Evaluation of ischaemia in patients with atrial fibrillation: impact of stress protocol on myocardial perfusion imaging accuracy

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Background
To evaluate the accuracy of myocardial perfusion imaging (MPI) on a novel cadmium-zinc-telluride camera in detecting significant coronary artery disease (CAD) in patients with atrial fibrillation (AF).

Methods and results
Seventy-four subjects with AF submitted to stress–rest MPI and coronary angiography were consecutively enrolled. One hundred and forty-eight patients in sinus rhythm, matched for age, sex, and type of stress–test protocol and with known coronary anatomy served as controls. The summed difference score, as measure of reversible myocardial ischaemia, was calculated. A coronary stenosis ≥70% was considered significant. The prevalence of significant CAD did not differ between AF patients and controls. At receiving operating characteristic analysis MPI showed relevant accuracy in unmasking the presence of significant CAD both in AF and in control patients (areas under the curve 0.71 vs. 0.80, P for difference: 0.212). However, after stratifying patients according to the stress protocol, a significant interaction between the presence of AF and MPI diagnostic power was evident. While in the case of a vasodilator stress–test MPI diagnostic accuracy remained high in both groups of patients (P for difference: 0.664), in those submitted to an exercise stress–test the diagnostic power of MPI was significantly lower in the presence of AF (P for difference: 0.039), because of a lower specificity. Interestingly, at multivariate analysis, a lower exercise duration (P = 0.017) was the major predictor of reduced MPI specificity.

Conclusion
The presence of AF impairs MPI accuracy on the detection significant CAD. This effect was only apparent in the case of an exercise stress–test, while disappeared in patients submitted to vasodilator stress.

Keywords
Myocardial perfusion imaging • Atrial fibrillation • Coronary artery disease • Cadmium-zinc-telluride • Diagnostic accuracy

Introduction
Despite the occurrence of myocardial perfusion abnormalities in patients with suspected CAD, it is generally linked to the presence of flow-limiting coronary luminal narrowing, significant left ventricular (LV) blood flow impairment may develop in the absence of anatomically significant coronary artery disease (CAD), still maintaining a significant adverse prognostic impact.

Accordingly, a precise definition of the location and quantitation of the extent myocardial ischaemia has become a key step in the functional evaluation of patients with suspected CAD. To this respect, myocardial perfusion imaging (MPI) at single-photon emission computed tomography (SPECT) allows a reproducible, semi-quantitative, evaluation of myocardial perfusion, still representing one of the most diffuse modalities for the non-invasive assessment of patients with suspected or known CAD. Nevertheless, in some relevant categories of subjects, such as those with atrial fibrillation (AF), the accuracy of SPECT-MPI has been shown to fall significantly. Interestingly, while some studies have associated the reduced accuracy of SPECT-imaging in the presence of AF to a
higher frequency of false-positive results, others have attributed the significantly lower diagnostic yield to a consistently reduced sensitivity.

Up to now, despite the relationship between the presence of AF and the accuracy of SPECT-MPI has been already investigated, a full understanding of this relevant topic is lacking and a more complete evaluation of the predictors of the reduced accuracy of SPECT-imaging in patients with AF highly needed.

The introduction of dedicated cardiac cameras equipped with cadmium-zinc-thallium (CZT) detectors, demonstrating a higher accuracy in the detection of significant CAD than traditional SPECT cameras with consistently reduced radiation burden, should allow the assessment of more subtle alteration of myocardial blood flow regulation. With these considerations in mind, we sought to assess the relationships between the presence of AF and the accuracy of MPI in the detection of significant CAD in a population of patients with suspected or known ischaemic heart disease (IHD).

