# Relationship between atrial fibrillation and blunted hyperemic myocardial blood flow in patients with hypertrophic cardiomyopathy.

# Relationship between atrial fibrillation and blunted hyperemic myocardial blood flow in patients with hypertrophic cardiomyopathy

Roberto Sciagrà, MD,[a] Barbara Sotgia, MD,[a] Iacopo Olivotto, MD,[b] Franco Cecchi, MD,[b] Stefano Nistri, MD,[b] Paolo G. Camici, MD, FACC, FESC, FAHA, FRCP,[c] and Alberto Pupi, MD[a]

***Background.*** **Atrial fibrillation (AF) and coronary microvascular dysfunction (CMD) are common in hypertrophic cardiomyopathy (HCM), but whether they are associated is unclear. We assessed the relationship between AF and CMD in HCM.**

***Methods and Results.*** **Global hyperemic myocardial blood flow (hMBF) was measured in 95 HCM patients (16 with, 79 without paroxysmal or chronic AF) by N-13 ammonia positron emission tomography (PET) after dipyridamole infusion. AF patients were older (50.5 ± 13.4 vs. 38.7 ± 14.9 years, $P < .0005$), had larger left atrial diameter (49.8 ± 7.4 vs 38.6 ± 5.7 mm, $P < .00001$), and left ventricular end-systolic diameter (30.4 ± 6.7 vs 25.5 ± 5.3 mm, $P < .005$) compared with those in stable sinus rhythm. In patients with AF, hMBF was significantly lower (1.23 ± 0.44 vs 1.87 ± 0.90 mL/min/g, $P < 0.0001$). In multivariate logistic regression analysis, hMBF, left atrial diameter, and age were independently associated with AF ($P < .05$ for all).**

***Conclusions.*** **HCM patients with paroxysmal or chronic AF have lower hMBF than those in stable sinus rhythm. The association between CMD and AF is independent of other known predictors of AF, suggesting a causal link between these two features. (J Nucl Cardiol 2009;16:92–6)**

**Key Words: Myocardial perfusion imaging • PET • coronary blood flow • hypertrophic cardiomyopathy • dipyridamole • atrial fibrillation**

## INTRODUCTION

Atrial fibrillation (AF) is among the most common complications of hypertrophic cardiomyopathy (HCM), occurring in over 20% of unselected patients, and usually implies an adverse prognosis due to increased prevalence of heart failure-related complications.[1,2] Among the various parameters that have been suggested as determinants for development of AF, left atrial dimensions and function are considered the most important.[2,3]

Coronary microvascular dysfunction (CMD), documented by positron emission tomography (PET) as a blunted response of myocardial blood flow to pharmacologically induced hyperemia (hMBF), is also a well-known feature of HCM.[4,5] CMD has been identified as a powerful predictor of adverse outcome due to heart failure progression and death in HCM patients.[6-9] To date, it is unknown whether AF and CMD are associated, and whether the clinical consequences of CMD may be partly mediated by increased susceptibility to arrhythmia. Thus, the aim of the present study was to explore the possible relationship between these two unfavorable features in a large HCM patient cohort studied by PET.

## METHODS

### Patient Population

The study cohort included 95 patients (66 males and 29 females; age 40.7 ± 15.3 years, range 11-74) from the population followed by physicians with expertise and long-standing interest in HCM at our Regional Referral Center. The diagnosis of HCM was based on the echocardiographic

From the Nuclear Medicine Unit, Department of Clinical Physiopathology,[a] University of Florence, Florence, Italy; Regional Referral Center for Myocardial Diseases,[b] Azienda Ospedaliera Universitaria Careggi, Florence, Italy; Medical Research Council Clinical Sciences Centre,[c] Hammersmith Hospital, Imperial College; London, United Kingdom.

Received for publication May 14, 2008; final revision accepted Aug 13, 2008.

