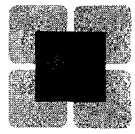

Atrial natriuretic factor and catecholamine levels during exercise in patients with and without coronary artery disease

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■ To investigate the effects of exercise-induced ischemia on the release of atrial natriuretic factor (ANF), we measured peripheral plasma ANF, epinephrine and norepinephrine in 18 male patients with and without coronary artery disease. The patients underwent tomographic thallium treadmill stress tests. After exercise, patients with coronary artery disease showed higher increments of plasma ANF than patients without coronary disease, but the increase of ANF was not related to exercise-induced ischemia, nor to changes in catecholamines, heart rate, or blood pressure. This suggests that ANF release is not associated with myocardial ischemia per se, but to other factors which are more pronounced in the presence of coronary disease, such as changes in intracardiac pressures associated with exercise. Further studies are needed to clarify the role of myocardial ischemia on ANF release.

□ INDEX TERMS: NATRIURETIC PEPTIDES, ATRIAL; CATECHOLAMINES; CORONARY DISEASE; EXERCISE TEST □ CLEVE CLIN J MED 1991; 58:493–499

The main stimulus for atrial natriuretic factor (ANF) release into the circulation is an increase in atrial pressure leading to stretch.[1–4] Other proposed triggering or modulating mechanisms for its release include acetylcholine,[5] epinephrine,[6] and arginine vasopressin.[6] Since changes in atrial pressure and plasma catecholamine levels are part of the physiologic response to physical activity, exercise is a valuable tool to study the release of ANF in health and disease.

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Dynamic exercise is associated with an increase in plasma ANF in healthy subjects,[3,4,7–18] as well as in patients with cardiac disease.[3,4,7,15,17] In normal individuals, this exercise-induced increase in ANF has shown significant correlation with changes in right atrial pressure,[3] pulmonary capillary wedge pressure,[4] heart rate,[9,10] systolic blood pressure,[10] and norepinephrine.[10]

In patients with coronary artery disease, the elevation on ANF produced by exercise is greater than in normal subjects,[4,7,15,17] and it correlates with changes in right atrial[15] and pulmonary capillary wedge pressures.[4,15] This disproportionate increase in ANF has been attributed to the larger increases in cardiac filling pressures (as compared with normal subjects) which occur in patients with myocardial ischemia,[19–21] and which frequently precede angina and electrocar-

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TABLE 1
CLINICAL CHARACTERISTICS OF PATIENTS STUDIED

	Age (yrs)	History	Symptoms	Cardiac medications	Rest ECG	Cardiac catheterization*
Group I						
1	30	Negative	Asymptomatic	None	Normal	NA
2	43	Negative	Asymptomatic	None	Normal	NA
3	38	Diabetes	Atypical chest pain	None	Normal	NA
4	45	Negative	Asymptomatic	None	Normal	NA
5	65	Hypertension	Atypical chest pain	None	Normal	NA
6	71	PVD	Asymptomatic	Aspirin, dipyridamole	NSSTT	NA
Mean	48.7					
Group IIA						
1	56	CABG	Asymptomatic	Aspirin, dipyridamole	Normal	LAD
2	47	CABG	Atypical chest pain	None	Normal	Cx, RCA
3	52	PTCA	Asymptomatic	Aspirin, diltiazem	Normal	LMT
4	44	PTCA	Asymptomatic	Aspirin, diltiazem	Normal	LAD
5	50	CABG, PTCA	Asymptomatic	Digitalis, dipyridamole, nifedipine	NSSTT	LAD, Cx
Mean	49.8					
Group IIB						
1	60	PTCA	Angina	Aspirin, dipyridamole, diltiazem, nitrates	NSSTT	Cx, RCA
2	52	CABG	Asymptomatic	Aspirin, dipyridamole, atenolol, captopril	Normal	LAD, Cx, RCA
3	52	CABG	Angina	Aspirin, dipyridamole, diltiazem	Normal	LAD, RCA
4	60	PVD	Atypical chest pain	Aspirin	Normal	Cx
5	41	Diabetes	Asymptomatic	None	Normal	LAD, Cx, RCA
6	69	CABG, PTCA, HTN	Asymptomatic	Aspirin, dipyridamole	LVH	LAD, Cx, RCA
7	70	CABG, PVD	Asymptomatic	Aspirin, dipyridamole, nitrates	Normal	LAD, Cx, RCA
Mean	57.7					

CABG, coronary artery bypass grafting; LVH, left ventricular hypertrophy; NSSTT, nonspecific ST and T changes; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease

*Either not available (NA) or showing severe lesions in left main trunk (LMT), left anterior descending (LAD), circumflex (Cx) or right coronary artery (RCA).

diographic changes. However, documentation of myocardial ischemia during exercise has only been presented in two recent articles that reported on ANF levels in patients with ischemic electrocardiographic changes during stress tests[17,22]; these studies obtained conflicting results. Thus, the available information on plasma ANF levels during exercise-induced myocardial ischemia is scanty and controversial.

