrinsic pathways related to the heart rhythm irregularity itself.[8,9] In the present study, we sought to investigate the acute effect of heart rate (HR), heart rhythm irregularity, and left atrial pressure (LAP) on plasmatic levels of NPs either during induced paroxysm of AF or during fast regular pacing. We hypothesized that induction of AF would increase the level of NPs independently of the HR and LAP. In addition, this study investigated the relation between the baseline NP concentrations in SR and during induced AF. Better understanding of this relation may have clinical implications for the management of AF in patients with HF.

Methods

The study enrolled 46 patients with non-valvular paroxysmal AF, who were scheduled for catheter ablation. Only patients with a documented stable SR for at least 18 hours before the procedure (as documented by telemetry monitoring) were included. The study protocol was approved by the institutional ethical committee, and all patients signed informed consent with the procedure.

The hemodynamic study was conducted at the beginning of the ablation procedure, after obtaining transseptal access to the left atrium (LA) but before delivering any ablation lesions. The patients were under mild conscious sedation with fentanyl and midazolam and on uninterrupted oral anticoagulation. LAP was measured using a stiff fluid-filled

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sheath (8 Fr SL1, Abbott, United States) placed in the LA cavity. Another SL1 sheath for measurement of right atrial pressure (RAP) was placed in the right atrium. Pressure signals were analyzed in real time from at least 10 consecutive beats using a dedicated system (CardioLab, GE HealthCare, Little Chalfont, United Kingdom). Mean LAP and RAP were obtained from the electronic means of the pressure curves. Systemic blood pressure was measured noninvasively by an arm cuff. HR was obtained from a 5-lead surface electrocardiogram.

Venous blood samples for assessment of NPs were drawn from a sheath in the common femoral vein into ethylenediaminetetraacetic tubes and stored at −70°C until the batch analysis. B-type NP (BNP) was assessed by chemiluminescent microparticle immunoassay (Architect assay, Abbott Diagnostics) with a sensitivity of 10 ng/L. N-terminal pro-brain NP (NT-proBNP) was assessed using an electrochemiluminescence immunoassay (Elecsys assay, Roche Diagnostics, Pleasanton, California) with a sensitivity of 50 ng/L. Mid-regional pro-atrial NP (MR-proANP) was analyzed by luminometric immunoassay (Kryptor assay; Brahms GmbH, Hennigsdorf, Germany) with a sensitivity of 2.1 pmol/L. BNP levels of <35 ng/L, NT-proBNP of <125 ng/L, and MR-proANP of <116 pmol/L were considered normal.

At baseline, all patients underwent hemodynamic assessment along with blood sampling for evaluation of NPs. Subsequently, in the first 24 consecutive patients, a sustained paroxysm of AF was induced by rapid atrial pacing. Hemodynamic assessment and blood sampling were repeated after 20 minutes of ongoing AF. In the latter 22 consecutive patients, the baseline measurement was followed by regular atrial pacing from the proximal coronary sinus at 100 beats/min (i.e., control group), and the hemodynamic assessment and blood sampling were repeated after 20 minutes (Figure 1). The pacing rate of 100/min was chosen to match the average HR during induced AF in the first group of patients (HR of 99.6 ± 13/min) and to ensure 1:1 atrioventricular conduction.

Statistical analyses were conducted in R (*http://www.R-project.org*). Baseline variables are reported as means ± SD or counts (proportions). They were compared using