Reprint requests: Roberto Sciagrà, MD, Nuclear Medicine Unit, Department of Clinical Physiopathology, University of Florence, Viale Morgagni 85, 50134 Florence, Italy; *r.sciagra@dfc.unifi.it.*

1071-3581/$34.00



doi:10.1007/s12350-008-9005-5

evidence of a hypertrophied and non-dilated left ventricle (LV) (wall thickness ≥15 mm) in the absence of any other known cardiac or systemic cause of LV hypertrophy.[1] Coronary artery disease was excluded in HCM patients at the time of enrollment by maximal, symptom-limited treadmill or cycloergometer exercise test (performed routinely in our HCM patients), followed by coronary angiography in patients with a positive or dubious test result. Furthermore, patients with diabetes or actively treated hypertension were excluded. All patients gave informed consent to participate in the study, which was approved by the Ethics Committees of our Institution.

## Definition of Atrial Fibrillation

Documentation of AF was based on ECG recordings obtained either following acute onset of symptoms, or during routine medical examination. For the purpose of the present study, AF was defined as paroxysmal when either self-terminating or successfully cardioverted to sinus rhythm; AF was considered chronic when it became permanent.

## Positron Emission Tomography

All PET scans were performed after an appropriate period of pharmacologic washout using an already described procedure.[4,10] Briefly, patients were positioned on the PET scanner and a transmission scan was recorded. Then, dipyridamole was administered intravenously (0.56 mg/kg of body weight/4 minutes).[4] After 3 minutes of dipyridamole infusion, a bolus of 370 MBq of nitrogen-13 ammonia (N-13 ammonia) diluted in 10 mL saline solution was injected intravenously over a period of 15 to 20 seconds. A dynamic scan was acquired for the duration of 4 minutes, followed by a prolonged static acquisition of 15 minutes. MBF was calculated from the dynamic data by fitting the arterial input function and tissue time-activity curves to a compartmental model for N-13 ammonia and the average hMBF for the entire LV was obtained.[11] We did not measure baseline MBF in order to minimize patient exposure, taking into account that previous studies demonstrate that this parameter is not significantly different between HCM patients and healthy controls[4] and that hMBF is superior to coronary flow reserve in predicting LV remodeling and outcome in HCM patients.[8,9] All studies were analyzed by expert observers, completely unaware of the patient clinical and echocardiographic data.

## Echocardiography

All patients underwent baseline echocardiography at the time of positron emission tomography. Echocardiographic studies were performed with commercially available instruments. Standard measurements of left atrial, LV end-diastolic, and end-systolic diameter were obtained in the parasternal long-axis view.[12] Obstruction of the LV outflow was considered present when a peak outflow gradient of ≥30 mm Hg was present under baseline conditions.[1]

## Statistical Analysis

Results are shown as mean ± standard deviation. The comparisons between groups were performed by the Student *t*-test for unpaired samples. The comparison of proportions was performed with the Fisher's exact test or the Yates corrected chi-square, as appropriate. Multivariate logistic regression analysis to identify independent predictors of AF was performed by a forward-stepwise algorithm, with the entry probability for each variable set at 0.05. A *P*-value <.05 was considered statistically significant. All calculations were performed using the SPSS statistical package version 12.0.

# RESULTS

## Clinical and Echocardiographic Features

Patients predominantly had mild or no symptoms (New York Heart Association Class I in 50, Class II in 40, and Class III in 5 patients only). Mean left atrial diameter was 40.4 ± 7.4 mm. In 71 patients the left atrial diameter was <45 mm, and in 7 it was >50 mm. Maximal LV wall thickness measured by echocardiography was 23 ± 6 mm. LV end-diastolic and end-systolic diameters were 44 ± 5 mm and 26 ± 5 mm, respectively. Eleven patients had dynamic LV outflow obstruction (≥30 mm Hg) in resting conditions. None had LV systolic dysfunction (i.e., were in the end-stage phase) or more than mild-to-moderate mitral regurgitation.