We prospectively studied patients with and without coronary disease, with the goal of contributing to a better understanding of this problem. We postulated that the exercise-related increase in ANF is greater when there is concomitant myocardial ischemia. We also tried to determine if changes in plasma catecholamines correlate with those in ANF during exercise. This has not been previously investigated in patients with documented myocardial ischemia.

METHODS

Patients

The study population was composed of 18 nonconsecutive male patients undergoing tomographic thallium exercise stress testing for diagnostic purposes and without a history of any of the following conditions: congestive heart failure (or prior evidence of left ventricular dysfunction on invasive or noninvasive tests), chronic atrial tachyarrhythmias, valvular heart disease, cor pulmonale, pericardial disease, and renal diseases associated with edema. The interpretation of the exercise stress tests and the measurements of plasma ANF and catecholamines were performed by observers who were blind to the results of other tests in the patients. All the patients gave informed oral consent for participation in the study. The investigation protocol was approved by the Research Programs Committee of The Cleveland Clinic Foundation.

Exercise stress test

After obtaining a resting 12-lead electrocardiogram in the supine and standing positions, a graded treadmill stress test was conducted in the usual fashion, using the Bruce protocol. The patients were exercised until exhaustion or until achieving at least 85% of the maximal predicted heart rate for age, unless there was an indication to terminate the test prematurely. The

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criteria used for premature termination of the test were: (a) ST-segment elevation or depression of ≥2 mm, with or without symptoms, in the absence of conditions known to be associated with false-positive results (eg, left ventricular hypertrophy, mitral valve prolapse, Wolf-Parkinson-White syndrome, digitalis use); (b) sustained ventricular tachycardia; (c) sustained supraventricular tachycardia; and (d) drop in systolic blood pressure of ≥20 mm Hg in two consecutive stages of the exercise protocol.

The electrocardiographic criteria for a positive stress test were ST-segment depression or elevation of ≥1 mm, measured 80 msecs after the J-point, in the absence of treatment with digitalis, electrolyte abnormalities, and baseline secondary repolarization changes. A thallium scan was performed immediately after exercise and 4 hours later (using a Siemens Dual Rota-Camera). It was considered positive for ischemia in the presence of postexercise reversible defects. A stress test was considered positive for ischemia if both the electrocardiographic and the thallium criteria were met, or if only the thallium scan was positive.

Study groups

The 18 patients were divided into three groups: group I consisted of patients with no history of coronary artery disease and a negative stress test (n = 6); group IIA, patients with a history of coronary artery disease (documented myocardial infarction or previous angiogram showing at least one major coronary artery with luminal obstruction of 70% or greater) and a negative stress test (n = 5); and group IIB, patients with a history of coronary artery disease and a positive stress test (n = 7). The clinical characteristics of individual patients are summarized in *Table 1*.

ANF and catecholamine measurements

After having the patient stand for at least 5 minutes before the stress test, 15 cc of blood was drawn using a large forearm or antecubital vein for measurement of plasma ANF (10 cc) and epinephrine and norepinephrine (5 cc). At the end of the stress test, another 15 cc of blood were drawn in the same way to measure ANF and catecholamines, with the patient in the standing position or, if not tolerated, immediately after sitting down.

Plasma ANF was measured by a radioimmunoassay technique developed in our laboratory. Two milliters of blood were collected in chilled polyethylene tubes containing aprotinin (2000 kallikrein inactivated units) and EDTA (2 mg). Blood was centrifuged at 1,500 g for 15 minutes at 4° C, and plasma was stored frozen at −70° C until assay. Plasma was usually assayed within 1 week after collection. Samples from each set of experiments were analyzed as a batch to minimize day-to-day variability in the assay. Plasma was extracted using Bond Elut columns (Analytichem International). The within-assay variation is 6.5%. Normal values in fasting, supine, resting subjects on normal dietary sodium average 30.4 ± 2.5 pg/mL.

