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CORRESPONDENCE

Research Correspondence

Absence of Acute Effects of Angiotensin II on Atrial Electrophysiology in Humans

To the Editor: In recent years, the pioneering work of Wijffels et al. (1) has demonstrated the importance of atrial remodeling in development of an atrial substrate conducive to sustained atrial fibrillation (AF). A range of factors has been implicated in this process. Among these factors, indirect evidence suggests a role for the renin-angiotensin system. In differing animal models, angiotensin-converting enzyme inhibition or angiotensin II (AII) antagonists has been shown to prevent both acute (hours) (2) electrical remodeling and chronic (weeks) structural remodeling (3). Although the mechanism for these effects remains uncertain, the inhibition of acute AF-induced remodeling by these agents suggests that AII may have direct effects on atrial electrophysiology. In the current study, we examined the acute effects of AII on atrial electrophysiology in humans.

Our study population included 12 patients with supraventricular tachycardia who were undergoing curative ablation. Autonomic blockade was administered at commencement. Continuous heart rate and blood pressure monitoring was performed. Multipolar catheters included: 1) a coronary sinus (CS) catheter; 2) a crista terminalis (CT) catheter; 3) a lateral right atrium (RA) catheter; and 4) a His bundle catheter.

Atrial effective refractory period (ERP) was measured at the distal CS and high lateral RA at cycle lengths of 600, 500, and 400 ms. Dispersion of atrial ERP was defined as the difference between the averaged atrial ERP at both sites. Atrial conduction was measured in both atria at pacing cycle lengths of 600, 500, and 400 ms. Local conduction time was measured along the lateral RA and CS catheters.

Conduction delay was analyzed by the presence of discrete double potentials and fractionated electrograms and assessed during pacing at 600, 500, and 400 ms and during extra stimulus testing from distal CS and high lateral RA. The inducibility of AF (>5 s) was recorded during ERP testing.

Angiotensin II was obtained from Clinalfa AG (Laufelfingen, Switzerland). The pure peptide was then dissolved in normal saline before infusion. Electrophysiology measurements were performed at three different AII time points: 1) baseline, 2) low-dose infusion (2 ng/kg/min), and 3) high-dose infusion (5 ng/kg/min). These doses were chosen as those that have previously resulted in a significant vasopressor effect (4). The AII levels were measured at these time points and at 10 min after the AII infusion.

Data are expressed as mean ± SEM. For multiple comparisons between groups, data were analyzed by repeated-measures analysis of variance followed by the Scheffé test for multiple comparisons. Statistical significance was assumed at $p < 0.05$.

Twelve patients (8 female/4 male, mean age 37.7 ± 4.2 years) underwent an electrophysiology study. Plasma AII levels were 57.0 ± 14.8 pg/ml at baseline, 85.5 ± 18.7 pg/ml at low dose, 414 ± 153 pg/ml at high dose, and 117.1 ± 51.9 pg/ml at completion ($p < 0.05$). A significant hemodynamic response was observed during both low- and high-dose AII infusion (Fig. 1). Systolic/diastolic blood pressures were 117.0 ± 2.2/76 ± 2.4 mm Hg at baseline; 123.0 ± 2.3/81.6 ± 2.2 mm Hg at low dose ($p < 0.01$); 138.0 ± 3.6/91.5 ± 2.9 mm Hg at high dose ($p < 0.01$); and 111.6 ± 2.3/73.9 ± 2.3 mm Hg at completion, respectively (Fig. 1).

Atrial refractoriness did not show a significant acute change in response to AII at any of the sites and cycle lengths tested (Fig. 2). There was no significant increase in dispersion of ERP in response to AII. Dispersion at 400 ms at baseline was 35.4 ± 9.4 ms, at low-dose AII was 36.1 ± 8.5 ms, and at high-dose AII was 32 ± 6.9 ms. Conduction times as measured in both right and left atria were not significantly altered by AII (Fig. 2). Conduction delay along the CT as determined by the number and width of double potentials and fractionated signals was not significantly altered by AII. There was no significant change in AF inducibility or duration during either low- or high-dose AII.

This study presents detailed prospective information on the acute atrial electrophysiological effects of AII in humans. No

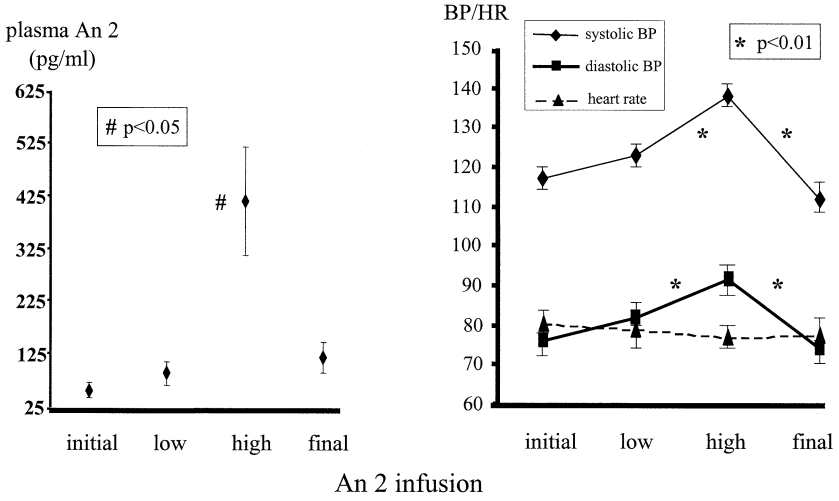

Figure 1. The angiotensin II (An 2) infusion resulted in a significant elevation in plasma levels **(left panel)** as well as systolic blood pressure (BP) ($p < 0.01$) and diastolic BP ($p < 0.01$) **(right panel)** without alteration in heart rate (HR).