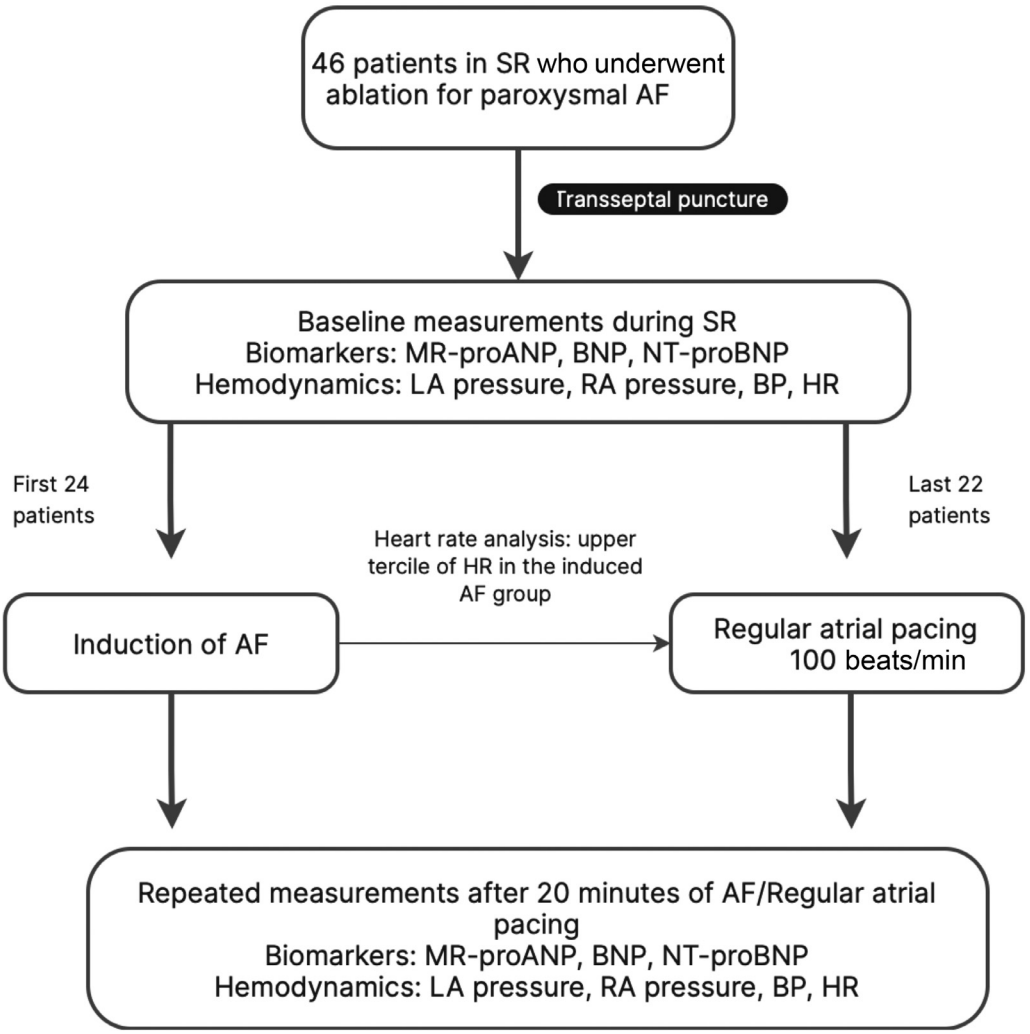

Figure 1. Study protocol flowchart. BP = blood pressure.

Student *t* test and Fisher's exact test as appropriate. NP levels (NT-proBNP, MR-proANP, and BNP) are provided as medians and interquartile range. They were compared by the Mann−Whitney *U* test. The changes in NP concentrations within patients' groups were compared using a paired *t* test. The relation between NP levels during AF and SR was evaluated by univariable and multivariable linear regression analysis with log-transformed NP values. In the group of patients with induced AF, Pearson's correlation and linear regression were also used to assess the relation between NP values measured during induced AF and SR. A $p < 0.05$ was considered significant.