The blood obtained for catecholamine determination was collected in heparnuzed tubes, which were immediately placed on ice. Plasma was separated by centrifugation at 2,500 rpm for 10 minutes at 46° C and frozen at −70° C until analysis. Plasma epinephrine and norepinephrine levels were measured using a radioenzymatic technique. Normal values in our laboratory for fasting, supine, resting individuals are 218 ± 92 pg/mL for norepinephrine and 42 ± 18 pg/mL for epinephrine.

Statistical analysis

The duration of the stress test, pre-test, and post-test ANF levels and the rate of change of the levels of ANF, catecholamines, heart rate, and systolic and diastolic blood pressure were compared within each group and among the three groups. Because the assumption of equal variances was not met, comparisons between groups was done using the Kruskal-Wallis test, which is a non-parametric technique that does not assume either normality or equal variances. Pearson correlation coefficients were obtained to correlate change in ANF with changes in catecholamines, heart rate and systolic blood pressure, and rate of ANF change (per minute) with the rate of change in these other parameters. A paired T-test was used to determine if the changes during exercise in ANF, epinephrine and norepinephrine were significant for each group.

RESULTS

Stress test

The results of the treadmill thallium stress test by individual patient and by group are listed in *Table 2*. At least 85% of the maximal predicted heart rate for age was achieved by all patients, except for patient 6 in group I and patient 5 in group IIA (both reached 81% of their maximal predicted heart rate), and patient 1 in group IIB (who achieved 71% of this rate). The latter patient was the only one in the study in whom the stress test was terminated prematurely because of significant ST-segment depression associated with angina

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TABLE 2
RESULTS OF EXERCISE STRESS TEST, WITH PLASMA ANF AND CATECHOLAMINE LEVELS

	ECG	Thallium scan	Duration (min)	Heart rate (beats/min)		Systolic blood pressure(mmHg)		Diastolic blood pressure(mmHg)		ANF (pg/mL)		Epinephrine (pg/mL)		Norepinephrine (pg/mL)	
				Rest	Max	Pre	Max	Pre	Max	Pre	Max	Pre	Max	Pre	Max
Group I															
1	Neg	Neg	17.0	83	198	124	196	90	86	24	67	29	67	273	1701
2	Neg	Neg	12.0	53	160	130	210	90	85	42	128	59	100	607	1658
3	Neg	Neg	12.0	79	166	110	175	80	80	3	10	46	99	245	726
4	Neg	Neg	11.0	60	179	120	190	84	80	20	68	85	106	366	1993
5	Neg	Neg	9.0	78	163	158	202	92	92	13	38	144	777	933	6031
6	Neg	Neg	9.0	76	116	160	230	80	80	38	63	25	40	583	1348
Mean ± SEM			11.7±1.2	72±5	164±11	134±8	201±8	86±2	84±2	23±6	62± 16*	65±18	198±116	501±102	2243±778
Median										22	65	53	100	475	1680
Group IIA															
1	Neg	Neg	11.3	64	157	130	192	80	90	3	75	41	62	870	1682
2	Pos	Neg	12.0	92	176	156	210	100	110	44	173	94	134	451	2007
3	Neg	Neg	12.0	62	148	140	205	98	100	21	107	22	64	329	1499
4	Neg	Neg	12.0	68	164	116	194	72	76	21	52	75	100	603	2544
5	Neg	Neg	9.8	74	138	110	200	70	74	41	130	23	72	325	2908
Mean±SEM			11.4±0.4	72±5	157±7	130±8	200±3	84±6	90±7	26±8	108±21†	51±14	86±14	516±102	2128±264
Median										21	107‡	41	72	451	2007
Group IIB															
1	Pos	Pos	9.0	61	114	138	168	70	78	41	180	89	232	430	1448
2	ND	Pos	10.5	71	164	170	240	95	104	16	82	74	133	280	839
3	Neg	Pos	12.0	60	166	130	200	90	90	19	78	43	317	411	2509
4	Neg	Pos	10.0	64	143	150	200	90	80	4	96	54	138	607	2482
5	Neg	Pos	11.3	63	156	160	220	90	80	25	144	264	388	491	1825
6	ND	Pos	9.5	73	157	128	164	96	104	19	94	95	102	966	3068
7	Pos	Pos	8.4	64	147	114	174	66	80	30	76	94	838	445	5784
Mean±SEM			10.1±0.5	65±2	150±7	141±7	195±11	85±5	88±4	22±4	105±15†	102±28	307±97	519±83	2565±606
Median										19	94‡	89	232§	445	2482