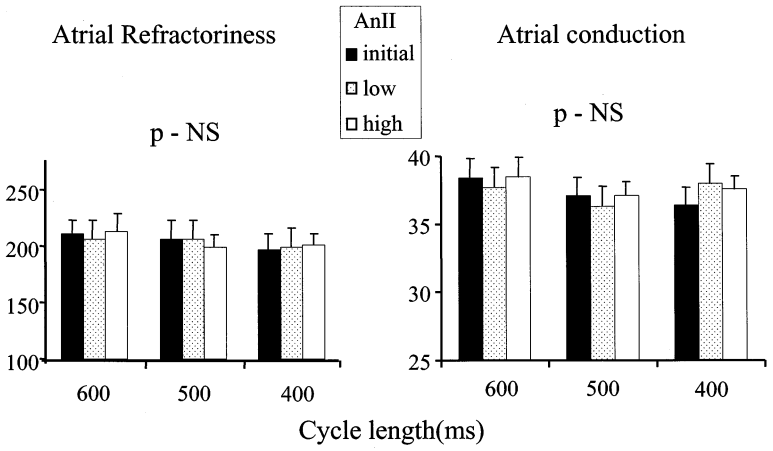

Figure 2. Atrial refractoriness and conduction times measured at the distal coronary sinus **(left panel)** and high lateral RA **(right panel)** at three cycle lengths demonstrated no significant change in response to angiotensin II (AnII).

significant direct effects on atrial electrophysiology were observed in response to an infusion of AII sufficient to produce a seven-fold increase in the plasma level of AII and a highly significant hemodynamic response. The AII level achieved was significantly greater than that observed in heart failure (5).

The renin angiotensin system has been implicated previously in acute atrial electrical remodeling. In the rapid atrial pacing model, it has been shown that AII levels increase in the first 24 h and then plateau for the duration of rapid atrial pacing (6). Nakashima et al. (2) demonstrated that dogs treated with either candesartan or captopril showed complete inhibition of electrical remodeling seen in response to 3 h of rapid atrial pacing. They concluded that AII might be implicated in the mechanism of acute remodeling. However, Shinagawa et al (7) observed no effect of enalapril on atrial remodeling in dogs subjected to rapid atrial pacing for seven days.

Several previous animal studies have demonstrated that AII may have direct electrophysiologic effects via modification of ion channel function. However, these effects generally were seen at concentrations beyond physiologic levels.

The renin angiotensin system also has been implicated in chronic atrial remodeling in animals (2,3,6,8) and humans (9). Seminal work by Li et al. (3) in dogs with heart failure found that enalapril attenuated the effects of heart failure on atrial conduction, fibrosis, and AF promotion. Clinical studies have suggested that AII antagonists or angiotensin-converting enzyme inhibitors may be effective in reducing AF in patients with heart failure or after cardioversion (10,11).

Angiotensin II infusion at doses sufficient to produce significant hemodynamic effects does not have any measurable effect on atrial electrophysiology in humans. It is therefore unlikely to be implicated in the mechanism of acute electrical remodeling. However, these results do not exclude it from having an important role in chronic fibrosis-related remodeling.

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REFERENCES

1. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954–68.
2. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. Circulation 2000;101:2612–7.
3. Li D, Shinagawa K, Pang L, et al. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. Circulation 2001;104:2608–14.
4. Clarkson PB, Wheeldon NM, MacLeod C, Tennent M, MacDonald TM. Effects of angiotensin II and aldosterone on diastolic function in vivo in normal man. Clin Sci (Lond) 1994;87:397–401.
5. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 1990;82:1730–6.
6. Willems R, Sipido KR, Holemans P, Ector H, Van de Werf F, Heidbuchel H. Different patterns of angiotensin II and atrial natriuretic peptide secretion in a sheep model of atrial fibrillation. J Cardiovasc Electrophysiol 2001;12:1387–92.
7. Shinagawa K, Mitamura H, Ogawa S, Nattel S. Effects of inhibiting Na(+)/H(+)-exchange or angiotensin converting enzyme on atrial tachycardia-induced remodeling. Cardiovasc Res 2002;54:438–46.
8. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. J Am Coll Cardiol 2003;41:2197–204.
9. Goette A, Arndt M, Rocken C, et al. Regulation of angiotensin II receptor subtypes during atrial fibrillation in humans. Circulation 2000;101:2678–81.

