Impaired myocardial perfusion and perfusion reserve associated with increased coronary resistance in persistent idiopathic atrial fibrillation

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Aims Patients with atrial fibrillation (AF) present with symptoms of myocardial ischaemia despite exclusion of coronary artery disease. A small vessel disease has been suggested. We quantified myocardial perfusion, perfusion reserve, and coronary vascular resistance (CVR) in AF patients using positron emission tomography (PET).

Methods and results Twenty-five male patients (age: 58 ± 13 years) with persistent idiopathic AF were compared with 13 age- and risk-matched male controls (age: 56 ± 8 years). Using H215O-PET, myocardial blood flow (MBF) was quantified at rest, at hyperaemia (adenosine), and during cold-pressor-testing (CPT). Scans were repeated 4.1 ± 2.3 months after cardioversion in 10 AF patients. In AF, resting MBF (0.95 ± 0.19 vs. 1.14 ± 0.22 mL/min/mL; P = 0.009), hyperaemic MBF (2.07 ± 0.80 vs. 3.33 ± 0.78 mL/min/mL; P < 0.001), and MBF under CPT (0.90 ± 0.25 vs. 1.14 ± 0.25 mL/min/mL; P < 0.014) were significantly reduced compared with matched controls. Hyperaemic CVR was increased in AF (47 ± 21 vs. 29 ± 7 mmHg × mL/min/mL; P = 0.012) but unchanged at rest and under CPT. After cardioversion, resting MBF and MBF under CPT in AF were similar to matched controls, however, hyperaemic MBF and CVR were not recovered.

Conclusion In AF, MBF at baseline, at hyperaemia, and at CPT is reduced, whereas CVR under hyperaemic conditions is increased. Following electrical cardioversion, these findings are partly reversible and therefore most likely secondary to the arrhythmia.

Keywords Atrial fibrillation; Myocardial perfusion; Myocardial blood flow; Coronary vascular resistance; Positron emission tomography

Introduction Atrial fibrillation (AF) is the most common sustained arrhythmia, particularly in the elderly. It often requires medical treatment and is associated with increased morbidity and mortality. Even in the absence of coronary artery disease (CAD), there is a high incidence of angina-like chest pain in AF patients. This may be unspecific owing to sensation of abnormal cardiac motion but may also result from an impaired myocardial perfusion. Early experimental studies in dogs demonstrated that artificially induced AF resulted in an impaired vasodilator response.1 In patients suffering from persistent AF and mitral valve stenosis, early studies suggested an impaired coronary blood flow.2 Furthermore, recent studies demonstrated short-term adverse effects of artificially induced acute AF on myocardial blood flow (MBF).3

These studies were hampered by either the lack of quantitative non-invasive methods to study MBF or investigations in artificially induced, acute AF. In the present study, we therefore investigated for the first time myocardial perfusion and perfusion reserve quantitatively in patients with idiopathic persistent AF using positron emission tomography (PET) and radioactively labelled water (H215O-PET).

Methods

Study population Patients Twenty-five male patients (age: 58 ± 13 years) with idiopathic persistent AF (duration: 32 ± 41 months) were enrolled in this study. Structural heart disease was excluded by detailed investigations in all patients. Table 1 shows the clinical characteristics of the group.
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AF, duration of atrial fibrillation; NYHA, New York Heart Association; ANP/BNP, atrial/bra brain natriuretic peptide; na, not available.
Table 2  Age- and risk-matched controls: characteristics, medication

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AF, duration of atrial fibrillation; NYHA, New York Heart Association; ANP/BNP, atrial/brain natriuretic peptide; na, not available.

Effect of electrical cardioversion on myocardial blood flow and coronary vascular resistance in atrial fibrillation patients.