Pre, before exercise; Max, at peak exercise; Neg, negative; Pos, positive; ND, nondiagnostic.
*P = 0.02 vs pre-stress level; †P <0.01 vs pre-stress test level; ‡P = 0.05 vs group I; §P = 0.02 vs group I and IIA.

pectoris. All the patients in group I had a normal electrocardiographic response to exercise, and only one patient in group IIA had significant ST-segment changes. In group IIB, two patients had ischemic ST-segment changes, two had non-diagnostic results because of underlying repolarization changes, and three had no significant alterations on the electrocardiogram. All patients in groups I and IIA had a negative thallium scan, while patients in group IIB had a positive thallium scan for ischemia.

The duration of exercise was similar in the three groups. Baseline and maximal values for heart rate, systolic blood pressure and diastolic blood pressure did not differ among groups.

ANF levels

There were no statistically significant differences for resting ANF levels in the different groups. All the groups showed a significant elevation of ANF with exercise: from 23 ± 6 pg/mL to 62 ± 16 pg/mL in group I (P = 0.02), from 26 ± 8 pg/mL to 108 ± 21 pg/mL in group IIA (P = 0.007), and from 22 ± 4 pg/mL to 105 ± 15 pg/mL in group IIB (P = 0.0005). The ANF elevation was greater in groups IIA and IIB as compared with group I (P <0.05), but was not different between groups IIA and IIB (*Figure*).

Catecholamine levels

As expected, norepinephrine levels increased with exercise (P <0.05) for the three groups when resting and peak exercise levels were compared. Epinephrine levels increased with exercise in all groups. This increase was statistically significant in group IIA (P = 0.003), but not in group I (P = 0.2) or IIB (P = 0.08). There were no differences on resting and maximal levels of epinephrine and norepinephrine among the groups.

Correlations between ANF and other parameters

No significant correlations were found in any groups between change in ANF and changes in epinephrine, norepinephrine, heart rate and systolic blood pressure. The rate of change of ANF was negatively correlated with the rate of change in heart rate and systolic blood

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pressure in group IIB (r –0.87, $P<0.02$). However, no other correlation between rate of change of ANF and rate of change of other parameters was observed in any of the groups.

DISCUSSION

We measured plasma ANF levels before and after treadmill thallium exercise stress tests in patients without a history of coronary artery disease and with normal response to exercise (group I), and in patients with coronary artery disease. The latter were further subdivided into those with no ischemic changes (group IIA) and those with exercise-induced ischemia (group IIB) during exercise. All the patients with ischemic heart disease had angiographic documentation of severe coronary artery lesions, and exercise-induced ischemia was demonstrated by reversible defects on thallium scan, the accepted gold-standard for the diagnosis of myocardial ischemia. Only male patients were studied since the catecholamine response to exercise shows sex-related differences.[23,24]

Our results confirm the rise of ANF brought on by dynamic exercise and show a significantly higher increase of ANF ($P<0.05$) in the presence of coronary artery disease (groups IIA and IIB). This higher release of ANF could not be attributed to differences in heart rate, systolic blood pressure, diastolic blood pressure, or catecholamine levels, since these parameters were comparable among groups at baseline and after the stress test.

Arterial hypertension[25] and the use of beta blockers[26,27] are associated with higher ANF levels after exercise, but it is very unlikely that these conditions altered our results, since only two patients (patient 5 in group I and patient 6 in group IIB) were hypertensives, and only one (patient 2 in group IIB) was using beta blockers. Furthermore, the response of ANF levels to exercise in these three patients did not differ from that in other members of their respective groups (*Table 2*).

Dynamic supine bicycle exercise in young adults produces no change or a fall in left ventricular end-diastolic pressure (LVEDP).[28,29] Older normal subjects or patients with atypical chest pain and normal coronary arteries generally have slight increases in LVEDP during supine and upright bicycle exercise.[19,20,30,31] In patients with coronary artery disease and exercise-induced ischemia, a marked rise in LVEDP is common.[19–21] On the basis of these studies and more recent investigations showing good correlation between changes in ANF and the respective changes in right atrial and pulmonary capillary pressures,[32] we hypothetize that groups IIA and IIB had more ANF release than group I, probably because of higher elevation of intracardiac pressures due to exercise-induced left ventricular dysfunction.