## Atrial Fibrillation

Overall, 16 patients had documented AF (17%) at the time of PET. Of these, 12 had a history of one or more paroxysms of AF, but were in sinus rhythm at the time of enrolment. The remaining 4 patients were in chronic AF. In 4 patients, AF occurred despite a left atrial diameter <45 mm. The clinical, echocardiographic, and hemodynamic features of the 16 patients with AF vs the 79 patients in stable sinus rhythm are described in Table 1. AF patients were significantly older, had a slightly worse New York Heart Association class distribution, clearly larger atrial diameter, significantly larger LV end-systolic diameter, and lower ejection fraction.

## Relationship Between hMBF and Atrial Fibrillation

Average hMBF for the entire LV was 1.76 ± 0.87 mL/min/g (range 0.59 to 5.57 mL/min/g). In patients with AF, hMBF was significantly lower compared to those in stable sinus rhythm (1.23 ± 0.44 mL/min/g vs 1.87 ± 0.90 mL/min/g, respectively; $P < .0001$) (Figure 1).

**Table 1.** Comparison of clinical and echocardiographic variables in patients with history of AF vs those without

| | AF | No AF | *P* |
|---|---|---|---|
| Age | 50.5 ± 13.4 years | 38.7 ± 14.9 years | <.0005 |
| Male | 14 (88%) | 52 (66%) | NS |
| Angina | 5 (31%) | 24 (30%) | NS |
| Dyspnea | 8 (50%) | 29 (37%) | NS |
| NYHA functional class (I/II/III) | 4 (25%)/10 (63%)/2 (12%) | 46 (58%)/30 (38%)/3 (4%) | <.05 |
| Left atrial diameter | 49.8 ± 7.4 mm | 38.6 ± 5.7 mm | <.00001 |
| LV wall thickness | 22.9 ± 4 mm | 23 ± 6.5 mm | NS |
| LV end-diastolic diameter | 45.5 ± 5.3 mm | 43.7 ± 4.9 mm | NS |
| LV end-systolic diameter | 30.4 ± 6.7 mm | 25.5 ± 5.3 mm | <.005 |
| LV ejection fraction | 62 ± 19% | 72 ± 10% | <.01 |
| LV outflow obstruction | 15.6 ± 19.4 mmHg | 13.4 ± 17.7 mmHg | NS |
| Baseline | | | |
| Heart rate (beats/min) | 69 ± 15 | 63 ± 10 | NS |
| Systolic blood pressure (mmHg) | 101 ± 15 | 114 ± 18 | NS |
| Diastolic blood pressure (mmHg) | 69 ± 11 | 70 ± 10 | NS |
| Dipyridamole | | | |
| Heart rate (beats/min) | 81 ± 19 | 88 ± 17 | NS |
| Systolic blood pressure (mmHg) | 105 ± 20 | 112 ± 14 | NS |
| Diastolic blood pressure (mmHg) | 65 ± 14 | 68 ± 9 | NS |

*AF*, Atrial fibrillation; *LV*, left ventricular; *NYHA*, New York Heart Association.

Such difference remained significant when only the patients with normal or mildly enlarged left atrium (<45 mm) were examined: 0.95 ± 0.37 mL/min/g in the AF group vs 1.87 ± 0.88 mL/min/g in the group in sinus rhythm, $P < .05$. Specifically, in the four patients with AF and a left atrial diameter <45 mm, hMBF was very severely impaired, ranging from 0.59 mL/min/g to 1.31 mL/min/g. The proportion of patients with AF in the lowest (≤1.29 mL/min/g) and middle (1.30-1.89 mL/min/g) tertiles of hMBF was 13- and 5.5-fold greater, respectively, compared with those with relatively preserved flow in the highest tertile (>1.89 mL/min/g) (Figure 2).

At univariate logistic regression analysis, AF was significantly associated with hMBF, age, New York Heart Association class, left atrial diameter, LV end-systolic diameter, and LV ejection fraction. Conversely, no significant relation was found with LV wall thickness and end-diastolic diameter, or with resting LV outflow obstruction. In a multivariate model including all the significant variables at univariate analysis and using a forward-stepwise procedure, the association of AF with hMBF remained significant ($P < .03$, model $\chi^2$ 38.1) and independent of the other two selected variables, i.e., left atrial diameter ($P < .00001$, model $\chi^2$ 27.5) and age ($P < 0.03$, model $\chi^2$ 32.8). The $R^2$ of the final model was 0.56.

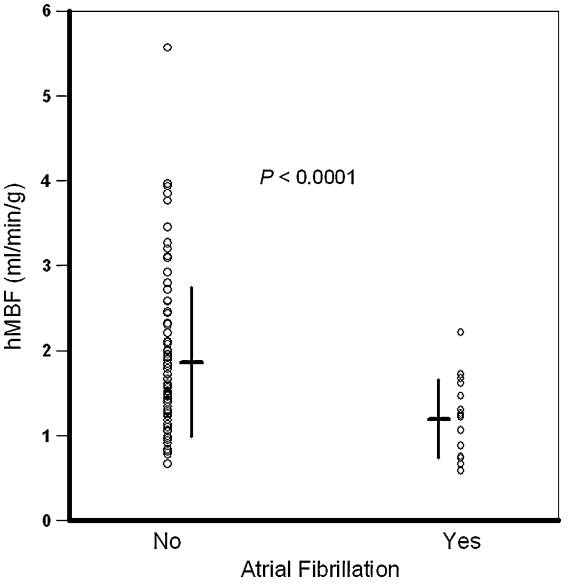


**Figure 1.** Comparison of hMBF in patients with AF vs those without. *Circles* represent the individual data points; *lines* represent mean ± standard deviation.

## DISCUSSION

The main finding of the present investigation is that HCM patients with paroxysmal or chronic AF have a

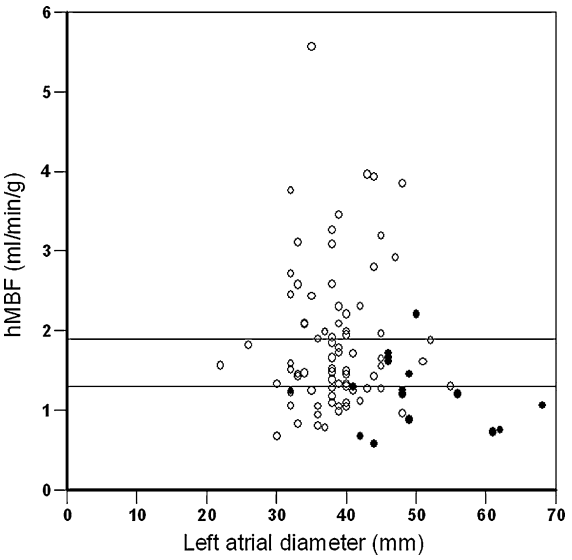


**Figure 2.** Scatterplot of left atrial diameter vs hMBF. *Solid circles* represent the patients with AF, *open circles* the patients without. The two horizontal lines represent the limits of hMBF tertiles.

substantially more severe impairment of coronary microvascular function than patients in stable sinus rhythm. In our cohort, the proportion of patients with AF in the lowest tertile of hMBF was 13-fold greater than that in the highest tertile. Of note, the association between AF and CMD proved to be independent of other well-known, powerful predictors of AF such as left atrial dimensions and age, and remained significant when only those patients with normal or mildly enlarged left atrium were analyzed.