To elucidate the effect of restoration of sinus rhythm by cardioversion, 17 patients were successfully converted into sinus rhythm electrically, another two with the help of catheter ablation. Of these, 17 patients were admitted to our institution for cardioversion of AF. Patients after cardioversion were not enrolled in the study. Valvular regurgitation lower than grade 2 was tolerated whereas any grade of valvular stenosis resulted in exclusion of the patient. Antiarrhythmic medication was performed in all patients to assess atrial fibrillation recurrence (Tables 1 and 2) and to achieve a normal heart rhythm after catheter ablation, when applicable. If at least 2 h after fasting, patients were monitored including caffeine-containing beverages, chocolate and smoking to avoid an interference with adenosine. At the time of scan, patients were taken before PET scans to obtain rate control only. Blood samples were taken before PET scans to obtain rate control only.
Young control group
In addition we compared AF patients to a group of nine young healthy male volunteers (age 33 ± 2 years) with sinus rhythm, normal heart rate, and a low likelihood for CAD as assessed by a low cardiovascular risk profile (young controls).

Study design
Non-invasive measurement of myocardial perfusion in vivo
MBF was assessed by dynamic PET (ECAT-921, Siemens/CTI, Knoxville, TN, USA) and 15O-labelled water. Briefly, MBF was measured after intravenous bolus injection of 500 MBq H215O over 20 s while performing a 26-frame dynamic PET acquisition over 5 min. The emission data were reconstructed (Hanning filter, PWHM 7.3 mm, zoom factor 2.3, 47 planes, matrix size 128 × 128). Factor images were generated from the dynamic H215O-scans and re-sliced into short-axis images perpendicular to the long axis of the left ventricle. This transformation matrix was also used to re-slice the dynamic water images. Regions of interest (ROIs) were placed manually on the short-axis planes of the factor images encompassing myocardial tissue, the left atrial cavity, and the right ventricular cavity. Arterial, venous, and tissue time-activity curves were fitted to a single-compartment model to quantify regional and global MBF (mL/min/mL) and perfusable tissue fraction (tf; mL of tissue perfusable by water/mL ROI).5

All patients and control subjects gave written informed consent to the study protocol being approved by the Ethics Committee of the University Hospital, Münster, Germany.

Hyperaemic flow reserve
In addition, hyperaemic MBF was measured from a second injection of H215O 2 min after initiation of a 7 min adenosine infusion at a rate of 140 μg/kg body weight/min. The hyperaemic coronary flow reserve (CFR) was calculated as the ratio of hyperaemic and baseline MBF.

Endothelium-dependent flow response
To assess maximal MBF triggered by an exogenous endothelial stimulus, MBF was additionally quantified during a CPT, i.e. with ice packs on hand and forearm. Another H215O bolus was injected after 90 s of this cold stimulus.

Haemodynamics
Heart rate and systolic, diastolic, and mean arterial blood pressures were determined for each subject during PET scans. Because of the unreliability of heart rate detection by an ECG monitor in AF, mean heart rates were calculated from Holter recordings (R-R intervals SDNN) at baseline, under adenosine, and at CPT.

Coronary vascular resistance
CVR in different settings (baseline, adenosine, cold-stress) was calculated by dividing mean arterial pressure with the respective MBF.

Neurohumoral parameters
Venous blood samples were taken at the baseline scan. Atrial and brain natriuretic peptide (ANP/BNP) were measured by an immunoradiometric assay (Nichols Institute Diagnostics BV, Wychen, the Netherlands; CIS-Bio International, Dreieich, Germany).

Statistical analysis
Results are expressed as mean ± SD. After testing for equality of variances (Levene test), Student’s t-tests were used for comparison between groups for the global values of MBF, CFR, and CVR. The Pearson correlation coefficient r was calculated to investigate associations between possible confounders and measured data. A P-value <0.05 was considered significant.

Results

Haemodynamics
Haemodynamics are given in Table 4. To eliminate potential inter-individual differences in cardiac workload, MBF was corrected at rest and following CPT for rate-pressure-product (RPP) (MBFcorrected = MBF/RPP × 10.000).6 In the AF patients enrolled, MBF was correlated with RPP (r = 0.55, P = 0.005), thus justifying RPP correction in this group as well. Adenosine-induced MBF remained uncorrected because the MBF-increase stimulated by adenosine is grossly independent of RPP.7

Myocardial blood flow
In AF patients, MBF at rest (0.95 ± 0.19 vs. 1.14 ± 0.22 mL/min/mL; P = 0.009, Figure 1) and hyperaemic MBF under adenosine (2.07 ± 0.80 vs. 3.33 ± 0.78 mL/min/mL; P < 0.001, Figure 1) were markedly reduced when compared with age- and risk-matched controls and even more pronounced when compared with young controls (young controls: MBF rest 1.14 ± 0.18 mL/min/mL, P = 0.015; MBF adenosine 3.92 ± 0.93 mL/min/mL; P < 0.001, Figure 1). Hyperaemic CFR was lower, but not significantly different between AF patients and matched controls (2.51 ± 1.04 vs. 3.24 ± 1.03; P = 0.07; Figure 2), however, compared with young controls this finding reached significance (2.51 ± 1.04 vs. 3.51 ± 0.94; P = 0.02, Figure 2).

