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Long-term Prognostic Value of Dobutamine Stress Echocardiography in Patients With Atrial Fibrillation*

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Study objective: **To assess the long-term prognostic value of dobutamine stress echocardiography (DSE) for cardiac events (cardiac death, myocardial infarction, and late revascularization) in patients with atrial fibrillation (AF).**
Methods: **Baseline ECGs were studied in patients undergoing DSE between 1989 and 1998. Sixty-nine patients had AF before DSE. Prognostic value of DSE in these patients was compared with a control group who had sinus rhythm (n = 1,664). The presence of stress-induced ischemia was noted for every patient. The mean follow-up period was 35 months (range, 6 to 84 months). Data are presented as hazards ratio (HR) with 95% confidence interval (CI).**
Results: **Heart rate at rest was higher in patients with AF (77 ± 15 beats/min vs 73 ± 14 beats/min; p = 0.04); however, double product at peak stress was not different between patients with AF and sinus rhythm (17,602 vs 17,169, respectively; p = 0.46). In patients with AF, target heart rate was achieved at a lower dobutamine dose (33 ± 8 μg/kg/min vs 35 ± 9 μg/kg/min; p = 0.01). Cardiac arrhythmias occurred more frequently (12% vs 5%; p = 0.001) in patients with AF during DSE. During a follow-up period of 7 years, cardiac death occurred in 5 patients, myocardial infarction in 2 patients, and late revascularization in 10 patients. Prognostic value of DSE for all late cardiac events was similar in patients with AF (HR, 3.0; 95% CI, 0.9 to 9.5) and sinus rhythm (HR, 3.4; 95% CI, 2.7 to 4.3; p = 0.85).**
Conclusion: **The prognostic value of DSE for late cardiac events is maintained in patients with AF.**
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Key words: atrial fibrillation; dobutamine stress echocardiography; long-term prognostic value

Abbreviations: AF = atrial fibrillation; CAD = coronary artery disease; CI = confidence interval; DSE = dobutamine stress echocardiography; HR = hazards ratio; NWMA = new wall motion abnormalities

The prevalence of atrial fibrillation (AF) increases with patient age and is about 5% in Americans > 65 years old.[1] AF is commonly associated with heart disease; however, up to 30% of the patients have no detectable organic heart disease (lone AF).[1] Dobutamine stress echocardiography (DSE) is a clinically useful method for evaluating presence and prognosis of underlying coronary artery disease (CAD), especially in patients with inadequate exercise capacity due to noncardiac diseases like stroke or claudication and in patients with preexisting ECG abnormalities. However, certain factors may impair the diagnostic accuracy of DSE in patients with AF. These include unpredictable heart rate response and side effects during dobutamine infusion. Additionally, alteration of inotropic status between long and short cycles may interfere with proper interpretation of wall motion during stress. The test end point of DSE is a maximal age- and gender-related heart rate or signs of myocardial ischemia. In patients with AF, infusion of the synthetic sympathomimetic agent dobutamine may result in an increased atrioventricular node conduction velocity and hence ventricular rate.[2] If heart rate is achieved at a lower dobutamine infusion rate, compared to subjects with a sinus rhythm, this may result in a reduced cardiac workload and sensitivity of the detection of CAD.[3] Also, dobutamine-induced cardiac arrhythmias may interrupt the stress test prematurely.

Several studies have evaluated the prognostic value of DSE for cardiac events during vascular surgery,[4] after acute myocardial infarction,[5] and in

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patients with severe left ventricular dysfunction.[6] We have shown the high predictive value of DSE for long-term cardiac events in a large group of patients.[7] The principal purpose of this study was to assess the prognostic value of DSE for late cardiac events in patients with AF compared to patients with sinus rhythm.

Materials and Methods

Patient Selection

We reviewed 2,500 DSE studies performed between 1989 and 1998 at the Thoraxcentre, Rotterdam, the Netherlands. Excluded were patients in whom the test was used for evaluation of interventional therapy. Of the remaining 1,733 patients, 69 patients (3.9%) had AF at the time of DSE. Sixty of these patients were included in a previous analysis focusing specifically on long-term outcome in relation to DSE results.[7] However, the impact of AF on prognosis in relation to DSE results has not been addressed previously. The test was requested for diagnostic reasons (63%) or preoperative cardiac risk evaluation (37%). Follow-up was complete in all patients. Baseline clinical cardiac risk factors are reported in Table 1. Patients who underwent coronary revascularization within 3 months after DSE were excluded from the analysis. In patients with sinus rhythm, this occurred in 72 patients; in patients with AF, it occurred in 2 patients. In these patients, the decision to revascularize was already made on clinical grounds and coronary angiography results. The prognostic data from the remaining 67 patients with AF and 1,592 patients in sinus rhythm are reported.

DSE

DSE was performed as previously described.[4] β-Blocker medication was not discontinued for the study. Two independent investigators performed off-line assessment of echocardiographic images. In the period 1989 to 1993, a 14-segment, 4-point score was used[8]; after 1993, a 16-segment, 5-point score (1 = normokinesia, 2 = mild hypokinesia, 3 = severe hypokinesia, 4 = akinesia, and 5 = dyskinesia) was used.[9] Ischemia was defined as worsening or new wall motion abnormalities (NWMA) during stress, with the exception of akinesia becoming dyskinesia, which was considered to be a mechanical phenomenon.[10] For each patient, the number of abnormal segments at rest were scored and a wall motion score index (total score divided by the number of assessable segments) was calculated at rest and during peak stress based on the standard 14- or 16-segment model. The intraobserver and interobserver agreement of the interpretation of the echocardiographic images was 92% and 90%, respectively. In case of disagreement between two observers, a third observer resolved the dispute.

Table 1—*Clinical Characteristics of Patients With AF and Sinus Rhythm

Characteristics	AF (n = 69)	Sinus Rhythm (n = 1,664)	p Value
Mean (± SD) age, yr	66.5 ± 9.6	61.6 ± 12	0.0001
Male gender	52 (75)	1177 (71)	NS
Angina pectoris	9 (13)	401 (24)	NS
Previous myocardial infarction	36 (52)	721 (43)	NS
Diabetes mellitus	7 (10)	137 (8)	NS
Hypertension	24 (34)	487 (29)	NS
Hypercholesterolemia	5 (7)	235 (14)	NS
Digoxin medication	10 (14)	73 (4)	0.001
β-blockers	10 (14)	370 (22)	NS
ACE inhibitors	15 (21)	337 (21)	NS

*Data are presented as No. (%) unless otherwise indicated. ACE = angiotensin-converting enzyme; NS = not significant.

Follow-up

Follow-up data were obtained in 1998 for the period between 1993 and 1998. The mean period of follow-up was 35 months (range, 6 to 84 months) after DSE. Physicians who were unaware of patients' stress test results assessed events. The present status was determined by contacting the patient's general physician and/or review of the hospital records. The date of the last interview or review was used to calculate the follow-up time. Evaluated end points were death, myocardial infarction, and coronary revascularization. Cardiac death was defined by clinical data of acute myocardial infarction and/or significant cardiac arrhythmias and/or refractory congestive heart failure, together with ECG and autopsy studies when available. Elevations of cardiac isoenzyme levels and development of new ECG changes defined a nonfatal myocardial infarction. Revascularization by coronary angioplasty or bypass surgery > 3 months after the original DSE was considered to reflect new or progressive symptoms. In patients with more than one cardiac event, the worst event was chosen: documented cardiac death (worst), nonfatal infarction (less worst), coronary revascularization (least worst).

Statistical Analysis

Continuous variables are presented as mean ± SD. Unpaired Student's *t* tests are applied to evaluate differences between patients with sinus rhythm compared to those with AF. Dichotomous variables are presented as percentages; differences between groups are evaluated by χ^2 tests or Fisher's Exact Tests, as appropriate. To evaluate whether the prognostic value of DSE was different in patients with sinus rhythm compared to those with AF, interaction terms between DSE results (NWMA, rest wall motion abnormalities, angina, and ST-segment changes during DSE) and the baseline rhythm were added to Cox proportional-hazards regression models predicting late cardiac events. Separate hazard ratios (HRs) and 95% confidence intervals (CIs) of DSE results were presented for patients with sinus rhythm vs AF, whereas differences between the HR were evaluated by χ^2 tests on the interaction terms. The probability of the absence of cardiac events was calculated by the Kaplan-Meier method. Log-rank tests were applied to compare event-free survival between groups. The statistical significance of all tests was stated at the 0.05 probability level.

Results

DSE

DSE results of patients with AF and sinus rhythm (control group) are presented in Tables 2, 3. Patients with AF receiving β-blocker therapy before the test

Table 2—*Hemodynamic Data of Patients With AF and Sinus Rhythm During DSE

Variables	AF (n = 69)	Sinus rhythm (n = 1,664)	p Value
Rest heart rate, beats/min	77 ± 15	73 ± 14	0.04
Peak heart rate, beats/min	126 ± 19	125 ± 21	NS
Rest systolic BP, mm Hg	137 ± 23	136 ± 24	NS
Peak systolic BP, mm Hg	140 ± 29	139 ± 30	NS
Rest diastolic BP, mm Hg	76 ± 14	77 ± 13	NS
Peak diastolic BP, mm Hg	73 ± 16	72 ± 16	NS
Double product at peak, beats/min × mm Hg	17,169	17,550	NS

*Data are presented as mean ± SD unless otherwise indicated. See Table 1 legend for abbreviation.

Table 4—*Side Effects of DSE in Patients With AF and Sinus Rhythm

Side Effects	AF, %	Sinus Rhythm, %	p Value
Hypotension	15.1	16.9	NS
Hypertension	0.19	0.20	NS
Arrhythmias	11.6	5.2	0.001

*Cardiac arrhythmias in patients with AF are defined as wide QRS-complex tachycardia (short, < 10 complexes; sustained, ≥ 10 complexes). Cardiac arrhythmias in patients with sinus rhythm are defined as AF, ventricular fibrillation, wide QRS-complex tachycardia (short or sustained). Hypertension is defined as BP > 240/130 mm Hg. Hypotension is defined as a decrease of systolic BP of > 20 mm Hg. See Table 1 legend for abbreviation.

required atropine more frequently (3 of 10 patients; 30%) than those who were not (4 of 59 patients; 7%; p = 0.008). Side effects of the test are presented in Table 4. There were no myocardial infarctions or fatal complications of the stress test.

Wide QRS-complex tachycardia, either short (< 10 complexes) or sustained (≥ 10 complexes), occurred more frequently in patients with AF during DSE compared to patients in sinus rhythm (12% vs 2%, respectively; p = 0.001).

In patients with AF, there was no relation between stress-induced ischemia and the occurrence of arrhythmias or hypotension (decrease of systolic BP of > 20 mm Hg). NWMA occurred in patients with and without cardiac arrhythmias (6.5% vs 6.5%, respectively; p = 1.0) and in hypotensive patients (15.1% vs 16.9%, respectively) without hypotension (p = 0.58). Side effects caused a premature interruption of the test in 7% in patients with AF vs 3% in patients with a sinus rhythm (p = 0.61).

Follow-up Results

The two patients who were referred for coronary revascularization within 3 months after DSE had stress-induced myocardial ischemia. Cardiac events in patients with AF during follow-up were as follows: documented cardiac death (n = 5), nonfatal myocardial infarction (n = 2), and late coronary revascularization (n = 10).

Predictive Value of Clinical Data and DSE Results

In patients with AF, any cardiac event occurred in 15 of 67 patients (22.4%) during 4-year follow-up vs 367 of 1,592 patients (23.1%) in patients with sinus rhythm (p = 0.90). In Figure 1, the event-free survival of patients with and without NWMA of the two different groups is presented. The annual cardiac event rate of patients without NWMA in sinus rhythm was 4.3% vs 4.0% in patients with AF. In patients with NWMA, the annual cardiac event rate was 9.3% in patients with sinus rhythm vs 10.3% in patients with AF. A multivariable Cox model was used to identify the predictive value for cardiac events for stress test results. The significant results for cardiac death or (re)infarction and all cardiac events in patients with AF are presented in Fig 2, 3. The HR of DSE results for the prediction of late cardiac events was not significantly different between patients in sinus rhythm and AF. The stron-

Table 3—*Dobutamine Stress Test Results of Patients With AF and Sinus Rhythm During DSE

Variables	AF (n = 69)	Sinus Rhythm (n = 1,664)	p Value
Mean dobutamine dose, μg/kg/min	33 ± 8	35 ± 9	0.01
Rest wall motion score index	1.39 ± 0.41	1.33 ± 0.46	NS
NWMA	19 (28)	538 (32)	NS
ST segment ⇅ changes	30 (44)	561 (34)	NS
Angina during test	9 (13)	401 (24)	0.04
Test end point, %			
Target heart rate	84	84	NS
Maximum dose dobutamine/atropine	4	6	NS
Signs of ischemia†	5	8	NS
Side effects	7	3	NS

*Data are presented as mean ± SD or No. (%) unless otherwise indicated. See Table 1 legend for abbreviation.
†Signs of ischemia during dobutamine stress test: NWMA, angina, and ST-segment ⇅ changes.

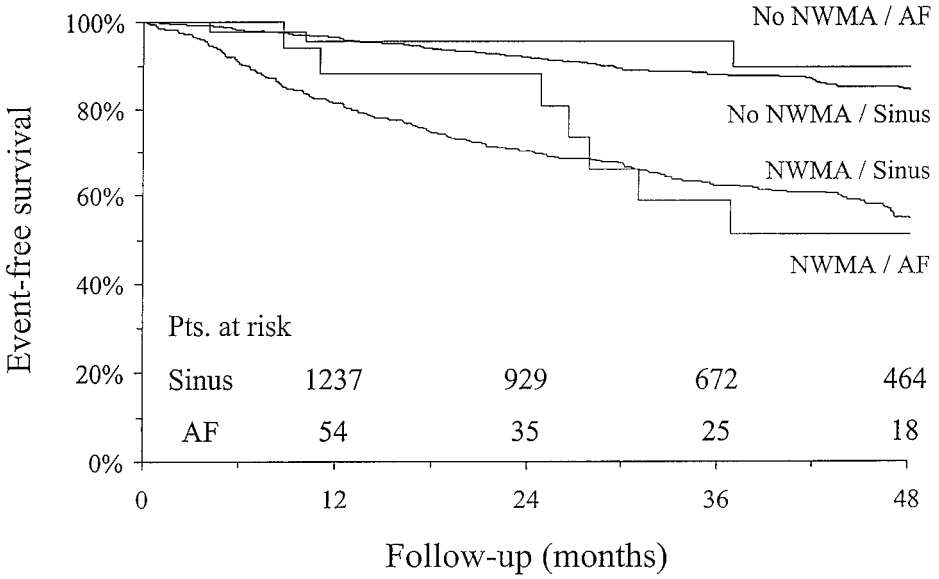

FIGURE 1. Kaplan-Meier curves for all cardiac events (cardiac death, infarction, and late revascularization) during follow-up by results of DSE (with or without NWMA). Each plot represents the cumulative percentage of patients (Pts.) remaining event free. There is a significant difference in event-free survival in patients with NWMA compared to patients with a normal DSE, but no difference between patients with AF and sinus rhythm.

gest multivariable predictor for any cardiac event was NWMA in patients with AF and in patients in sinus rhythm (HR, 3.0; 95% CI, 0.9 to 9.5 vs HR, 3.4; 95% CI, 2.7 to 4.3; p = 0.85).