Results

The study protocol was completed in all patients without clinical complications. The baseline characteristics and hemodynamic measurements were comparable between study groups; however, patients in the regular atrial pacing group had a higher body mass index (31 ± 5 vs 27 ± 4, p = 0.01) and larger left atrial diameter (43 ± 6 vs 40 ± 6, p = 0.07) compared with the induced AF group (Table 1). One patient in the induced AF group (4%) and 2 patients in the atrial pacing group (9%) had a previous history of an episode of HF triggered by new-onset AF, but at the time of the study, all the 3 patients had normal left ventricular ejection and no signs and symptoms of HF, with NP concentrations ranging within the interquartile range of the respective study groups (MR-proANP: 84.8, 154.7, and 43.3 pmol/L; BNP: 19.3, 145.8, and 45.8 ng/L; and NT-proBNP: 45.1, 258.8, and 71.5 ng/L, respectively). At baseline, normal MR-proANP, BNP, and NT-proBNP concentrations were observed in 12 patients (50%), 9 patients (37.5%), and 13 patients (54%) in induced AF group and 15 patients (68%), 11 patients (50%), 16 patients (72%) in fast atrial pacing group, respectively. Twenty minutes after induction of AF, the mean concentrations of MR-proANP increased from the baseline by 64% (95% confidence interval [CI] 49% to 103%, p <0.001). The corresponding values for BNP were 51% (95% CI 43% to 82%) and for NT-proBNP 7% (95% CI 3% to 16%, all p <0.001), although LAP did not change significantly (Figures 2 and 3, Table 2). Normal MR-proANP, BNP, and NT-proBNP concentrations were observed in 29%, 13%, and 29% of the patients during induced AF, compared with 68%, 41%, and 64% of the patients with rapid regular pacing. During rapid atrial pacing, there were no significant changes of the NP concentrations, regardless of the baseline concentrations. During induced AF, the relative increase of MR-proANP and NT-proBNP was 98% (95% CI 56% to 141%) and 13% (95% CI% −1 to 26%) in the patients with normal baseline concentrations and 58% (95% CI 10% to 107%) and 8% (95% CI 4% to 12%) in the patients with elevated baseline concentrations (p = 0.4 and 0.6 for normal vs. elevated baseline concentrations). In contrast, BNP increased by 54% (95% CI 33% to 75%) in the patients with normal baseline NP level compared with 75% (95% CI 37% to 113%) in the patients with elevated baseline concentrations (p = 0.4 for normal vs elevated baseline concentrations). The 95th percentile values of NPs during induced AF were 324 pmol/L for MR-proANP, 274 ng/L for BNP, and 506 ng/L for NT-proBNP. Rapid regular atrial pacing caused a mild decrease in LAP because of the LA unloading but did not significantly affect the NP concentrations (Figure 3). In multivariable linear regression analysis, including data from all 46 patients, only the presence of AF and the baseline levels of NPs, but not LAP or any other hemodynamic variables, were independently associated with the increase of NPs

Table 1
Baseline clinical characteristics

	Induced Atrial Fibrillation (n=24)	Regular Atrial Pacing (n=22)	P value
Age (years)	59 ± 10	61 ± 10	0.42
Male	18 (82 %)	16 (73 %)	0.40
Body mass index (kg/m^2)	27 ± 4	31 ± 5	0.01
LV EDD (mm)	51 ± 5	55 ± 7	0.09
LV EF (%)	60 ± 1	58 ± 6	0.17
LAVi (mL/m^2)	39 ± 10	37 ± 8	0.38
LAD (mm)	40 ± 6	43 ± 5	0.07
Creatinine (μmol/L)	84 ± 19	87 ± 23	0.64
GFR (mL/s/1.73m^2, CKDEPI)	1.3 ± 0.3	1.3 ± 0.4	0.42
CHA_2DS_2-VASc	1.5 ± 1.2	1.5 ± 1.1	0.78
History of stroke	1 (4 %)	2 (9 %)	0.60
History of heart failure	1 (4 %)	2 (9 %)	1.00
Coronary artery disease	3 (14 %)	1 (5 %)	0.33
Hypertension	13 (59 %)	12 (55 %)	0.74
Diabetes	3 (14 %)	3 (14 %)	1.00
Beta-blockers	17 (77 %)	15 (68 %)	0.44
Antiarrhythmic drugs	15 (68 %)	18 (82 %)	0.85

Data are provided as means ± standard deviations or counts (proportions).

GFR = glomerular filtration rate; LAD = left atrial diameter; LAVi = left atrial volume index; LV EDD = Left ventricular end-diastolic diameter; LV EF = left ventricular ejection fraction.