**Methods**

**Patient population**

Between January 2011 and May 2014, 4170 subjects with anginal chest pain and suspected or known CAD were referred to our institution for a scintigraphic evaluation of myocardial perfusion at rest and after stress with a CZT camera. Among those, 74 consecutive patients with persistent or permanent AF, also submitted to invasive or computed tomography (CT) coronary angiography, were enrolled. From the same population of patients, a control group of subjects with sinus rhythm (SR), known coronary anatomy, and similar baseline clinical characteristics (particularly regarding age, sex, and pre-test likelihood of CAD) were also selected. In order to ensure an effective comparison of the two populations, SR and AF patients were selected with a 2:1 ratio and matched for CZT stress protocol (exercise vs. pharmacological). In the entire population, both patients with AF and controls were submitted to invasive or CT coronary angiography within 3 months from the CZT study, as indicated by the referring physicians. Specifically, 50 patients (with normal EF and a summed stress score [SSS] < 5) were submitted to CT, while the remaining 172 underwent invasive coronary angiography. A coronary stenosis ≥ 70% was considered significant. Exclusion criteria were: recent (<6 months) acute coronary syndrome, haemodynamic instability, severely symptomatic heart failure, and more than moderate valvular disease. The study was approved by the Local Ethical Committee and conformed to the Declaration of Helsinki on human research. Written informed consent was obtained from every patient.

**Patient preparation and stress protocols**

Patients discontinued β-blockers, calcium-antagonists, and nitrates for 24 h before testing. Ninety-six patients (32 AF vs. 64 SR, 43%) underwent bicycle exercise (stepwise increments of 25 W every 2 min) while 126 (42 AF vs. 84 SR, 57%) dipyridamole (0.56 mg/kg IV over 4 min) stress testing, depending on patients’ ability to exercise or according to clinical reasons. Of the patients undergoing exercise stress testing, 62 (24 AF vs. 38 SR, P = NS) reached 85% of the age-predicted maximum heart rate (%HR). Among the remainders, 12 (3 AF vs. 11 SR, P = NS) reached a peak rate pressure product > 26,000, while 28 were injected because of typical angina (4 AF vs. 17 SR, P = NS) and/or positive exercise ECG (3 AF vs. 15 SR, P = NS). In each patient, the predicted maximal workload (Watt_max) was calculated and the percentage of the reached Watt_max (%Watt_max) determined.

**Acquisition protocol**

Patients underwent stress—rest CZT imaging with a single-day protocol (185–222 MBq of 99mTc-tetrofosmin during stress and 370–444 MBq at rest). Patients with known prior myocardial infarction were injected at rest after sublingual administration of nitrates. In all patients, stress and rest CZT imaging were acquired as previously described. Stress acquisitions were started 10 min (exercise) to 15 min (dipyridamole) after the completion of the stress protocols, while rest scans were started 30 min after injection. Patients were imaged in the supine position with arms placed over their head without any detector or collimator motion. All images were acquired with a 32 × 32 matrix and a 20% energy window centred at the 140 keV photopake of 99mTc.

List mode files were acquired and stored. Images were reconstructed on a standard workstation (Xeleris II; GE Healthcare, Haifa, Israel) using a dedicated iterative algorithm. All studies were reconstructed using a standard iterative algorithm with ordered-subset expectation maximization with 50 iterations, without resolution recovery or attenuation correction. A Butterworth post processing filter (frequency 0.37, order 7) was applied to the reconstructed slices. The tomographic studies were also re-projected into 60 planar projections to emulate a standard SPECT layout.

**Semi-quantitative analysis of perfusion images**

Stress and rest images were semi-quantitatively scored according to the 17-segment LV model and a five-point scale (0: normal, 1: equivocal, 2: moderate and 3: severe reduction in radioisotope uptake, and 4: absence of detectable tracer uptake). Accordingly, the SSS, rest score, and difference score (SDS) were calculated. Two experienced nuclear cardiologists performed the semi-quantitative analysis independently and consensus was reached on all analyses. An SDS value of >3 was identified as a measure of significant reversible perfusion ischaemia.

**Analysis of gated images**

LV function analysis was performed from 16-frames reformatted images using a commercially available software (Corridor4DM, Invia, Ann Arbor, MI, USA). In patients with inadequate border detection manual editing was performed. End-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction were automatically calculated. Moreover, the same software automatically fits the left ventricular volume curve with a fourth-order harmonic function in order to derive the peak filling rate (EDV’s⁻¹) as indicator of LV diastolic function. All functional measurements were obtained from rest and stress ECG-gated 99mTc-tetrofosmin images.