10. Madrid AH, Bueno MG, Rebollo JM, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. Circulation 2002;106:331–6.

11. Vermes E, Tardif JC, Bourassa MG, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. Circulation 2003;107:2926–31.

The Prognostic Importance of Body Mass Index After Complicated Myocardial Infarction

To the Editor: Obesity is related to cardiovascular risk factors and is an independent risk factor for coronary artery disease (CAD) and premature death (1,2). However, the importance of obesity to mortality and morbidity in patients with established CAD is not well defined. The present analysis evaluated the importance of body mass index (BMI) to prognosis after complicated acute myocardial infarction (AMI).

In post-hoc analysis, we examined the impact of baseline BMI on all-cause death, cardiac death (death from AMI, chronic heart failure [CHF], other cardiac causes, and sudden cardiac death), cancer death, and AMI and CHF hospitalization in 5,388 patients with complicated AMI who were included in the OPtimal Trial In Myocardial infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) (3). Prior to data analysis, patients were categorized into four BMI groups: underweight, <22.00; normal weight, 22.00 to 24.99; overweight, 25.00 to 29.99; obese, ≥30.00 kg/m^2. Univariate and multivariate logistic regression analysis and analysis of variance were performed (StatView 5.0.1, SAS Institute, Cary, North Carolina). Multivariate analyses adjusted for 46 variables comprising demographics, patient history, medication, physical examination, and biochemical analyses. Mean study drug dose percent (MSDD%) was calculated as mean percentage of the study drug target dose (captopril/losartan) during each patient's follow-up. We denoted significance to be $p < 0.05$.

Baseline BMI ranged from 13.2 to 49.4 kg/m^2. Table 1 depicts baseline characteristics. Median follow-up was 2.8 years (range 1 to 1,471 days). Table 2 shows the main results of univariate and multivariate analyses. Additionally, BMI categories had similar adjusted risk of cancer death (n = 83), CHF hospitalization (n = 585), and number of CHF hospitalizations (n = 916) and CHF hospitalization days (n = 8,646). One-week mortality was comparable among BMI categories (1.8% to 2.5%). The BMI category was independently ($p = 0.018$) related to the number of AMIs (n = 975)—adjusted relative frequency compared with normal-weight: underweight, 0.93; overweight, 0.78; obese, 0.82.

In univariate analysis, there was a significant association between BMI category and MSDD%: underweight, 68.55; normal weight, 70.24; overweight, 74.13; obese, 76.91. In univariate analysis, a higher MSDD% was significantly protective of all end points ($p < 0.0001$), except cancer death. However, the addition of MSDD% to the multivariate analyses did not attenuate the independent associations shown in Table 2.

Table 1. Baseline Characteristics by Baseline BMI Group

	Baseline BMI Group							
	Underweight n = 485 (9%)		Normal n = 1421 (26%)		Overweight n = 2520 (47%)		Obese n = 962 (18%)	
Baseline Characteristic	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (yrs)	70.3	10.70	68.9	10.02	66.6	9.55	65.5	9.19
Pulse rate (beats/min)	75.6	14.17	74.6	14.49	75.3	13.94	75.3	14.06
Systolic blood pressure (mm Hg)	120.3	17.85	120.7	16.09	123.0	16.72	126.5	17.42
Triglycerides (mmol/l)	1.60	0.66	1.72	0.76	1.97	0.93	2.18	1.10
HDL (mmol/l)	1.24	0.34	1.19	0.32	1.15	0.29	1.12	0.28
LDL (mmol/l)	3.42	1.03	3.33	1.03	3.38	1.12	3.32	1.23
Hemoglobin (g/l)	129.8	15.41	132.0	14.29	135.0	13.87	136.0	14.54
Potassium (mmol/l)	4.17	0.49	4.16	0.44	4.16	0.46	4.14	0.45
Uric acid (μmol/l)	321.3	111.7	330.4	101.9	345.6	93.6	362.7	96.8
Serum creatinine (mmol/l)	97.6	26.27	100.1	24.51	100.4	20.95	99.4	22.68
Glucose (mmol/l)	7.09	2.80	7.19	2.90	7.56	3.15	7.98	3.16
	n	%	n	%	n	%	n	%
Female gender	209	43.1	388	27.3	605	24.0	342	35.6
Current smoker	216	44.5	487	34.3	796	31.6	303	31.5
History of CHF	37	7.6	102	7.2	121	4.8	74	7.7
History of diabetes	48	9.9	179	12.6	448	17.8	255	26.5
History of hypercholesterolemia	121	24.9	434	30.5	836	33.2	374	38.9
History of AMI	92	19.0	259	18.2	444	17.6	179	18.6
In-hospital aspirin	457	94.2	1357	95.5	2412	95.7	92.1	95.7
In-hospital beta-blocker	354	73.0	1166	82.1	2098	83.3	796	82.7
In-hospital diuretic	315	64.9	918	64.6	1655	65.7	705	73.3
In-hospital statin	176	36.3	641	45.1	1242	49.3	501	52.1
In-hospital thrombolytic	253	52.2	747	52.6	1437	57.0	516	53.6

AMI = acute myocardial infarction; BMI = body mass index; CHF = chronic heart failure; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol.