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The hemodynamic effect of simulated atrial fibrillation on left ventricular function

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Abstract

Introduction: Atrial fibrillation (AF) is the most common sustained arrhythmia in humans. The onset of the arrhythmia can significantly impair cardiac function. This hemodynamic deterioration has been explained by several mechanisms such as the loss of atrial contraction, shortening of ventricular filling, or heart rhythm irregularity. This study sought to evaluate the relative hemodynamic contribution of each of these components during in vivo simulated human AF.

Methods: Twelve patients undergoing catheter ablation for paroxysmal AF were paced simultaneously from the proximal coronary sinus and the His bundle region according to prescribed sequences of irregular R–R intervals with the average rate of 90 and 130 bpm, which were extracted from the database of digital ECG recordings of AF from other patients. The simulated AF was compared to regular atrial pacing with spontaneous atrioventricular conduction and regular simultaneous atrioventricular pacing at the same heart rate. Beat-by-beat left atrial and left ventricular pressures, including LV dP/dT and Tau index were assessed by direct invasive measurement; beat-by-beat stroke volume and cardiac output (index) were assessed by simultaneous pulse-wave doppler intracardiac echocardiography.

Results: Simulated AF led to significant impairment of left ventricular systolic and diastolic function. Both loss of atrial contraction and heart rate irregularity significantly contributed to hemodynamic impairment. This effect was pronounced with increasing heart rate.

Conclusion: Our findings strengthen the rationale for therapeutic strategies aiming at rhythm control and heart rate regularization in patients with AF.

KEYWORDS

arrhythmia, atrial fibrillation, hemodynamics, his bundle pacing

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; CI, cardiac index; CO, cardiac output; HB, His bundle; HR, heart rate; ICE, intracardiac echocardiography; LA, left atrium; LAP, left atrial pressure; LV, left ventricle; LVEDP, end-diastolic pressure; RV, right ventricle; SBP, systolic blood pressure; SDRR, standard deviation of R-R intervals; SV, stroke volume; VTI, velocity-time integral.

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia affecting 2% of people.[1] It can significantly impair the cardiac performance, which can clinically manifest with a spectrum ranging from mild symptoms to severe heart failure. The deleterious hemodynamic effect of AF has been explained by several pathophysiological mechanisms, including the loss of atrial kick, shortening of left ventricular (LV) diastolic filling, or heart rhythm irregularity causing neurohumoral activation.[2–7] However, the relative hemodynamic contribution of each of these mechanisms has not yet been elucidated, mainly because of the lack of a realistic hemodynamic model of human AF. On the other hand, a better understanding of the individual hemodynamic components of AF can have important clinical implications, especially for individualized nonpharmacological therapeutic strategies aiming at rate or rhythm control.

This study aimed to evaluate the relative contribution of the main hemodynamic effects of AF to the impairment of cardiac function during simulated arrhythmia. To this end, we used our previously validated in vivo model of human AF that allows us to reproduce the hemodynamics in AF by simultaneous atrial and His bundle pacing, using prescribed sequences of irregular R–R intervals extracted from the database of digital ECG recordings of AF from other patients.[8] We hypothesized that the loss of atrial contraction, heart rhythm irregularity, and shortening of LV diastolic filling by tachycardia would all independently impair cardiac performance and that these alterations would be augmented at a higher heart rate (HR).

2 | METHODS

2.1 | Study population and catheter ablation

The study included 12 patients who were indicated for catheter ablation of paroxysmal AF and maintained a stable sinus rhythm, documented by telemetric monitoring, for at least 24 h before the procedure. The required sample size was estimated based on previous studies.[2,3,5] According to our previously described protocol, the ablation procedures were performed under conscious sedation with fentanyl and midazolam.[9] Electrical isolation of the pulmonary venous ostia was performed by 3.5-mm irrigation-tip radiofrequency catheter (Navistar Thermocool; Biosense Webster), using the support of a three-dimensional electroanatomical mapping system (CARTO; Biosense Webster) The hemodynamic study was performed at the end of the ablation procedure during a stable sinus rhythm. The study was approved by the institutional ethics committee (docket ID 845/14), and all patients signed informed consent to the investigation.