**Statistical analysis**

Continuous variables were expressed as mean ± SD, and categorical variables as percentages. Groups were compared for categorical data using Fisher’s exact test and for continuous variables using analysis of variance followed by Fisher’s protected least significant difference for multiple comparisons. All tests were two sided; a P value of <0.05 was considered to be significant. The accuracy of CZT in unmasking the presence of significant coronary stenoses both in AF and SR patients was assessed by the receiving operating characteristic (ROC) analysis. Accordingly, the pertinent areas under the curves (AUCs) with the appropriate 95% confidence intervals (CIs) were determined. Finally, the predictors of a reduced diagnostic specificity (‘true-negative rate’) at CZT-MPI were assessed at multivariate logistic regression analysis and the odds ratios (OR) with the pertinent 95% CIs determined. Only variables with a P value of <0.05 at univariate logistic analysis were entered in the multivariate model. Statistical analyses were performed using JMP statistical software (SAS Institute Inc., version 4.0.0) and Stata.
software (Stata Statistical Software: release 10, StataCorp. 2007, College Station, TX, USA).

Results

Characterization of the study population

The characteristics of the study population regarding demographics, risk profile, coronary anatomy, and CZT-MPI stress protocol are summarized in Table 1. Patients with SR and AF showed a similar clinical characteristics as well as prevalence of major cardiovascular risk factors and of presence and extent of significant CAD. This prevalence was very similar to the pre-test likelihood of significant CAD based on clinical variables and risk profile (66 ± 17%). In both groups, no significant adverse events were observed during the stress protocols.

The relationships between measures of LV regional perfusion heterogeneity, functional variables and the presence and extent of significant CAD are detailed in Table 2. As expected, in the overall population, there was a significant relationship between CAD extent and increasing ischaemic burden at MPI (P < 0.001). Moreover, a significant association between the presence of significant CAD and stress-induced LV systolic impairment was also evident (Table 2). The relationships between CAD extent, LV perfusion impairment, and post-stress myocardial contractile abnormalities were unrelated to patients’ heart rhythm abnormalities, as confirmed both in subjects with SR and AF (Figure 1). As a matter of fact, at ROC analysis, independently of the presence of AF, quantitative measure of reversible myocardial ischaemia, identified by the SDS, showed a significant accuracy in detecting CAD (P < 0.001 for both, Figure 2).

Relationship between stress protocol and MPI accuracy

As shown in Figure 3, in patients undergoing a vasodilator stress–test, MPI showed a significant accuracy in unmasking significant CAD independently of patients’ heart rhythm abnormalities (P for difference = NS). Nevertheless, in those submitted to an exercise stress–test, a significant interaction between patients’ heart rhythm and MPI accuracy was evident. In fact, in this subgroup, the presence of AF was associated with a significantly lower accuracy in detecting significant CAD (P for difference = 0.039; Figure 3), related to a significantly lower specificity (54 vs. 80%, P = 0.016), despite a preserved sensitivity (71 vs. 76%, P = NS).