These findings have potentially relevant implications. First, the concomitant presence of more severe CMD in HCM patients with AF reinforces the adverse prognostic significance of arrhythmia, and suggests a synergistic mechanism of these two unfavorable features in determining disease progression and adverse outcome.[1,2,13-17] Specifically, the severely blunted hMBF observed in AF patients might reflect more aggressive disease expression involving not only the LV but also the atrial myocardium, causing atrial dysfunction and AF.[3,15]

Second, and of particular relevance, our observations suggest the novel concept that, rather than just coexisting independently, CMD and AF might be directly linked in HCM patients. The fact that the statistical association in our cohort was independent of a powerful predictor of AF such as left atrial size strongly supports such connection. Indeed, the intriguing subgroup of patients who developed AF despite normal or only mildly enlarged left atrial size suggests the possibility that arrhythmia may be directly related to CMD, and not necessarily mediated by an advanced disease state, nor by extensive left atrial remodeling.

Among the mechanisms that can be proposed to explain the association of CMD and AF, the most likely involves recurrent ischemia leading to abrupt worsening of LV (prevalently diastolic) function, increased LV filling pressures and left atrial stretch, finally triggering AF. Similar mechanisms have also been proposed to explain AF onset in the context of acute coronary syndromes, an occurrence also associated with adverse prognostic significance.[18,19] The present hypothesis has recently found support in the observation that ST-T segment abnormalities during exercise stress testing in HCM patients predict subsequent occurrence of AF,[20] suggesting that inducible ischemia does play a role in this regard. Other potential mechanisms may include more diffuse and substantial collagen metabolism abnormalities favoring atrial fibrosis and arrhythmogeneicity, and recurrent mitral regurgitation, caused by regional ischemic LV dysfunction, ultimately reflecting upon left atrium structure and function.[3] Finally, it is possible that AF may represent a direct consequence of atrial ischemia due to dysfunction of the atrial microcirculation. To date, however, these mechanisms remain speculative.[3,15] Unfortunately, a number of technical limitations of currently available PET scanners, including their limited spatial resolution, did not allow appropriate assessment of atrial MBF.

Of note, the profile of the present study cohort is relatively benign, with regard to prevalence of resting LV outflow obstruction and severity of congestive symptoms, compared to other reported in the literature.[1] However, there was no particular attempt to exclude patients with more severe disease in the present study, the features of our patients pointing rather to the absence of significant selection bias.[21] The fact that PET proved predictive in this patient cohort, perceived to be at somewhat lower risk of events including arrhythmias, strengthens the association between microvascular dysfunction and AF in HCM patients.

An unavoidable limitation of the present study lies in the potential underestimation of the real prevalence of AF, due to the occurrence of asymptomatic paroxysms in patients otherwise considered to be in stable sinus rhythm. However, the acute onset of paroxysmal AF is poorly tolerated and generally associated with symptoms in the vast majority of HCM patients, due to the profound hemodynamic consequences of rapid ventricular rates and the loss of atrial function upon a hypertrophic, non-compliant left ventricle.[2] Thus, we doubt that the occurrence of asymptomatic AF may have significantly affected our study findings.

In conclusion, this study demonstrates that HCM patients with paroxysmal or chronic AF have a more

severely blunted hMBF as compared to those in stable sinus rhythm. The association between CMD and AF in HCM patients seems independent of other known predictors of AF, such as left atrial enlargement and age, raising the novel concept of a direct causal link between these two unfavorable disease features. Further, prospective investigations on patient population including a larger number of arrhythmic patients are warranted to define the mechanisms and clinical impact of the association between CMD and AF in HCM.