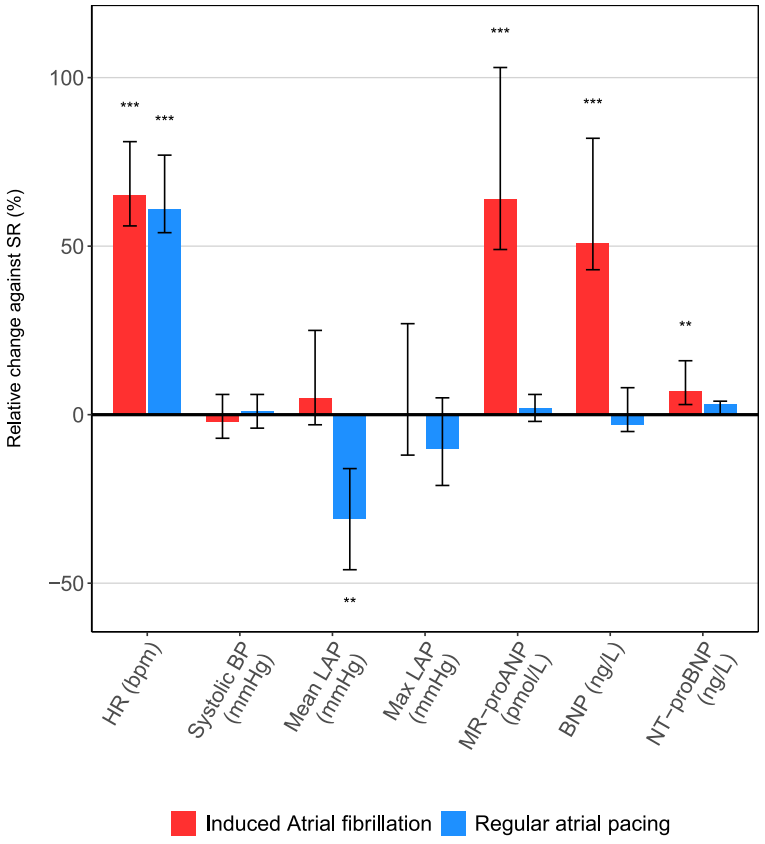

Figure 2. Relative change of study indexes compared with baseline. Percentage change of mean heart rate, natriuretic peptides, and hemodynamic parameters after induction of atrial fibrillation or during regular atrial pacing. **/***p <0.01/0.00. BP = blood pressure.

(Table 3). In a subgroup analysis of patients with induced AF, there was a strong correlation between concentrations of all 3 NPs during AF and during SR (Figure 4). The average ratio of concentrations during AF and SR was 0.62 for MR-proANP, 0.65 for BNP, and 0.92 for NT-proANP. Rapid regular atrial pacing caused a mild decrease in LAP, likely because of the LA unloading; however, without a significant change in NP concentrations (Figure 3).

Discussion

The present study showed that plasma concentrations of MR-proBNP, BNP, and NT-proBNP increased during AF independently of LAP and HR and that the increase appeared to be explained by HR irregularity. From a clinical perspective, these findings imply that NPs should not be used alone as surrogate markers of hemodynamic overload in patients with AF without overt HF. In addition, the study proposed 95th percentile "normal" cut-off values of NPs for hemodynamic stable patients with AF and also proposed conversion ratios between AF and SR that could help interpret NPs in patients with AF. Further studies should confirm whether the HR irregularity per se could be detrimental by inducing myocyte stress reflected by the NP release. The latter would strongly support non-pharmacological therapeutic strategies for AF aiming at heart rhythm regularization when SR cannot be maintained.

The results of this study must be seen in the context of a very complex interaction of many contributing factors, including atrial and ventricular rate and their relation. Previous works demonstrated a significant increase in NP levels in patients with regular supraventricular tachycardias, where the atrial stress caused by simultaneous AV activation during atrioventricular nodal reentry tachycardia or atrioventricular reentry tachycardia was the most probable mechanism responsible for NP release. The association between AF and increased NPs has been described in many studies, although the underlying pathophysiological mechanism has not been fully clarified.[9–16] It was shown that restoration of SR by electric cardioversion or catheter ablation leads to a decrease of NPs. However, direct evidence demonstrating an increase of NP after the onset of AF is scarce.[8] Most studies could not determine whether the increase of NPs was related to impaired hemodynamics during AF because they employed less sensitive, noninvasive methods.[5,6,15–18] One invasive hemodynamic study in patients with HF found that the relation between NT-proBNP and AF was independent of pulmonary capillary wedge pressure.[19] In our previous preliminary study, we found significantly higher MR-proANP and BNP levels in 31 patients with

