Impaired Exercise-Induced Vasodilatation in Chronic Atrial Fibrillation

— Role of Endothelium-Derived Nitric Oxide —

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Exercise capacity is often reduced in patients with atrial fibrillation (AF), but very few studies have focused on changes in endothelial function as a potential mechanism for the exercise limitation. The present study used venous occlusion plethysmography to investigate whether nitric oxide (NO)-mediated vasodilatation is attenuated during exercise in patients with AF by measuring forearm blood flow (FBF) in 10 patients at rest and immediately after 2 levels of rhythmic handgrip exercise, before and after inhibition of NO synthesis with N^G-monomethyl-L-arginine (L-NMMA, 100 μmol). The measurements were repeated 1 day after restoration of sinus rhythm by cardioversion. FBF responses to graded doses of acetylcholine (ACh) were also observed before and after cardioversion. Heart rate decreased after cardioversion, but blood pressure did not change. FBF at rest was not affected by cardioversion, but at the highest level of exercise it increased from 28.4±2.3 ml·min⁻¹·dl⁻¹ before to 39.4±3.2 ml·min⁻¹·dl⁻¹ after cardioversion (*p*<0.05). L-NMMA significantly decreased FBF at rest (*p*<0.01) and depressed the increase in FBF response to exercise after (*p*<0.01), but not before cardioversion. The FBF response to ACh was also accelerated significantly after cardioversion. The present results provide new evidence that NO bioavailability is depressed at rest and during exercise in patients with AF. (*Circ J* 2002; 66: 583–588)

Key Words: Cardioversion; Forearm blood flow; NO synthesis

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice¹ and patients with chronic AF often have reduced exercise capacity^{2,3} which is usually ascribed to insufficient cardiac output to meet the increased demand. Skeletal muscle arterioles vasodilate in response to exercise to augment oxygen delivery to working muscle⁴ and the endothelium plays an important role in the functional hyperemia of skeletal muscle, probably through the release of endothelium-derived relaxing factors^{5,6}. Nitric oxide (NO) has been identified as one of the most important of these factors in metabolic vasodilatation during exercise in humans^{7–10} but the extent to which endothelium-derived NO contributes to vasodilatation during exercise in patients with AF is unknown.

The present study investigated endothelium-derived NO-mediated vasodilatation during exercise before and after cardioversion in patients with chronic AF, using venous occlusion plethysmography to measure forearm blood flow (FBF) at rest and immediately after rhythmic handgrip exercise, before and after inhibition of endogenous NO synthesis by arterial administration of a substituted arginine analog N^G-monomethyl-L-arginine (L-NMMA).

Methods

Study Population

Thirteen patients with AF of more than 1 month's duration were enrolled (mean age, 66±10 years; 9 males, 4 females): 3 had underlying heart disease and 10 had lone AF. Patients with hyperthyroidism, left atrial thrombus on transesophageal echocardiography, or coronary artery disease were excluded. Of the 3 patients with underlying heart disease, 1 had dilated cardiomyopathy and 2 had had aortic and mitral prosthetic valve replacement surgery with mild transvalvular leakage. Lone AF was defined by the absence of cardiovascular disease by history, physical and laboratory examination, 12-lead electrocardiogram (ECG), echocardiogram, left ventriculography and coronary angiography. Smokers were also excluded. Seven patients were taking digitalis, 3 were taking diuretics, and 1 was taking angiotensin converting enzyme (ACE) inhibitor. One patient was receiving bezafibrate for hypercholesterolemia. There were no cases of diabetes mellitus or hypertension.

The protocol was approved by the institutional Medical Ethics Committee and written informed consent was obtained from each participant.

Study Design

All participants were instructed to abstain from eating food and drinking caffeinated beverages for at least 12 h before the study. Those taking digitalis were instructed to discontinue treatment 7 days before the study, and all vasoacting agents except antiarrhythmic agents were discontinued 48 h beforehand. Diuretics were discontinued on

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Table 1 Reproducibility of Forearm Blood Flow (FBF) Measurements at Rest and During Rhythmic Hand Grip Exercise

	First exercise		Second exercise	
	Exercise level (kg)	FBF (ml·min ⁻¹ ·dl ⁻¹)	Exercise level (kg)	FBF (ml·min ⁻¹ ·dl ⁻¹)
Rest		3.4±0.4		3.3±0.3
Ex 1	13.2±2.2	19.6±2.9	12.9±2.2	19.9±2.2
Ex 2	23.0±2.5	30.5±4.7	22.7±3.3	31.2±4.1

Values are mean±SE.

the morning of the study. During this preparatory period, the patients were closely monitored for any evidence of cardiac decompensation.

The study was performed with the patients supine in an air-conditioned room at a temperature of 25–26°C. FBF (ml·min⁻¹·dl⁻¹ forearm tissue volume) was determined by venous occlusion plethysmography as described elsewhere^{11,12}. Briefly, under local anesthesia with 1% lidocaine, the brachial artery of the non-dominant arm (the left arm) was cannulated for pressure monitoring and drug infusion with a 22-gauge polyethylene catheter (RA-4122, Arrow Inc, Reading, PA, USA). This arm was slightly elevated above the level of the right atrium, and a mercury-filled silicone strain gauge was placed on the widest part of the forearm. The strain gauge was connected to a Hokanson EC-5R Plethysmograph (Hokanson Inc, Bellevue, WA, USA) that was calibrated to measure the percent change in volume, and this was connected in turn to a chart recorder to record the flow measurements. For each measurement, a cuff placed around the upper arm was inflated to 40 mmHg with a rapid cuff inflator (E-10, Hokanson Inc) to occlude venous outflow from the extremity. A wrist cuff was inflated to suprasystolic pressure 1 min before each measurement to exclude the hand circulation. The venous occluding cuff was inflated for 5 s at 10-s intervals. FBF at rest was determined as the average of 4 flow measurements. Systemic blood pressure was measured with a cuff sphygmomanometer placed on the contralateral arm, and arterial pressure was continuously monitored on the side of the FBF measurements with a Life Scope 12 polygraph (Nihonkoden Inc, Tokyo, Japan). Heart rate (HR) was monitored electrocardiographically. Forearm vascular resistance (mmHg·ml⁻¹·min⁻¹·dl⁻¹ forearm tissue volume) was calculated by dividing the mean arterial pressure (diastolic pressure plus one-third of pulse pressure) by the FBF. Each measurement was independently calculated by 2 of the authors and the results were used for later analysis.

Study Protocol At least 30 min were allowed to elapse after placement of the catheter and the strain gauge for the subjects to become accustomed to the study conditions before beginning the experiment.

Endothelium-Dependent Vasodilatation Using Acetylcholine FBF measurement was performed at baseline and then repeated during intra-arterial infusion of graded doses of ACh (3.75, 7.5, 15 and 30 µg/min). Each dose was infused over 4 min and FBF was measured during the last 2 min.

FBF Measurements at Rest and Immediately After Exercise During Control Conditions After completion of the FBF measurement during the infusion of ACh, the patients rested until FBF returned to baseline (approx 40 min), after which they performed rhythmic handgrip exercise using a quantitative handgrip (My-Gripper, Yamasa Tokei Inc, Japan). Subjects rhythmically squeezed the handgrip dynamometer in 2-s cycles of 1 s of handgrip pressure alternat-

ing with 1 s of rest. Two levels of exercise, corresponding to 25% (Ex 1) and 50% (Ex 2) of a previously determined maximal voluntary contraction, were performed for 3 min each. Total work for each level was measured by the quantitative handgrip, and exercise strength was calculated by dividing the total work by the exercise time. FBF was measured immediately after cessation of exercise and for 3 min thereafter. Hand circulation was not arrested during measurement of FBF in the exercise protocol, because the inflated wrist cuff considerably restricts handgrip exercise.

FBF Measurements at Rest and Immediately After Exercise in NO Synthesis Inhibition At a minimum of approximately 90 min after exercise, when FBF had returned to the baseline level, L-NMMA (Cinalfa Co, Läuelfingen, Switzerland) was infused intra-arterially at a dose of 100 µmol over 5 min (the dose has been demonstrated to be effective in inhibiting NO synthase activity in isolated vascular tissue and in the intact human forearm circulation¹¹). Five minutes after the infusion was completed, baseline hemodynamics were measured and the exercise was repeated.

The same protocols were repeated 1 day after restoration of sinus rhythm by cardioversion.

Reproducibility of FBF Measurement During Handgrip Exercise To determine the reproducibility of FBF measurement during exercise, an additional 6 patients with lone AF performed rhythmic handgrip exercise at 25% (Ex 1) and 50% (Ex 2) of maximal voluntary contraction twice at 1 or 2 day intervals without any other intervention. Their FBF measurements during exercise were unchanged over time (Table 1).

Cardioversion Procedures All patients were anticoagulated with warfarin at doses adjusted to achieve an International Normalized Ratio of 2.0–3.0 for at least 2 weeks before cardioversion. Antiarrhythmic agents (aprindine at 40 mg/day or cibenzoline at 150 mg/day) were administered for at least 2 weeks before cardioversion and were continued throughout the study. Cardioversion was performed under light anesthesia with thiopental sodium and ventilatory assistance. The patients were continuously monitored electrocardiographically. Synchronized cardioversion was performed with an initial shock of 100 or 200 J and was repeated up to 360 J if the attempt was unsuccessful.

Transthoracic echocardiography was performed in all patients before and 2 days after cardioversion to measure left atrial diameter, left ventricular diameter and left ventricular function. Overall 24-h cardiac cycles were measured by Holter ECG monitoring (Marquette Laser Holter Systems, Milwaukee, WI, USA) before and 1 day after cardioversion.

Statistical Analysis

Data are expressed as mean±SE unless otherwise indicated. The effects of cardioversion were compared using ANOVA for repeated measures. When significant differences were observed, individual comparisons were made

Table 2 Clinical Characteristics of the 10 Patients Restored to Sinus Rhythm

Case no.	Age (years)	Sex	Heart disease	Duration of AF (months)	NYHA	Echocardiography				Medications
						LA	LVDd	LVDs	%FS	
1	44	M	Lone AF	2	—	42	49	34	31	apiridine
2	56	F	Lone AF	2	II	35	46	32	30	digoxin, apiridine
3	72	M	Lone AF	6	I	50	44	29	34	cibenzoline
4	75	F	Lone AF	3	II	48	40	21	48	digoxin, apiridine
5	56	M	Lone AF	14	II	47	51	38	25	apiridine
6	66	M	Lone AF	8	II	46	48	31	35	apiridine
7	74	M	Lone AF	20	I	49	51	27	47	apiridine
8	63	F	Post DVR	5	II	49	41	24	41	digoxin, flosemide, cibenzoline
9	56	F	Post DVR	3	I	41	42	30	29	digoxin, cibenzoline
10	76	M	DCM	4	III	56	69	59	14	digoxin, enalapril, flosemide, apiridine

AF, atrial fibrillation; DCM, dilated cardiomyopathy; DVR, aortic and mitral valve replacement; LA, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; NYHA, New York Heart Association functional class; %FS, percent fractional shortening.

Table 3 Effects of L-NMMA on Hemodynamics at Rest and During Exercise Before and After Direct Cardioversion

	Exercise level (kg)		Heart rate (beats/min)		Mean BP (mmHg)		FBF (ml·min ⁻¹ ·dl ⁻¹)		FVR (mmHg·ml ⁻¹ ·min ⁻¹ ·dl ⁻¹)	
	Control	L-NMMA	Control	L-NMMA	Control	L-NMMA	Control	L-NMMA	Control	L-NMMA
<i>Before DC</i>										
Rest			82±8	85±7	93±4	94±3	3.1±0.4	3.0±0.4	29.9±5.3	31.3±7.1
Ex 1	12.5±1.5	12.6±0.9	88±8	90±8	95±4	99±3	21.5±1.5*	20.0±2.1*	4.4±0.4*	4.6±0.6*
Ex 2	18.3±1.8	18.8±2.1	99±10*	96±8*	100±3*	101±3*	28.4±2.3*	26.1±2.4*	3.5±0.3*	3.9±0.4*
<i>After DC</i>										
Rest			66±4‡	65±4‡	90±3	93±2	3.4±0.3	2.7±0.7‡	26.2±3.3	36.5±4.6‡
Ex 1	12.4±1.2	12.1±1.4	70±3‡	71±3‡	93±3	102±2	27.2±2.4‡	17.5±2.4‡	3.3±0.4‡	5.9±0.6‡
Ex 2	18.2±2.1	18.4±1.9	74±4‡	76±4‡	100±3*	108±2*	39.4±3.2‡	23.8±2.2‡	2.4±0.3‡	4.5±0.4‡

Values are mean±SE. BP, systemic blood pressure; DC, direct cardioversion; Ex, hand grip exercise; FBF, forearm blood flow; FVR, forearm vascular resistance. **p*<0.05 vs corresponding value at rest, †*p*<0.05 vs corresponding value in control, ‡*p*<0.05 vs corresponding value before DC.

Fig 1. Forearm blood flow (FBF) response to 2 levels of handgrip exercise before (○) and after (●) cardioversion in individual cases with chronic atrial fibrillation.

using the Wilcoxon signed-rank test, with a modified Bonferroni correction for multiple comparisons. The effects of L-NMMA and cardioversion on the relationship between 2 variables was analyzed by multivariate regression analysis. Statistical significance was accepted at *p* values less than 0.05 (2-tailed).

Results

Conversion of AF to normal sinus rhythm was successful in 9 of the patients with lone AF and in all 3 patients with AF and underlying heart disease, but sinus rhythm could not be maintained in 2 of the patients with lone AF.

We therefore analyzed 7 patients with lone AF and 3 patients with AF and underlying heart disease (Table 2).

Hemodynamics at rest and during exercise are shown in Table 3, and FBF responses during exercise in Figs 1–3.

Hemodynamics Before and After Cardioversion During Control Conditions

Heart rate at rest decreased significantly from 82±8 to 66±4 beats/min after cardioversion (*p*<0.001), but mean blood pressure, FBF and forearm vascular resistance remained unchanged. Exercise increased HR both before and after cardioversion, but it was significantly lower during exercise after cardioversion. Mean blood pressure increased

Fig2. Forearm blood flow (FBF) responses to handgrip exercise during control conditions and after NO synthesis inhibition with L-NMMA before and after cardioversion (DC) in 10 patients with chronic atrial fibrillation.

Fig3. Effects of NO synthesis inhibition with L-NMMA on the percent changes in forearm blood flow from resting state (% changes in FBF) before and after cardioversion (DC) in 10 patients with chronic atrial fibrillation.

significantly during maximum exercise both before and after cardioversion, but there were no differences between before and after cardioversion. FBF increased significantly with the level of exercise, and forearm vascular resistance decreased significantly both before and after cardioversion. The increase in FBF during exercise was greater in 7 of 10 patients after cardioversion than before cardioversion, but it was unchanged in 3 patients with lone AF (cases 1–3; Fig 1). The mean FBF during exercise was significantly higher after cardioversion, and the slope of the regression line between FBF and the exercise level also increased significantly, from $1.39 \pm 0.13 \text{ kg} \cdot \text{ml}^{-1} \cdot \text{min}^{-1} \cdot \text{dl}^{-1}$ before cardioversion to $1.97 \pm 0.23 \text{ kg} \cdot \text{ml}^{-1} \cdot \text{min}^{-1} \cdot \text{dl}^{-1}$ after cardioversion ($p=0.01$) (Fig 2).

Effects of L-NMMA on Hemodynamics Before and After Cardioversion

L-NMMA did not have any effect on HR or blood pressure, either at rest or during exercise, before or after cardioversion. FBF at rest was significantly reduced by L-NMMA from $3.4 \pm 0.3 \text{ ml} \cdot \text{min}^{-1} \cdot \text{dl}^{-1}$ to $2.7 \pm 0.7 \text{ ml} \cdot \text{min}^{-1} \cdot \text{dl}^{-1}$ after cardioversion (% change from control: $-21 \pm 5\%$, $p=0.009$), whereas it was not affected before cardioversion (% change from control: $-3 \pm 4\%$, $p=0.96$). Similarly, fore-

Fig4. Effects of cardioversion (DC) on the percent changes in forearm blood flow from baseline (% changes in FBF) produced by intra-arterial infusion of acetylcholine in 10 patients with chronic atrial fibrillation.

arm vascular resistance at rest was significantly increased by L-NMMA ($p=0.01$) after but not before cardioversion. The FBF response to exercise was not affected by L-NMMA before cardioversion; however, the percent changes in FBF during exercise were significantly decreased by L-NMMA after cardioversion (Fig 3), and the slope of the regression line between FBF and exercise level was significantly depressed by L-NMMA after cardioversion ($1.18 \pm 0.14 \text{ kg} \cdot \text{ml}^{-1} \cdot \text{min}^{-1} \cdot \text{dl}^{-1}$, $p=0.002$) (Fig 2). The slope under NO synthesis inhibition after cardioversion was comparable to that before cardioversion ($1.26 \pm 0.18 \text{ kg} \cdot \text{ml}^{-1} \cdot \text{min}^{-1} \cdot \text{dl}^{-1}$, $p=0.12$) (Fig 2).

ACh-Induced Vasodilatation Before and After Cardioversion

The FBF response to intra-arterial infusion of ACh is shown in Fig 4. The drug infusion was well tolerated and caused no change in systemic hemodynamics at the doses used. There were dose-dependent increases in FBF before and after cardioversion: the baseline FBF before and after cardioversion was similar (3.0 ± 0.3 and $3.4 \pm 0.4 \text{ ml} \cdot \text{min}^{-1} \cdot \text{dl}^{-1}$, respectively, $p=0.16$), but the response of FBF to ACh was enhanced significantly after cardioversion. The percent change in FBF in response to the highest dose of ACh increased from $468 \pm 65\%$ before cardioversion to $642 \pm 136\%$ after cardioversion ($p=0.002$).

Holter Electrocardiographic and Echocardiographic Findings Before and After Cardioversion

The overall cardiac cycles per day decreased significantly after cardioversion from $129,177 \pm 14,600$ to $103,871 \pm 17,611$ beats/day ($p=0.02$). Echocardiographic examination showed no significant differences in left atrial diameter, left ventricular end-diastolic and end-systolic diameters or frac-

tional shortening between before and after cardioversion.

Discussion

The present study describes the effects of cardioversion on the increase in blood flow of the forearm in patients with AF in response to rhythmic handgrip exercise before and after regional inhibition of NO synthesis by administration of L-NMMA in the brachial artery. (1) FBF at rest was not affected by cardioversion, but its response to exercise was significantly increased by cardioversion. (2) L-NMMA significantly reduced FBF both at rest and during exercise after cardioversion, but not before cardioversion. (3) The response of FBF to exercise under inhibition of NO synthesis was not affected by cardioversion. The findings suggest that in patients with AF there is attenuated NO-mediated vasodilatation in the peripheral circulation during exercise and that this attenuation can be ameliorated or reversed by cardioversion.

Endothelium-derived NO plays an important role in the regulation of basal vasomotor tone and vasodilatation during exercise to maintain muscle blood flow.⁹ Previous studies have demonstrated that the endothelium-derived NO-mediated vasodilatation is impaired in patients with congestive heart failure,¹⁰ resulting in an insufficient increase in blood flow during exercise;¹³ however, the subjects of those studies were in sinus rhythm. The question of whether NO-mediated vasodilatation during exercise is impaired in patients with chronic AF has not been addressed, but it is of clinical relevance as a possible mechanism limiting exercise capacity in patients with AF. We have previously reported that endothelium-dependent vasodilatation in response to ACh is impaired in patients with lone AF compared with normal subjects in sinus rhythm, and that the impairment can be reversed by cardioversion.¹⁴ Minamino et al demonstrated that the plasma concentrations of nitrite and nitrate, which are stable end products of NO, are decreased in patients with AF compared with subjects in sinus rhythm.¹⁵ The present study shows that the effects of L-NMMA on FBF at rest and during exercise are increased after cardioversion and suggest reduced bioavailability of NO in AF.

However, the precise mechanism is unclear. First, although we did not observe cardiac output, it is possible that at the surface of the endothelial cell the decreased stroke volume in AF might decrease the shear stress, which is a potent stimulus of endothelium-derived NO synthesis.^{16,17} Second, the flow pattern in AF might also play an important role. Topper et al reported that expression of NO synthase mRNA from cultured human umbilical vein endothelial cells was markedly depressed in the turbulent flow conditions.¹⁸ It is possible that the irregularity of the pulsatile flow and pressure in AF similarly depresses NO synthase expression. Third, hemostatic factors such as fibrin monomer and fibrinogen degradation products,^{15,19} vasoactive molecules such as angiotensin II²⁰ and endothelin^{21,22} or the autonomic nervous system²³ may also be responsible. Finally, oxidative stress in AF should be considered. Recently, Mihm et al reported that levels of myofibrillar creatine kinase, which is highly sensitive to oxidative injury, were significantly reduced in patients with AF compared with controls in sinus rhythm, suggesting an increase in oxidative stress in AF.²⁴ In the present study, we could not determine whether the depressed bioavailability of NO was secondary to a decrease in the synthesis of NO and/or an increase in its deactivation. Further efforts to identify the

precise mechanism behind our observations are warranted.

In the present study, even after the inhibition of NO synthesis, exercise still produced a substantial increase in FBF and there were no differences in this response between before and after cardioversion. This suggests that non-NO-mediated metabolic vasodilator mechanisms that respond to the demands of the exercising muscle, or other endothelium-dependent vasodilators such as prostaglandins or endothelium-derived hyperpolarizing factor (EDHF), are preserved in AF. Additionally, in the present study, despite the decreased NO-mediated vasodilatation at rest before cardioversion, there were no significant differences in FBF at rest between before and after cardioversion, indicating that other vasodilator mechanism play a role in preserving the peripheral circulation at rest in patients with AF.

Study Limitations

Measurement of blood flow by plethysmography has methodological limitations. The reliability of blood flow measurements in AF is questionable, given the known beat-to-beat variations associated with AF rhythm. However, we demonstrated that the FBF measurements are reproducible both at rest and during exercise in the setting of AF. A second limitation is the possible effect of antiarrhythmic agents on endothelial function. In the present study, the patients were given either aprindine or cibenzoline for at least 2 weeks before cardioversion and throughout the study and these agents have endothelium-independent vasoacting properties in higher doses.^{25,26} However, because they were not discontinued for the study, their influence on the improvement of endothelial function after cardioversion is eliminated. Third, this study is limited by the relatively small number of subjects studied, which limits the statistical power of the data, possibly masking changes in hemodynamics before and after cardioversion. In particular, 3 patients (cases 1–3) showed no change in FBF response to exercise after cardioversion. In these patients, the administration of L-NMMA similarly decreased FBF both before and after cardioversion, suggesting preserved NO bioavailability even in AF. Although our present study provides new evidence of depressed NO bioavailability in the setting of chronic AF, the time sequence and interrelationships among NO bioavailability, humoral factors, hemodynamics and systemic exercise capacity remain to be determined.

Conclusions

This study examined whether the reduced exercise capacity in patients with chronic AF is associated with evidence of endothelial dysfunction. We have demonstrated for the first time that NO-mediated vasodilatation during exercise is impaired in AF rhythm, and that this response is improved early after restoration to sinus rhythm by cardioversion. Further studies to investigate the mechanisms and possible therapeutic implications of this impairment are warranted.

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