Cold-stress induced no changes in MBF, neither in AF patients nor in matched controls (∆MBF −0.02 ± 0.25 vs. 0.00 ± 0.24 mL/min/mL; P = ns, Figure 2), but the expected approximately 15% increase in MBF in young controls (∆MBF: 0.17 ± 0.34 mL/min/mL, Figure 2). However, MBF following CPT remained lower in AF patients when compared with matched controls (0.90 ± 0.25 vs. 1.14 ± 0.25 mL/min/mL; P = 0.014, Figure 1) and young controls (1.31 ± 0.29 mL/min/mL; P < 0.001 vs. AF patients, Figure 1).

AF patients did not show any difference with controls regarding symptoms during either adenosine or cold-stress. In addition to the global analysis of MBFs, we measured regional MBFs in four ROIs (anterior, lateral, inferior, and septal wall) and found the described findings homogeneously distributed throughout the left ventricular myocardium (not shown).

Coronary vascular resistance
Minimal CVR (Figure 3) under hyperaemic conditions was significantly higher in AF than in matched controls (47 ± 21 vs. 29 ± 7 mmHg/(mL/min/mL); P = 0.012) and in young controls (24 ± 6 mmHg/(mL/min/mL); P = 0.004). At baseline (119 ± 23 vs. 109 ± 21 mmHg/(mL/min/mL); P = 0.19) and under cold-stress (123 ± 37 vs. 105 ± 24 mmHg/(mL/min/mL); P = 0.17) CVR was unchanged in AF patients when compared with matched controls. However, CVR under hyperaemia and under cold-stress was significantly increased in AF patients when compared with young controls (baseline 110 ± 22 mmHg/(mL/min/mL); P = ns; adenosine 24 ± 6 mmHg/(mL/min/mL); P = 0.004; CPT 93 ± 20 mmHg/(mL/min/mL); P = 0.04).
Effect of electrical cardioversion in atrial fibrillation patients

PET studies were repeated in 10 patients $4.1 \pm 2.3$ months after successful cardioversion. This subgroup was representative for the whole AF group: prior to cardioversion, none of the MBF, CVR, or haemodynamic parameters indicated any difference between the subgroup of patients where a stable sinus rhythm could be established and the subgroup that showed recurrence of AF. As in the whole AF group, resting MBF ($0.88 \pm 0.10$ vs. $1.14 \pm 0.22$ mL/min/mL; $P = 0.004$) and MBF under adenosine ($1.98 \pm 0.87$ vs. $2.35 \pm 0.21$ mL/min/mL; $P = 0.001$) were lower in the subgroup of patients where a stable sinus rhythm could be established. The subgroups did not differ in terms of CVR at baseline, under adenosine, or following CPT. Impaired myocardial perfusion and perfusion reserve associated with increased coronary resistance.
3.33 ± 0.78 mL/min/mL; \( P = 0.001 \) were reduced prior to cardioversion when compared with matched controls. Cold-stress induced no increase to resting flow in the AF subgroup and matched controls, whereas absolute MBF during CPT was lower in the AF subgroup (0.90 ± 0.32 vs. 1.14 ± 0.25 mL/min/mL; \( P = 0.078 \)). Four months after successful cardioversion, MBF at rest (1.13 ± 0.30 vs. 1.14 ± 0.22 mL/min/mL; \( P = \text{ns} \)) and following CPT (1.12 ± 0.33 vs. 1.14 ± 0.25 mL/min/mL; \( P = \text{ns} \)) were normalized in the AF subgroup when compared with matched controls. Hyperaemic MBF improved after cardioversion but remained significantly reduced when compared with matched controls (2.50 ± 0.84 vs. 3.33 ± 0.78 mL/min/mL; \( P = 0.042 \)). Interestingly, the CFR of AF patients was unchanged after cardioversion (2.49 ± 1.20 vs. 3.24 ± 1.03; \( P = \text{ns} \) vs. matched controls) (Figure 4).

In the AF subgroup undergoing cardioversion, minimal CVR under adenosine was increased prior to cardioversion when compared with matched controls (51 ± 26 vs. 29 ± 7 mmHg/(mL/min/mL); \( P = 0.017 \)). CVR at rest and following CPT were not significantly changed in AF patients pre- and post-cardioversion. However, CVR under adenosine was reduced by approximately 20% post-cardioversion, but remained elevated when compared with matched controls (41 ± 13 vs. 29 ± 7 mmHg/(mL/min/mL); \( P = 0.032 \)) (Figure 5).

**Neurohumoral parameters**

In AF patients, plasma levels of the vasoactive peptides ANP and BNP were elevated above reference values in controls (ANP: >100 pg/mL in 19 of 23 and BNP: >60 pg/mL in 12 of 23 AF patients) (Table 1). No correlation was found between these plasma levels and MBF, CVR, or CFR.

**Potentially confounding factors**

**Gender**

Only male subjects were studied showing a higher incidence of AF.

**Age**

The matched controls and the AF patients were matched for age. As expected, differences aggravated comparing AF patients with young controls.

**Risk factors**

Neither the coronary risk factors nor blood lipid fractions and the Framingham score assessing the individual global cardiovascular risk (all listed in Tables 1 and 2), known to potentially influence MBF and CVR, showed any correlation with the PET measurements in AF patients. There was no difference between AF patients and matched controls in any single risk factor, blood lipid fractions, or the
Framingham score (12.8 ± 7.8 vs. 14.0 ± 6.9%, P = ns). AF patients were additionally compared with young controls.

Duration of AF
Testing revealed no correlation between MBFs and CVRs and the duration of AF.

Medical treatment
Distribution of medication within study groups is shown in Tables 1 and 2. We tested the influence of medication comparing subgroups with and without beta-receptor antagonists, flecainide, and amiodarone. Neither of the drugs showed any influence on the results of the PET scans in AF patients. Testing the subgroup under beta-receptor antagonists vs. the rest of the controls did not reveal any changes in MBFs or CVRs. Other subgroups were too small for statistical analyses.

Discussion
AF in the absence of structural heart disease is frequently associated with symptoms suggestive of myocardial ischaemia. These observations may be related to an impairment of myocardial perfusion and perfusion reserve on a microvascular level. Based on this hypothesis, we used sophisticated state-of-the-art PET technology uniquely able to quantify myocardial perfusion and perfusion reserve in vivo.

Myocardial blood flow and coronary resistance in atrial fibrillation
We measured approximately 20% diminished resting MBF in AF. This is a unique finding, since other techniques previously investigating perfusion in AF were not capable of quantifying baseline MBF in absolute terms.

Hyperaemic MBF in AF was diminished by approximately 40%, and hyperaemic flow reserve by approximately 22%. This finding is in line with reports of reduced hyperaemic MBF in dogs with AF. Interestingly, Kochiadakis et al., who artificially induced short-term AF in pacemaker patients invasively, found a decrease of CFR from 3.7 ± 0.9 to 2.2 ± 0.5 in the same patients when switching from sinus rhythm to AF. Furthermore, our findings are consistent with earlier studies comparing patients with mitral stenosis and AF to patients with sinus rhythm and to patients after successful electric cardioversion, observing a reduced hyperaemic CFR in non-idiopathic AF.

In our study, maximal hyperaemic flow was induced by adenosine. Although partly acting as an endothelium-dependent vasodilator, adenosine mainly induces flow by an endothelium-independent direct action on the A2-adenosine receptors on vascular smooth muscle cells. Therefore, the endothelium-independent flow reserve seems to be impaired in AF.

In addition, we calculated the minimal CVR in AF and found it markedly elevated by approximately 62% in AF when compared with controls. This coincides with a 67% increase of the Doppler-derived CVR index observed in artificially induced AF.