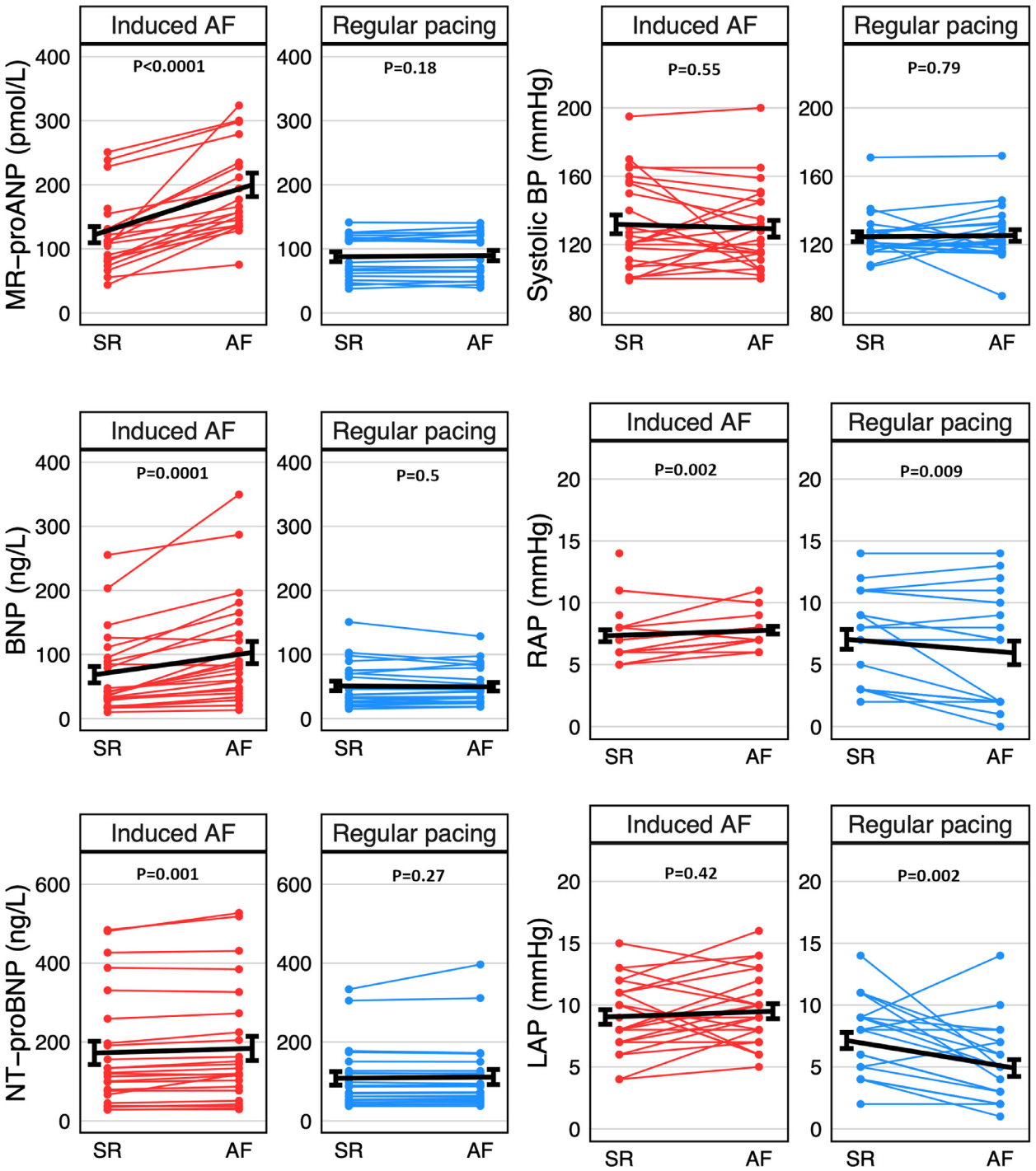

Figure 3. Absolute change of study indexes. Change of natriuretic peptides and hemodynamic parameters after induction of atrial fibrillation or during regular atrial pacing. Color lines connect the absolute values for individual patients. Black lines with error bars represent means and standard errors. The p values were assessed using a paired *t* test. BP = blood pressure.

AF compared with 31 patients in SR, selected using propensity-score matching for age, gender, HR, left ventricular ejection fraction, LA volume index, and directly measured LAP.[9] In the present study, we further elaborated these findings by directly demonstrating a significant increase of NP already 20 min after the onset of AF and by showing that the increase of NPs was unrelated to RAP or LAP changes. In addition, the unique feature of our study was that it included a control group of patients who underwent measurement of NP during rapid regular atrial pacing at the same HR as the average HR during induced AF. Such design of the experiment enabled us to demonstrate that the increase of NP was not caused by HR itself.