2.2 | Instrumentation

A steerable decapolar catheter for atrial pacing was introduced into the coronary sinus (CS). A 6-French fluid-filled pigtail catheter was introduced into the LV cavity through a transseptal sheath via the femoral vein approach. The ablation catheter was positioned at the His bundle (HB) on the right ventricular (RV) side of the interventricular septum. Stable His bundle capture was confirmed by consistently narrow QRS complex while pacing and this site was tagged on the three-dimensional mapping system. Finally, an intracardiac echocardiography (ICE) probe (AcuNav; Siemens Medical Solutions) was positioned via the femoral vein approach in the RV outflow tract to achieve a perpendicular view of the aortic valve and a parallel view of the proximal part of the ascending aorta (Figure 1).

2.3 | Cardiac pacing

Cardiac pacing was performed by a dedicated external cardiac stimulator (MicroPace), which was connected to a purpose-made electronic device that controlled the pacing sequence (further referred to as the "sequence controller").[8] The sequence controller was programmed to generate square-shaped trigger pulses (2 V/20 ms) to emulate the predefined R–R intervals. These pulses were sensed through an ECG input of the external cardiac stimulator that was set to triggered mode and that with negligible delay generated stimulation pulses (~10 V) through a splitter to the catheters in the CS and at the HB to achieve simultaneous atrioventricular (AV) pacing. The resulting QRS duration on the surface ECG was 126 ± 13 ms. The reproducibility of this method for simulation of LV hemodynamics in AF has been previously described.[8]

2.4 | Hemodynamic study

Hemodynamic parameters were assessed during four different pacing configurations, each of them with a mean HR of 90 and 130 bpm: (1) regular pacing from the CS to simulate normal sinus rhythm, (2) regular simultaneous AV pacing from the CS, and HB to evaluate the loss of atrial systole without impeding the natural electric activation of the ventricles, (3) irregular simultaneous AV pacing according to prescribed R–R sequences with R–R interval standard deviation (SDRR) of 20% (i.e., "less irregular" simulated AF), and (4) irregular simultaneous AV pacing according to prescribed R–R sequences with an SDRR of 30% (i.e., "more irregular" simulated AF) (Figure 2).

Each pacing episode lasted 2 min and was followed by a stabilization period of 30 s of regular CS pacing with the same rate. The stabilization period was excluded from the hemodynamic analysis. All patients were paced according to the same set of R–R sequences, but the order of the pacing episodes was random for each patient. The irregular R–R sequences for simulated AF were obtained from a database of Holter ECG recordings in patients with persistent AF (http://physionet.org, the Long-Term AF Database). Representative segments of AF with the desired duration, mean HR, and SDRR were selected with the help of a custom program written in