To assess the endothelium-mediated flow response, cold-stress was applied to AF patients and controls in this study for the first time. Both groups showed a blunted endothelial response, probably due to cardiovascular risk factors causing endothelial dysfunction. This was seen in at-risk groups in former studies. However, maximal MBF stimulated by CPT remained approximately 20% lower in AF patients when compared with matched and young controls associated with a approximately 20% elevation in CVR. Since the CPT-stimulated MBF was comparable between matched and young controls, this specific finding in AF patients might as well be connected with the arrhythmia.

Myocardial blood flow and coronary resistance after successful cardioversion
Cardioversion improved both MBF and CVR to normal levels at rest and under cold-stress. However, this improvement did not reach statistical significance, most likely due to the small sample size. At maximal hyperaemia, MBF improved by 25%, CVR declined by 20%. However, a significant difference when compared with controls remained in this small follow-up group. Overall, the tendency of improvement of MBF and CVR in AF due to conversion into sinus rhythm strengthens our presumption that AF is causal for the changes observed in the whole group of AF patients.

These findings are unique since, to our knowledge, no other study has measured these parameters in a follow-up design in AF patients. They might have clinical implications since they support the restoration of sinus rhythm. Ameliorated perfusion might be causal for the known improvement in quality-of-life after successful cardioversion.

Patients who stay free from relapse for our follow-up period of 4 months are most likely to stay free from AF constantly, whereas most relapses occur within the first 2 weeks after cardioversion. Whether the observed changes were secondary to the long relapse-free interval or vice versa cannot be answered by this study design. Studies with shorter follow-up intervals might investigate whether acute changes in MBF and CVR can predict the stability of the newly established sinus rhythm.

Pathophysiological considerations
Arrhythmia
Primarily, our observations could be attributed to the arrhythmia itself. Besides the acceleration in heart rate, the irregularity of ventricular cycle lengths in AF proved disadvantageous for haemodynamics and cardiac function. These functional deficits are re-ameliorated by a reduction of variance of cycle length by pacing or cardioversion to sinus rhythm. Since 4 months after cardioversion results are not normalized, the abnormalities in AF patients seem to be both triggered by the arrhythmia and maintained by additional mechanisms with longer recovery periods.

Sympathetic innervation
An activation of the sympathetic arm of the autonomic nervous system in AF is known. Besides β-adrenoceptor-mediated effects on cardiomyocytes, this should result in an enhanced vasoconstrictive tone of the arteries via α1-adrenoceptor-mediated activation of vascular smooth muscle cells. Ertl et al. found a reduced hyperaemic flow reserve under AF being normalized by the injection of an α1-adrenoceptor antagonist. Increased sympathetic activity might increase CVR and impair MBF in AF patients, both findings are present in our study population.
**Neurohumoral factors**

Tuinenburg et al.\textsuperscript{14} found plasma ANP elevated in patients with congestive heart failure and AF when compared to those with sinus rhythm. Accordingly, we found elevated levels of ANP and BNP in AF patients. These elevated levels of circulating vasoactive peptides can mediate a shift of the vascular tone towards vasoconstriction.

**Endothelial dysfunction**

Endothelial dysfunction is commonly seen in CAD and elevated cardiovascular risk factors. A marked decrease in endothelial nitric oxide synthase (eNOS) expression\textsuperscript{15} was also discovered in AF. As both groups show blunted endothelium-dependent flow responses in this study, it remains indefinite whether a reduced eNOS expression, the existing cardiovascular risk factors, or both are causal.

**Remodelling**

The underlying mechanism whose recovery outlasts acute effects of cardioversion may be myocardial remodelling.\textsuperscript{16} Reant et al.\textsuperscript{17} demonstrated over 1 year progressive reversibility of morphological remodelling after successful ablation of AF with an amelioration of ventricular function.

**Conclusions**

This study demonstrates an impairment of myocardial perfusion and hyperaemic perfusion reserve associated with an increase of coronary resistance in male patients suffering from idiopathic persistent AF. This might explain angina-like symptoms and diminished physical peak performance during AF. Perfusion abnormalities were not acutely and completely reversible after restoration of stable sinus rhythm. Therefore, the question if these are secondary to the arrhythmia, requires further studies to elucidate the underlying pathophysiological mechanisms.

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**References**