Interaction between AF and exercise stress–test parameters

The relationships among exercise stress protocol variables and underlying patients’ cardiac rhythm were explored (Table 3). When compared with patients with SR, the presence of AF associated with a considerably higher attained %HR (P = 0.012), despite a significantly lower total exercise time (P = 0.007). On the other hand, patients with AF showed considerably lower values of peak systolic blood pressure (P = 0.038) and of %Watt\text{max} (P = 0.029), as measures of significantly reduced exercise-related workload. Interestingly, after correction for clinical, electrocardiographical and other exercise variables, a shorter total exercise time (OR: 0.74, 95% CI 0.57–0.95; P = 0.017) remained the strongest, independent, predictor of a reduced diagnostic specificity at MPI.
Table 2  LV perfusion and function data according to coronary anatomy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall population (n = 222)</th>
<th>Normal coronaries or non-obstructive CAD (n = 67)</th>
<th>Single-vessel disease (n = 62)</th>
<th>Multi-vessel disease (n = 83)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summed rest score</td>
<td>4.1 ± 5.2</td>
<td>1.7 ± 3.4</td>
<td>3.7 ± 4.4*</td>
<td>6.3 ± 6.0**††</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Summed stress score</td>
<td>8.9 ± 6.4</td>
<td>4.2 ± 4.2</td>
<td>8.5 ± 4.7**</td>
<td>13.1 ± 6.2**††</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Summed difference score</td>
<td>4.8 ± 3.7</td>
<td>2.5 ± 2.5</td>
<td>4.8 ± 3.1**</td>
<td>6.7 ± 4.0**††</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV volumes and function at rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>52 ± 15</td>
<td>55 ± 13</td>
<td>53 ± 15</td>
<td>50 ± 16*</td>
<td>0.111</td>
</tr>
<tr>
<td>EDV (mL)</td>
<td>121 ± 48</td>
<td>115 ± 43</td>
<td>119 ± 44</td>
<td>129 ± 54</td>
<td>0.158</td>
</tr>
<tr>
<td>ESV (mL)</td>
<td>63 ± 44</td>
<td>56 ± 38</td>
<td>61 ± 39</td>
<td>72 ± 50*</td>
<td>0.061</td>
</tr>
<tr>
<td>Peak filling rate (EDV/s)</td>
<td>2.3 ± 0.7</td>
<td>2.6 ± 0.8</td>
<td>2.5 ± 0.7</td>
<td>2.3 ± 0.7**††</td>
<td>0.005</td>
</tr>
<tr>
<td>LV volumes and function after stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>52 ± 15</td>
<td>56 ± 12</td>
<td>53 ± 15</td>
<td>48 ± 17**</td>
<td>0.006</td>
</tr>
<tr>
<td>EDV (mL)</td>
<td>121 ± 51</td>
<td>109 ± 41</td>
<td>120 ± 50</td>
<td>131 ± 57*</td>
<td>0.036</td>
</tr>
<tr>
<td>ESV (mL)</td>
<td>64 ± 47</td>
<td>51 ± 36</td>
<td>63 ± 44</td>
<td>75 ± 54**</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak filling rate (EDV/s)</td>
<td>2.3 ± 0.7</td>
<td>2.7 ± 0.9</td>
<td>2.5 ± 0.7*</td>
<td>2.2 ± 0.6**††</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* and **P < 0.05 and P < 0.01 vs. ‘normal coronaries or non-obstructive CAD’; † and ††P < 0.05 and P < 0.01 vs. ‘single-vessel disease’.

Figure 1 Relationships between presence and extent of significant CAD, reversible myocardial ischaemia, and stress-induced LV systolic dysfunction in patients with sinus rhythm (A) and AF (B).
Discussion

Our study aimed at investigating the complex relationship between patients’ heart rhythm abnormalities and MPI accuracy using a new CZT cardiac camera. Specifically, presented data show that the presence of AF may profoundly diminish MPI predictive value on the detection significant coronary stenosis, despite the use of this novel, highly sensitive, imaging technique. This effect was only apparent in the case of an exercise stress—test, while disappeared in patients submitted to vasodilator stress, suggesting an interaction among the presence of AF and the diagnostic efficacy of the different stress—test protocols.

Relationships between AF and myocardial perfusion abnormalities

Atrial fibrillation is one of the most relevant cardiac arrhythmias, affecting both patients’ morbidity as well as long-term event-free survival, and significantly impacting cardiac-related sanitary costs. In the last years, the functional relationship among the occurrence of AF and the presence and extent of myocardial IHD has been investigated. However, the existence of a pathophysiological interaction between these two affections has not been conclusively demonstrated.

Independently from the presence of CAD, a consistent association among AF and the development of significant alterations of myocardial blood flow regulation at MPI has been suggested. As a matter of fact, the presence of AF has been shown to be significantly associated with relevant alterations of global myocardial perfusion at cardiac-PET, as indicated by increased coronary vascular resistances and diminished resting and hyperaemic perfusion. Similarly, AF has been reported to significantly affect regional myocardial perfusion heterogeneity at SPECT, diminishing MPI accuracy in identifying the presence of ischaemia. These perfusion abnormalities, only partially related to SPECT-related technical limitations,
Possible interaction between the presence of AF and exercise parameters

Exercise stress–test still represents a cornerstone of functional cardiac evaluation, giving key information on patients’ working-capacity and allowing to obtain robust indicators of adverse prognosis.16 Nevertheless, despite being highly standardized, the exercise stress protocol may provoke variable, non-entirely predictable, alterations of the some haemodynamic parameters that only partially correlate with the amount of external load.17 To this respect, while the obtained %HR and/or the peak rate pressure product are generally used to evaluate the efficacy of an exercise stress protocol, other parameters, such as the stress duration and the peak workload, have been shown to have independent significant prognostic values.16 Specifically, patients with AF show a pathological HR response to exercise with a significant HR acceleration despite a contained external load.18 This typical exercise-induced early HR-peaking frequently seen in AF subjects may be worsened by the suspension of specific anti-ischaemic drugs, i.e. β-blockers and calcium-antagonists, frequently done before stress–test. Our data confirm that AF patients show a significant HR response to exercise despite a consistently limited external load and exercise time and a limited blood pressure increase during exercise, as a further sign of reduced cardiac workload.