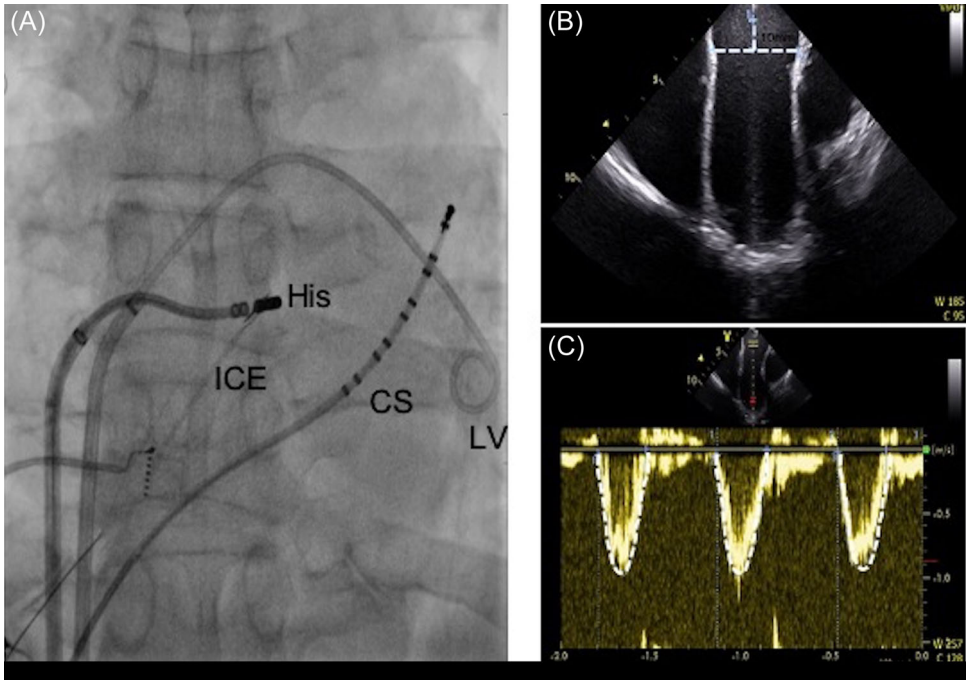
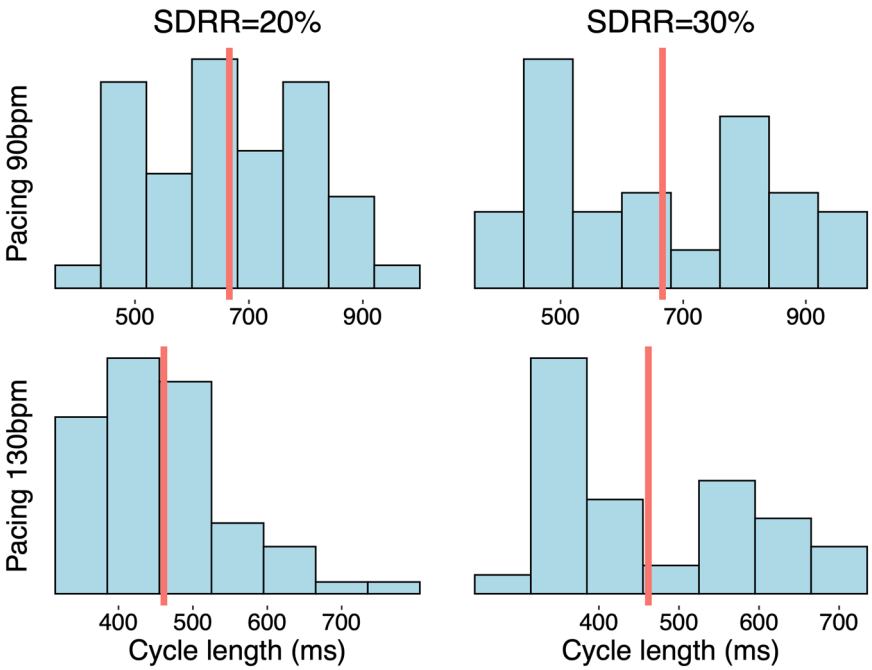


FIGURE 1 Stroke volume assessment by ICE. Fluoroscopic image of catheter setting (A). The aortic valve and ascending aorta were visualized by ICE in a long axis. The diameter of the aorta was measured at 10 mm above the aortic cusps (B). VTI was delineated manually at the level of the aortic root and was averaged over the entire pacing episode (C). In all cases, the angle of incidence during the measurement of VTI was <5°. CS, decapolar catheter introduced to the coronary sinus for atrial pacing; His, mapping catheter used for the pacing of the His bundle; ICE, intracardiac echocardiography probe, LV, pigtail catheter in the left ventricle.

FIGURE 2 Atrial fibrillation cycle length histograms. Histograms of the R–R interval that were used to simulate distinct types of atrial fibrillation: slow (90/min), fast (130/min), more regular (SDRR = 20%), and more irregular (SDRR = 30%). Means are represented by red lines. AF, atrial fibrillation, SDRR, standard deviation of R–R intervals.



Matlab (MathWorks) that enabled automated search and reviewing of the database.

Evaluated hemodynamic parameters included: (1) blood pressure (SBP), LV end-diastolic pressure (LVEDP), LV dP/dT max, and Tau index measured with pigtail catheter in the LV, (2) mean left atrium (LA) pressure measured by the transseptal sheath in the LA, and (3) cardiac output (CO) and cardiac index (CI) were measured simultaneously by pulse-wave Doppler ICE in the ascending aorta (Figure 1).

2.5 | Data acquisition and analysis

Trigger pulses from the sequence controller, surface ECG, and analogue blood pressure signals from the LA and LV were recorded at 1000 Hz by data acquisition hardware (Powerlab; ADInstruments). The data were analyzed in LabChart 7 (ADInstruments). SBP, LVEDP, mean LA pressure, maximum LV dP/dT, and Tau index were obtained beat-by-beat, and the values were averaged over each two-min pacing episode.