Table 2
Changes in biomarkers and hemodynamics

	Induced Atrial Fibrillation n= 24		Regular Atrial Pacing n= 22	
	SR	AF	SR	Pacing
HR (bpm)	60 ± 10	100 ± 13*	62 ± 10	100 ± 0†
BNP (ng/L)	42 (30-−91)	80 (44−136)*	35 (26−70)	38 (24−74)‡
NT-proBNP (ng/L)	121 (74−212)	126 (84−237)*	79 (53−125)	80 (54−125)
MR-proANP (pmol/L)	112 (81−131)	166 (139−235)*	79 (60−116)	83 (60−121)†
RAP (mmHg)	7.3 ± 2.3	8.0 ± 1.0	7.0 ± 3.7	5.9 ± 4.4
LAP mean (mmHg)	9.0 ± 4.9	9.5 ± 2.9	7.1 ± 4.6	4.9 ± 3.1§,†
LAP max (mmHg)	18.0 ± 4.9	18.0 ± 5.3	15.3 ± 4.6	13.8 ± 5.2‡
Systolic BP (mmHg)	132 ± 27	129 ± 24	125 ± 13	125 ± 16

Data (HR, RAP, LAP mean, LAP max and Systolic BP) are expressed as means ± standard deviations. Natriuretic peptide (NT-proBNP, MR-proANP, BNP) levels are provided as the median (interquartile range) and compared using the Mann-Whitney test.

AF = atrial fibrillation; BNP = B-type natriuretic peptide; BP = blood pressure; HR = heart rate; LAP = left atrial pressure; MR-proANP = Mid-regional pro-atrial natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide; RAP = right atrial pressure; SR = sinus rhythm.

* $p<0.001$ for AF or regular atrial pacing vs. SR.

† $p<0.001$ for regular atrial pacing vs. AF.

‡ $p<0.1$ for regular atrial pacing vs. AF.

§ $p<0.01$ for AF or regular atrial pacing vs. SR.

Table 3
Multivariable linear regression analysis of factors associated with NPs increase

	Beta coefficient [95% confidence interval]		
N = 46	Log (BNP)	Log (NT-proBNP)	Log (NT-proANP)
Presence of AF	0.38 (0.15−0.61)*	–	0.57 (0.4−0.8)*
Baseline (absolute) levels of NPs	0.012 (0.001−0.014)*	0.005 (0.004−0.006)*	0.006 (0.004−0.006)*
Age	–	0.01 (0.001−0.02)†	–

Natural log-transformed concentrations of NPs were used to assess factors associated with NPs increase. BNP: R2= 0.7, F = 74, $p < 0.0001$, intercept 3.11, NT-proBNP: r2 = 0.87, F = 74.3, $P <0.0001$, intercept 3.18, NT-proANP: R2 = 0.6, F = 95., $P < 0.0001$, intercept 3.8.

* P value < 0.001.

† P value < 0.05.

We can only speculate on how the heart rhythm irregularity alone could provoke an increase of NPs. Experimental studies indicated that the primary trigger for the release of NPs from myocytes is cellular stretch mediated by mechanosensitive ion channels, and the cellular signaling may involve activation of theCaMII kinase or calcineurin/nuclear factor of activated T-cells (NFAT) pathways.[9] Thus, it is conceivable that the heart rhythm irregularity could either cause alterations in the intracellular calcium handling or that the cyclic increases of LAP could stimulate NP release more potently than the elevation of the mean LAP.

This study was limited by a relatively small sample size, which could have affected the analyses of the baseline predictors of NPs. Nevertheless, our results indicate that the study was adequately powered for the evaluation of within-subject changes in NP concentrations. The study evaluated only acute changes of NP over 20 minutes of induced AF or fast pacing because a longer duration of the experiment (which was conducted during a routine AF ablation procedure) was discouraged by our ethical committee. For the same reason, the effect of HR was assessed in 2 independent patient groups because serial measurements during induced AF and fast regular pacing in one group would require long waiting time for NP concentrations to return to the baseline and would be ethically and logistically unacceptable. Although by the study design, the patients with AF did not differ from the patients with rapid atrial pacing in the average HR, it cannot be excluded that the fast HR could have impacted NP concentrations in some patients with AF. Moreover, this study was not designed to assess the relative impact of the AV relation on the NP release. Finally, the study investigated hemodynamically stable patients, mostly with preserved left ventricular ejection.