## References

1. Maron BJ. Hypertrophic cardiomyopathy: A systematic review. JAMA 2002;287:1308-20.
2. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation 2001;104:2517-24.
3. Losi MA, Betocchi S, Aversa M, Lombardi R, Miranda M, D'Alessandro G, et al. Determinants of atrial fibrillation development in patients with hypertrophic cardiomyopathy. Am J Cardiol 2004;94:895-900.
4. Camici PG, Chiriatti G, Lorenzoni R, Bellina CR, Gistri R, Italiani G, et al. Coronary vasodilation is impaired in both hypertrophied and nonhypertrophied myocardium of patients with hypertrophic cardiomyopathy: A study with nitrogen-13 ammonia and positron emission tomography. J Am Coll Cardiol 1991;17:879-86.
5. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med 2007;356:830-40.
6. Lorenzoni R, Gistri R, Cecchi F, Olivotto I, Chiriatti G, Elliott P, et al. Coronary vasodilator reserve is impaired in patients with hypertrophic cardiomyopathy and left ventricular dysfunction. Am Heart J 1998;136:972-81.
7. Choudhury L, Elliott P, Rimoldi O, Ryan M, Lammertsma AA, Boyd H, et al. Transmural myocardial blood flow distribution in hypertrophic cardiomyopathy and effect of treatment. Basic Res Cardiol 1999;94:49-59.
8. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med 2003;349:1027-35.
9. Olivotto I, Cecchi F, Gistri R, Lorenzoni R, Chiriatti G, Girolami F, et al. Relevance of coronary microvascular flow impairment to long-term remodeling and systolic dysfunction in hypertrophic cardiomyopathy. J Am Coll Cardiol 2006;47:1043-8.
10. Bellina CR, Parodi O, Camici PG, Salvadori PA, Taddei L, Fusani L, et al. Simultaneous in vitro and in vivo validation of $^{13}$N-Ammonia for the assessment of regional myocardial blood flow. J Nucl Med 1990;31:1335-43.
11. Hutchins GD, Schwaiger M, Rosenspire KC, Krivokapich J, Schelbert H, Kuhl DE. Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. J Am Coll Cardiol 1990;15:1032-42.
12. Cheitlin MD, Alpert JS, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, et al. ACC/AHA guidelines for the clinical application of echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Circulation 1997;95:1686-744.
13. Woo A, Williams WG, Choi R, Wigle ED, Rozenblyum E, Fedwick K, et al. Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. Circulation 2005;111:2033-41.
14. Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, et al. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). Am J Cardiol 2006;98:960-5.
15. Olivotto I, Maron BJ, Cecchi F. Pathophysiology and clinical consequences of atrial fibrillation in hypertrophic cardiomyopathy. In: Maron BJ, editor. Diagnosis and management of hypertrophic cardiomyopathy. Cambridge, MA: Blackwell Futura; 2004. p. 105-20.
16. Varnava AM, Elliott PM, Sharma S, McKenna WJ, Davies MJ. Hypertrophic cardiomyopathy: The interrelation of disarray, fibrosis, and small vessel disease. Heart 2000;84:476-82.
17. Basso C, Thiene G, Corrado D, Buja G, Melacini P, Nava A. Hypertrophic cardiomyopathy and sudden death in the young: Pathologic evidence of myocardial ischemia. Hum Pathol 2000;31:988-98.
18. Mehta RH, Dabbous OH, Granger CB, Kuznetsova P, Kline-Rogers EM, Anderson FA Jr, et al. Comparison of outcomes of patients with acute coronary syndromes with and without atrial fibrillation. Am J Cardiol 2003;92:1031-6.
19. Pedersen OD, Abildstrøm SZ, Ottesen MM, Rask-Madsen C, Bagger H, Køber L, et al. Increased risk of sudden and non-sudden cardiovascular death in patients with atrial fibrillation/flutter following acute myocardial infarction. Eur Heart J 2006;27:290-5.
20. Bunch TJ, Chandrasekaran K, Ehrsam JE, Hammill SC, Urban LH, Hodge DO, et al. Prognostic significance of exercise induced arrhythmias and echocardiographic variables in hypertrophic cardiomyopathy. Am J Cardiol 2007;99:835-8.
21. Maron BJ, Spirito P. Impact of patient selection biases on the perception of hypertrophic cardiomyopathy and its natural history. Am J Cardiol 1993;72:970-2.