Video output from ICE (the pulse-wave Doppler in the ascending aorta) was recorded to a computer with a resolution of 640 × 480 pixels and 30 frames/s and synchronized with blood pressure signals by the Video Capture Module in LabChart (ADInstruments). The recorded video loops were processed in ImageJ (http://ImageJ.net, the Fiji distribution). For each cardiac cycle, the envelope of the pulse-wave Doppler signal from the ascending aorta was manually outlined to obtain the velocity-time integral (VTI). The beat-by-beat VTI values were averaged over the entire two-min pacing episode. Stroke volume (SV) was calculated from the mean VTI and diameter of the ascending aorta at the sampling volume, according to the formula: $SV = \pi \times (\text{aorta diameter}/2)^2 \times VTI$.

2.6 | Statistical analysis

Statistical analyses were conducted in R (http://www.R-project.org). Continuous variables are displayed in means ± standard deviation. Hemodynamic changes within the individual patients were compared by paired *t* test with Holm's correction for repeated measurements. Between-group comparisons were performed using analysis of variance (ANOVA) with the Tukey post hoc test. A value of $p < .05$ was considered significant.

TABLE 1 Baseline characteristics of the study population

	N = 12
Age (years)	59 ± 5
Male gender	8 (67%)
Body mass index (kg/m^2)	29 ± 3
Arterial hypertension	6 (50%)
Diabetes mellitus	2 (16%)
History of stroke	2 (16%)
Antiarrhythmic drugs	5 (41%)
CHA2DS2-VASc score	1.7 ± 1.5
Left ventricular ejection fraction (%)	55 ± 9
Left atrial volume (ml/m^2)	39 ± 9

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

TABLE 2 Hemodynamic parameters during different pacing modes

	Pacing mode			
	Atrial regular	AV regular	AF (SDRR = 20%)	AF (SDRR = 30%)
Pacing 90 bpm				
SBP (mmHg)	142.1 ± 16.7	138.5 ± 14.4	131.9 ± 15.5	128.6 ± 15.9
LVEDP (mmHg)	12.0 ± 4.1	11.8 ± 4.2	15.2 ± 4.2	17.0 ± 3.6
LAP (mmHg)	9.6 ± 3.7	10.8 ± 4.1	11.8 ± 4.3	12.9 ± 4
LV dP/dT (mmHg/s)	2017 ± 302	1848 ± 320	1904 ± 315	1870 ± 329
Tau (ms)	39.2 ± 11.2	39.2 ± 10	50.6 ± 12.8	62.5 ± 11.9
SV (ml)	82.8 ± 10	74.4 ± 7.3	63 ± 10.7	63 ± 12.2
CI (L/min/m^2)	3.5 ± 0.4	3.1 ± 0.2	2.6 ± 0.4	2.6 ± 0.5
Pacing 130 bpm				
SBP (mmHg)	141.1 ± 20.8	124.1 ± 15.6**	116.6 ± 17.4***	114.8 ± 18.1
LVEDP (mmHg)	13.5 ± 3.7	14.7 ± 4.6	19.1 ± 5.5*	21.2 ± 6.7***
LAP (mmHg)	10.2 ± 4.8*	14 ± 3.5	14.6 ± 3.9	15.7 ± 3.8**
LV dP/dT (mmHg/s)	2300 ± 476*	1996 ± 383	1857 ± 380	1808 ± 402
Tau (ms)	41.5 ± 13.1	42.6 ± 13.1	61.6 ± 15.4**	71.4 ± 14.4**
SV (ml)	73.7 ± 12.9	50.8 ± 8.4***	41.7 ± 8.6***	42.6 ± 9.1***
CI (L/min/m^2)	4.5 ± 0.8**	3.1 ± 0.5	2.5 ± 0.5	2.6 ± 0.6

Note: Data are provided as means ± standard deviations.

Abbreviations: AF, atrial fibrillation; AV, atrio-ventricular; CI, cardiac index, LV, left ventricular; LAP, left atrial pressure; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; SBP, systolic blood pressure; SDRR, standard deviation of R–R intervals; SV, stroke volume.