Authors' Contributions

Substantial contributions to the conception and design or the acquisition, analysis, or interpretation of the data: Predrag Stojadinovic, Dan Wichterle, Masato Fukunaga, Vojtech Melenovsky, Janka Franekova, Petr Peichl, Marek Sramko. Substantial contributions to the drafting of the articles or critical revision for important intellectual

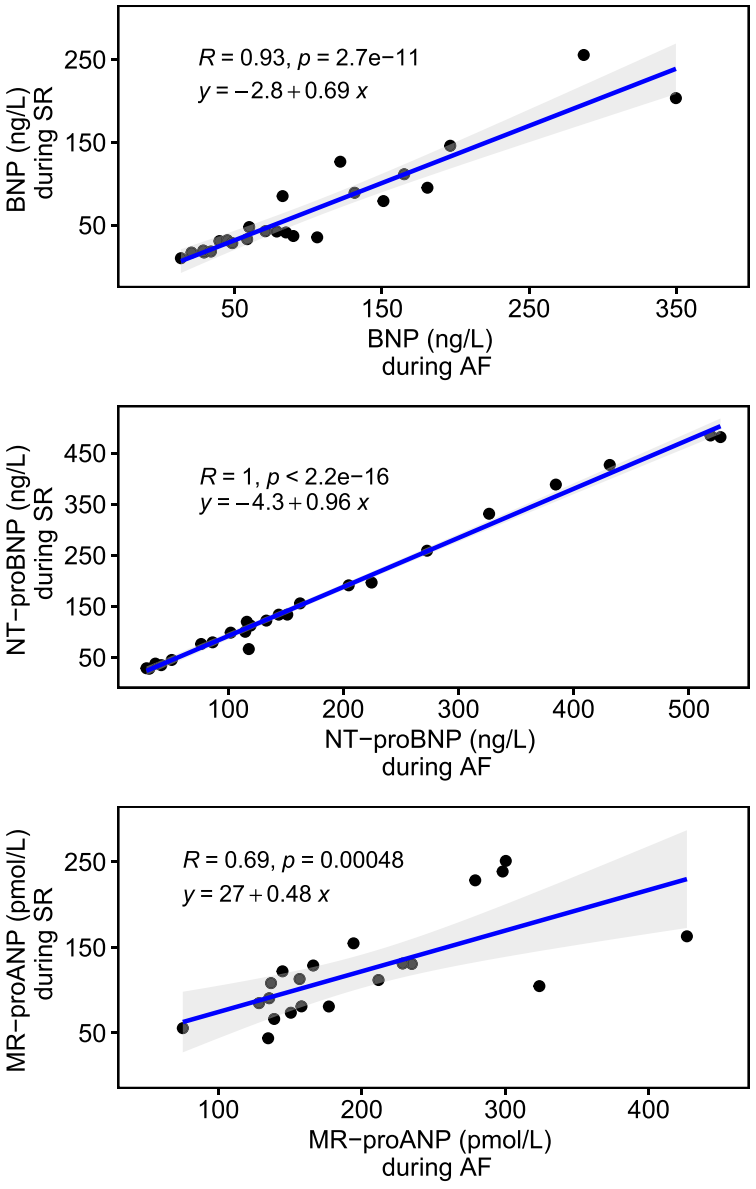

Figure 4. Relationship between NP levels during the sinus rhythm and induced atrial fibrillation. Scatterplot shows the relation between NP levels during the sinus rhythm and induced atrial fibrillation. Pearson's correlation coefficient (*R* value) is displayed along with p values and the equation of the estimated regression line. The gray band indicates the 95% confidence interval of the regression slope.

content: Predrag Stojadinovic, Dan Wichterle, Josef Kautzner, Petr Peichl, Marek Sramko. Final approval of the version to be published: Josef Kautzner, Marek Sramko. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved: Predrag Stojadinovic, Marek Sramko.

Declaration of Competing Interest

Dr. Sramko has received speaker honoraria from Biotronik and an educational grant from Boston Scientific. Josef Kautzner reports personal fees from Biosense Webster, Boston Scientific, GE Healthcare, Medtronic, and St. Jude Medical (Abbott) for participation in scientific advisory boards, and has received speaker honoraria from Biosense Webster, Biotronik, Boston Scientific, Medtronic, ProMED CS, St. Jude Medical (Abbott) and Viatris. Dr. Peichl has received speaker honoraria from St Jude Medical (Abbott) and has served as a consultant for Biotronik and Boston Scientific. The remaining authors have no disclosures.

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