On the one hand, present study shows that the peculiar response to exercise of AF-subjects, i.e. limited exercise time with a rapid HR elevation, may contribute to explain the reduced MPI accuracy frequency observed in those patients. As a matter of fact, our data show that a limited exercise duration was strictly associated with a reduced MPI diagnostic efficacy. Moreover, our results point to the limited value of some indicators of cardiac workload, such as %HR and maximal RPP, in correctly predicting the clinical efficacy of an exercise stress–test in AF patients. In fact, the excellent accuracy of CZT-MPI in predicting the presence of CAD in case of a standardized vasodilator stress protocol highlights the key role of an effective ischaemic stimulus as a precondition for a diagnostically accurate imaging modality.

Atrial fibrillation and MPI-related accuracy in detecting CAD

Despite the relationship between AF and the presence of underlying CAD has been already investigated,14 a full understanding of the possible association between the occurrence of AF and the presence and severity CAD-related myocardial ischaemia is still lacking.

As a matter of fact, while some have suggested a significant association between the presence of AF and patients’ atherosclerotic burden at CT coronary angiography,15 others have questioned the existence of a relevant functional relationship among AF and flow-limiting CAD.5 Nevertheless, different reports suggest that the presence of AF may reduce the accuracy of SPECT-MPI on the evaluation of the presence and extent of CAD-related myocardial ischaemia, and on the prediction of significant coronary luminal narrowing because of a higher prevalence of false-negative results.6

To this regard, our data show that the classical association between CAD extent, ischaemic burden and stress-induced myocardial contractile impairment persists also in patients with AF and are independent on the presence of heart rhythm abnormalities. Conversely, the presence of AF associated with a significantly lower accuracy in detecting CAD that, as showed by our preliminary results, may depend on the type of stress–test used, pharmacological vs. exercise. In AF patients the need for a careful evaluation of patients’ clinical characteristics and ability to exercise is strongly indicated.
According to present and previous reports, the choice of the more appropriate stress–test protocol, pharmacological vs. exercise, might be particularly relevant in patients with AF and suspected IHD. To this respect, our data show how in this category of patients a vasodilator stress–test might be preferable in order to maintain diagnostic accuracy and avoid false-negative results.

Limitations

The nature of the study prevented the enrolment of a homogeneous population of patients, i.e. with or without LV dysfunction. However, the population studied represents a close picture of the group of symptomatic AF patients that ordinarily undergo MPI.

Moreover, the fact that a subgroup of patients was injected despite a theoretically submaximal (%HR < 85%) exercise stress—test might have limited CZT-accuracy. However, considering that the proportion of those patients was similar in SR and in AF patients and that each one of those had presented electrocardiographical or clinical signs of ischaemia during stress protocol, the clinical impact of this variable should be considered limited. In fact, in patients with SR MPI accuracy after an exercise stress–test remained high, while in those with AF the diagnostic value of exercise-CZT confirmed to be depressed even after correction for the attained individual %HR.

Moreover, since in patients with a low pre-test probability of CAD, normal LV systolic function, and a limited extent of reversible ischaemia (23% of the population) coronary anatomy was evaluated at CT coronary angiography, some coronary stenoses could have been missed. Nevertheless, due to its elevated overall accuracy and significantly negative predictive value, CT coronary angiography is particularly suitable in this category of patients.

Finally, since no attenuation correction was used in the present study, the accuracy of CZT-MPI could have been slightly reduced.

Conclusions

In patients with suspected IHD, the presence of AF may substantially impair MPI accuracy in detecting significant CAD. The interaction between AF- and MPI-related diagnostic power was limited to patients submitted to an exercise stress protocol and was related to a substantially lower exercise duration and overall cardiac workload than in patients with SR. Therefore, while in the presence of AF a particularly careful evaluation of patients’ clinical characteristics and ability to exercise seems mandatory, the use of a vasodilator stress–test might be preferred.

Conflict of interest: none declared.

References