The significance level for the comparison between pacing 90 bpm and pacing 130 bpm within the same pacing mode is indicated as follows:

*$p \le .05$; **$p \le .01$; ***$p \le .001$ by paired *t* test.

3 | RESULTS

The hemodynamic study was completed on all 12 patients. Their baseline characteristics are summarized in Table 1. No procedure-related clinical complications occurred. Measurement of the LV pressure was available in all 12 patients, and assessment of CI by ICE was obtained in the last 8 patients.

3.1 | The effect of loss of atrial contraction

Compared to regular atrial pacing, regular simultaneous AV pacing significantly impeded LV contractility, which was reflected by decreased SV, CI, LV dP/dT, and SBP, both at 90 and 130 bpm (Tables 2 and 3, Figure 3A,B). Regular simultaneous AV pacing at 130 bpm also significantly impeded LV diastolic function, leading to an increase in the mean LA pressure.

3.2 | The effect of heart rhythm irregularity

Compared to regular simultaneous AV pacing, irregular simultaneous AV pacing (SDRR of 20%) significantly impeded LV diastolic function, which was reflected by increased Tau and LVEDP at 90 and 130 bpm (Table 2, Figure 3A,B). The increase of Tau was further pronounced during the more irregular AF pacing (SDRR of 30%) compared to the less irregular AF pacing (SDRR of 20%).

Compared to regular simultaneous AV pacing, AF pacing also significantly impeded LV contractility, which was reflected by decreased SV, CI, and SBP at both HR, and by decreased LV dP/dT at 130 bpm. Compared to the less irregular AF pacing, the more irregular AF pacing led to a more pronounced decrease of SBP at 90 bpm and a more pronounced change in Tau index at both pacing rates, while there were no differences in SV and CI. Compared to the regular simultaneous AV pacing, the mean LA pressure increased significantly only during the more irregular AF pacing at both pacing rates.

3.3 | The effect of fast HR

An increase of HR from 90 to 130/min during regular atrial pacing was accompanied by an expected increase in CI without affecting SV and LV diastolic function (Table 2). However, increased HR during regular AV pacing or AF pacing led to a significant decrease in SV, while the CI remained unchanged thanks to the compensation by tachycardia (Table 2). Moreover,

TABLE 3 Relative percent difference between pacing modes

	Relative percent difference			
	Atrial regular vs. AV regular	AV regular vs. AF (SDRR = 20%)	Atrial regular vs. AF (SDRR = 20%)	AF (SDRR = 20%) vs. AF (SDRR = 30%)
Pacing 90 bpm				
SBP (mmHg)	−2.5**	−4.8*	−7.2***	−2.5*
LVEDP (mmHg)	−2.1	28.9*	26.2*	11.9
LAP (mmHg)	11.8	9.4	22.3	9.6
LV dP/dT (mmHg/s)	−8.4*	3.1	−5.6*	−1.8
Tau (ms)	0	29.1*	29.1*	23.5***
SV (ml)	−10.2*	−15.3**	−24*	0
CI (L/min/m^2)	−10.3*	−15.2**	−24**	0.2
Pacing 130 bpm				
SBP (mmHg)	−12.1**	−6*	−17.4***	−1.6
LVEDP (mmHg)	8.7	30.3	41.6**	10.8
LAP (mmHg)	36.6***	4.1	42.2*	7.8
LV dP/dT (mmHg/s)	−13.2**	−6.9*	−19.2***	−2.7
Tau (ms)	2.7	44.6**	48.6**	15.9*
SV (ml)	−31.1**	−17.8**	−43.3***	2
CI (L/min/m^2)	−31**	−17.9**	−43.4***	2.4

Note: Abbreviations are the same as in Table 2.

The significance level for the difference is indicated as follows:

*$p \le .05$; **$p \le .01$; ***$p \le .001$ by paired t test with Holm's correction for repeated measurements.

the adverse hemodynamic impact of the loss of atrial contraction and heart rhythm irregularity on LV contractility and diastolic function was more pronounced at a higher HR (Tables 2 and 3).

4 | DISCUSSION

4.1 | Main findings

This study used a realistic in vivo model of human AF to evaluate the hemodynamic consequences of AF. The study demonstrated the negative impact of AF on various parameters of LV systolic and diastolic function. The loss of effective atrial contraction and heart rhythm irregularity significantly contributed to the adverse hemodynamics. Tachycardia itself augmented the impact of the loss of atrial kick and heart rhythm irregularity.

4.2 | Previous studies

Two earlier studies observed an improvement of CO by 23%–56% after electrical cardioversion of AF to sinus rhythm.[6,10] The magnitude of the increase of CO was similar to the decrease of CO we observed during the induction of simulated AF. The impact of the loss of atrial "kick" on the LV filling has been demonstrated by two

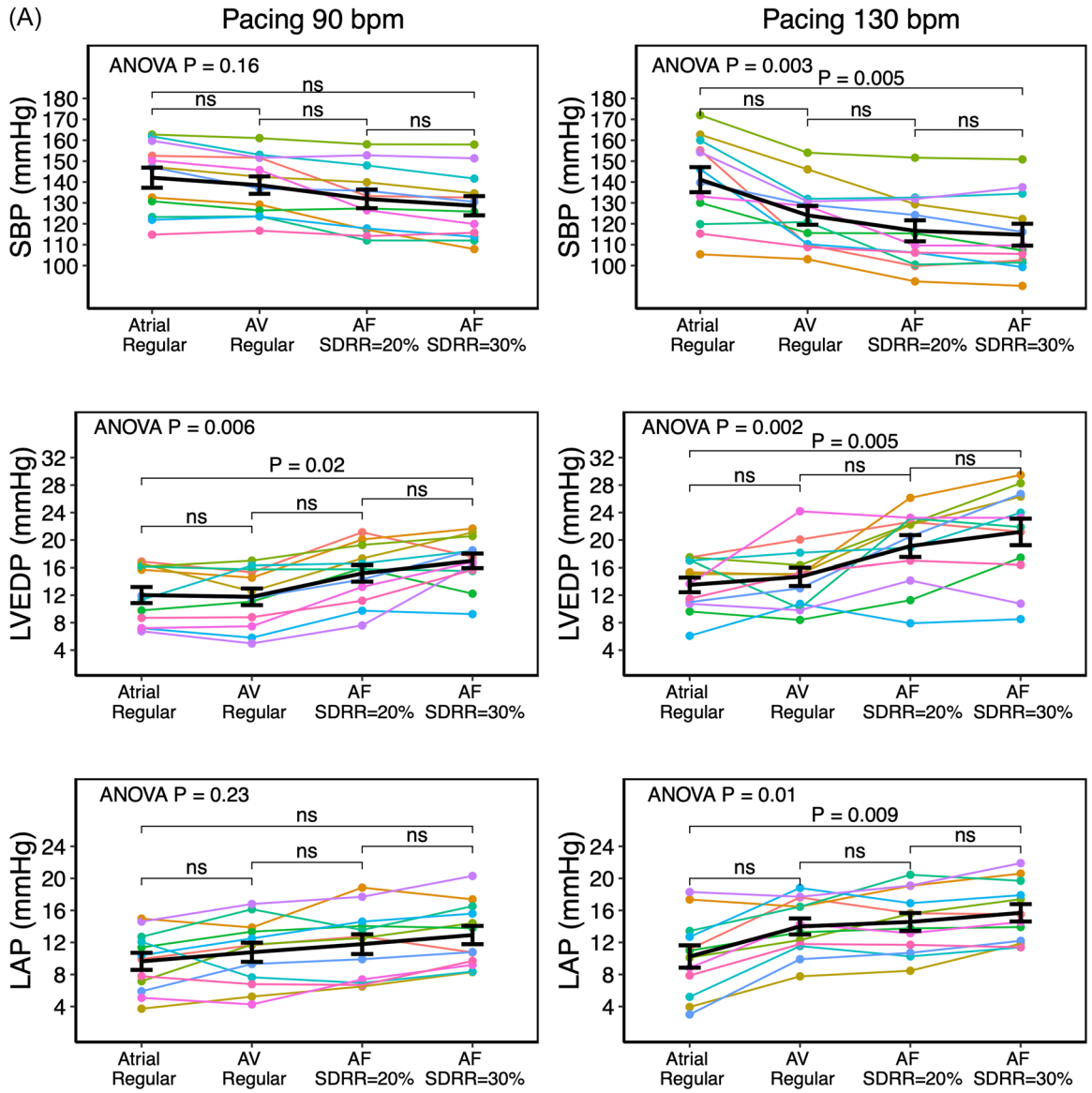


FIGURE 3 (A, B) The effect of individual pacing episodes on the hemodynamic parameters. Color lines connect the values for each patient. Black lines with error bars represent group means and standard errors. The group means were compared using analysis of variance (ANOVA) with the Tukey post hoc test. AF, atrial fibrillation, AV, atrioventricular, LAP, left atrial pressure, LVEDP, left ventricular end-diastolic pressure; SBP, systolic blood pressure; SDRR, standard deviation of R–R intervals.

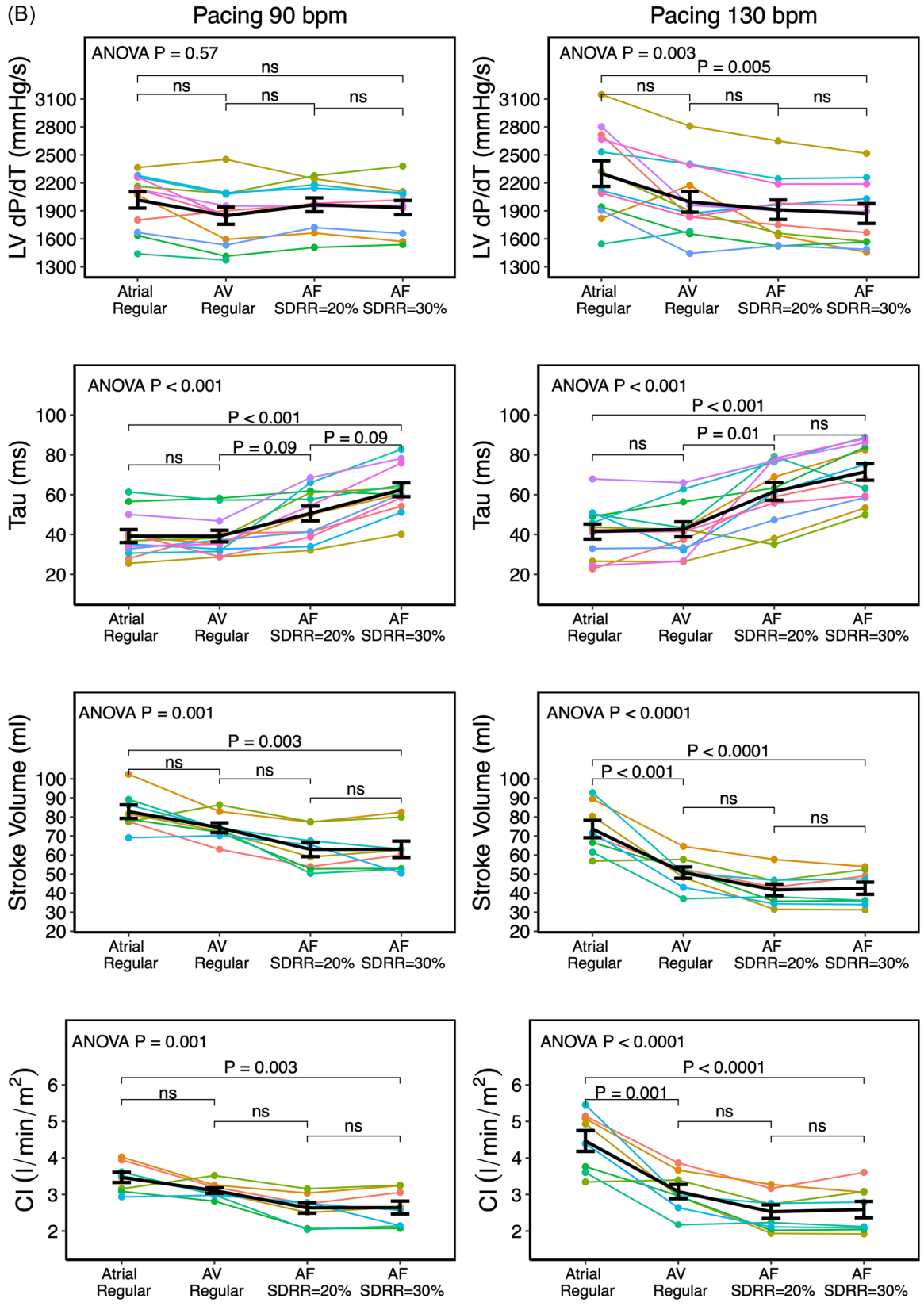


FIGURE 3 Continued

studies using simultaneous AV pacing in patients with sinus rhythm.[11,12] Our study corroborates these studies by the finding of a decreased SV by 10%–31% attributable to simultaneous AV pacing. Altogether, these findings underline the hemodynamic superiority of the sinus rhythm over AF, regardless of the actual HR.

The hemodynamic impact of heart rhythm irregularity was evaluated by two studies using RV pacing in patients with permanent AF who underwent ablation of the AV node.[3,5] The authors attributed to the heart rhythm irregularity a decrease of CO by 12% and 21%, respectively. These values are comparable to our finding of reduced CO by 15%–18% when comparing irregular AV pacing with regular AV pacing. We can only speculate whether the detrimental hemodynamic effect of heart rhythm irregularity could be related to the impairment of LV filling, changes in myocyte calcium handling, or neurohormonal activation.[3,13,14]

Of note, RV pacing alone can impair LV function.[15] This bias was partially overcome by the study of Melenovsky et al.,[16] which performed irregular pacing through exposed electrodes of a biventricular pacemaker in patients with chronic heart failure. A key feature of our hemodynamic model was the use of HB pacing, which enabled even more natural activation of the LV.

4.3 | Clinical implications

From a clinical perspective, results from this study provide the rationale to support strategies aiming at restoration and maintenance of sinus rhythm, such as electrical cardioversion, antiarrhythmic drugs, and catheter ablation. Patients in whom sinus rhythm cannot be achieved could benefit not only from rate control but also from the regularization of the heart rhythm by permanent selective HB pacing combined with AV node ablation.

4.4 | Study limitations

Our study investigated only acute hemodynamic changes during AF, not accounting for possible long-term compensatory mechanisms. The hemodynamics was not investigated during the patients' native (induced) AF. Such a design would not allow the evaluation of the hemodynamics of AF independently from the HR. Furthermore, our study included patients with preserved LV ejection fraction. It is conceivable that the hemodynamic impact