DISCUSSION

AF is a commonly encountered rhythm disturbance that increases with patient age. A substantial number of patients with AF have underlying CAD.[1] In these elderly patients, a nonexercise-dependent stress test is useful to assess the presence, severity, and prognosis of underlying CAD. This study showed that AF did not influence the prognostic value of DSE in a group of 67 patients compared to a control group in sinus rhythm. The prognostic value of NWMA during DSE for late cardiac events was not significantly different compared to the con-

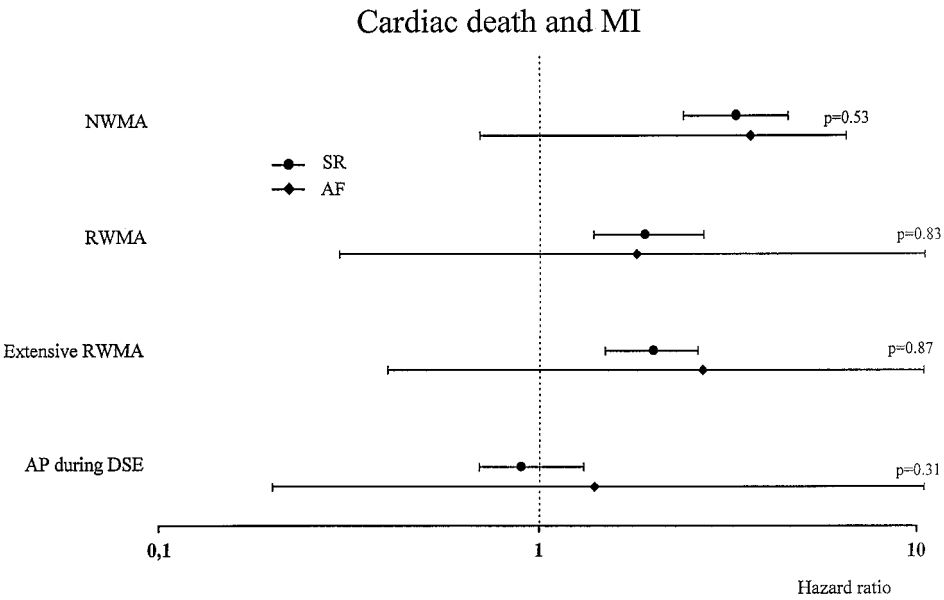

FIGURE 2. Multivariable predictive value (HR and 95% CI) of DSE test results for late cardiac death and myocardial infarction (MI). AP = angina pectoris; RWMA = rest wall motion abnormalities; SR = sinus rhythm.

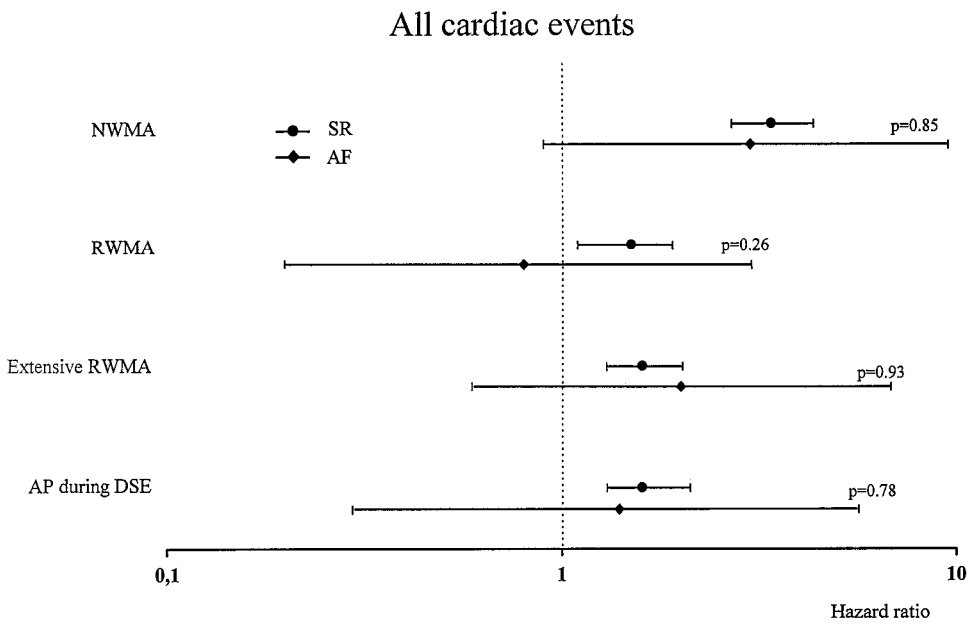

FIGURE 3. Multivariable predictive value (HR and 95% CI) of DSE test results for all cardiac events. See Figure 2 legends for abbreviations.

trol group (HR, 3.0 [95% CI, 0.9 to 9.5] vs 3.4 [95% CI, 2.7 to 4.3]; p = 0.85). However, wide QRS-complex tachycardia (short ventricular tachycardia or aberration) was more frequent during DSE in patients with AF.

Heart rate at rest was higher in patients with AF but was similar at peak stress. The double product at peak stress (heart rate times systolic BP), representing myocardial workload, was also similar in both groups. To achieve test end point, patients with AF required significantly lower doses of dobutamine and received atropine less often. However, this did not influence the prognostic value.

As shown in previous studies,[6] DSE has a high prognostic value for late cardiac events in patients with known or suspected CAD. This is related to the "combined" information of DSE, which provides information on left ventricular function at rest, functional improvement at low-dose dobutamine in segments with rest dyssynergy, and the presence and extent of myocardial ischemia. This study showed that the chance of late cardiac events in patients with AF was related with the presence and extent of CAD and not the presence of AF. In patients without NWMA, the chance of cardiac events during a 4-year follow-up period was 4.0%, increasing to 10.3% in patients with NWMA, similar to patients with sinus rhythm.

Comparison With Previous Studies

The only study specifically evaluating the diagnostic and prognostic value of DSE in patients with AF was performed by Hobday et al.[11] In a group of 92 patients, DSE was diagnostic for underlying CAD (all 12 patients with NWMA had significant coronary artery stenosis). During a follow-up period of 27 ± 20 months, 54 patients without NWMA had no cardiac events. In a group of 38 patients with NWMA, 14 cardiac events occurred during follow-up. The high prognostic value was confirmed by our study. However, in contrast to our study during DSE, no serious cardiac arrhythmias were noted.

Feasibility and Safety of Dobutamine-Atropine Stress Echocardiography

DSE was highly feasible in patients with AF. The test was inconclusive (*ie*, no target heart rate achieved despite maximal dose dobutamine/atropine or side effects interrupting the test) in 11% of the patients. This was mostly due to cardiac arrhythmias during DSE. The occurrence of wide QRS complexes in patients with AF during dobutamine infusion may represent aberrant ventricular conduction, which tends to perpetuate itself, once a bundle branch block occurred, or after a ventricular premature beat. Otherwise, it cannot be excluded that short ventricular tachycardia was induced by AF.[12–14] This caused a premature interruption of the test in 7%, without additional morbidity. This was not related to the induction of ischemia. In these patients, vasodilator-induced stress, like dipyridamole, may be preferred. So far, no study has directly studied the diagnostic accuracy and safety in patients with AF comparing dobutamine with dipyridamole.

Study Limitations

The study included a limited number of patients with AF; during follow-up, only seven "hard cardiac events" (cardiac death and MI) occurred. The limited number of patients with AF referred for testing may be related to the fear of the referring physicians for side effects, although not shown in any previous study, during DSE. Also, the data are obtained in a single center with a high volume and experience of DSE. These results may not be achieved in less "experienced" centers. However, major improvements are expected in the echo quality, with the introduction in the clinical area of second harmonic imaging and contrast echocardiography.[15,16]

Conclusion

DSE has prognostic value for late cardiac events in patients with AF during long-term follow-up. However, cardiac arrhythmias occur more frequently compared to patients in sinus rhythm.

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