of AF would be even more pronounced in patients with chronic LV systolic dysfunction. Measurement of CI by ICE was performed only in the last eight patients due to technical difficulties with the hardware setup in the first four patients. Nevertheless, the changes in CI were prominent enough to allow for an adequate statistical comparison by a paired *t* test.

Moreover, sinus rhythm was simulated by pacing from the proximal CS instead of the high RA to avoid catheter displacement during rapid pacing and to avoid atrial ectopic beats by mechanical irritation. This could have resulted in a slightly shorter AV delay during RA pacing, although the site of RA stimulation did not affect the hemodynamics during stimulated AF.

Another potential limitation is the absence of autonomic blockade during the study protocol, which could have theoretically altered the hemodynamics by sympathetic stimulation. To account for this potential bias, we applied different pacing sequences in random order and calculated the average values of the hemodynamic variables from repeated measurements. Moreover, each change in the pacing sequence included a blanking period of regular pacing to stabilize the hemodynamics.

5 | CONCLUSION

This study demonstrated the detrimental hemodynamic effect of AF and described the independent contribution of the absence of atrial kick, heart rhythm irregularity, and increased HR. These findings provide the translational basis for rhythm-control strategies in patients with AF and HR regularization strategies by permanent HB pacing if sinus rhythm cannot be maintained.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception and design or the acquisition, analysis, or interpretation of the data: Predrag Stojadinović, Aslesha Deshraju, Dan Wichterle, Masato Fukunaga, and Marek Šramko. *Substantial contributions to the drafting of the articles or critical revision for important intellectual content*: Predrag Stojadinović, Dan Wichterle, Petr Peichl, Josef Kautzner, and Marek Šramko. *Final approval of the version to be published*: Josef Kautzner and Marek Šramko. *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 Stojadinović and Marek Šramko.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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