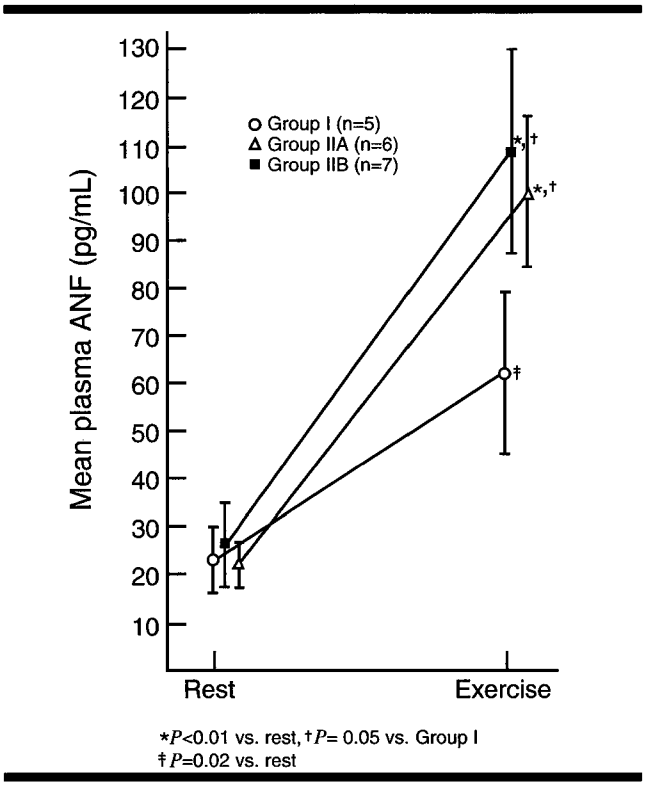

FIGURE. Plasma ANF levels at rest and after exercise in patients without (Group I) and with coronary artery disease (Groups IIA and IIB). Group IIB had evidence of exercise-induced myocardial ischemia, while Group IIA did not.

Contrary to what we expected, the ANF rise in patients with coronary artery disease was similar, whether or not ischemia was demonstrated by thallium scintigraphy, suggesting that ischemia per se is not the cause of ANF release. This is in agreement with results obtained during coronary angioplasty and atrial pacing. Ikaheimo and associates[22] measured peripheral venous and pulmonary artery ANF during percutaneous transluminal coronary angioplasty and found that, in the patients developing symptoms of myocardial ischemia, ANF increased significantly only when there was an associated rise in pulmonary capillary wedge pressure, a reflection of left ventricular dysfunction. Similarly, Thomassen and colleagues[33] found comparable levels of ANF during atrial pacing in control individuals and in patients with coronary artery

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disease, despite signs of myocardial ischemia in the latter.

A parallel investigation that supports some of our findings is that of Ikaheimo,[22] in which 25 patients with chronic stable angina pectoris underwent bicycle ergometry while not using anti-anginal drugs. They found that ANF levels were not different in 11 patients with and 14 patients without symptoms and signs of myocardial ischemia during exercise. However, plasma ANF levels did not increase significantly with exercise in either group, which goes against our results and the majority of studies in the literature on this subject.

A disproportionate elevation of ANF in five patients with abnormal treadmill electrocardiographic stress tests, as compared with five subjects with normal stress tests, was reported by Hu and colleagues.[17] Nevertheless, this study did not include a group of patients with coronary disease and negative stress tests, which could have helped to better interpret the role of myocardial ischemia on ANF release.

It is possible that our group IIB did not have higher ANF elevation than group IIA because the extension or duration of ischemia were not of sufficient magnitude. Supporting this assumption is a retrospective analysis of our tomographic thallium scans, revealing that myocardial ischemia in group IIB involved an average of 2.3 (range: 1 to 6) out of 32 segments of equal size in which the left ventricle was divided.

ANF has vagomimetic and hypotensive effects, and this could explain that the rate of change of ANF was negatively correlated with the rate of change in heart rate and systolic blood pressure in group IIB. However, the same may have been expected in the other two groups but was not observed.

Patients with coronary artery disease demonstrate increases in plasma catecholamine concentrations with physical exercise,[34–36] as our patients in groups IIA and IIB did. However, only one previous study has compared patients with coronary disease and normal control subjects.[36] In this investigation, McCance et al found that during exercise the increases in cardiac norepinephrine spillover were greater in patients with coronary artery disease who developed angina pectoris, as compared with patients with coronary artery disease who did not develop angina and patients in the control group. The increases in total norepinephrine spillover were similar in the three groups. Epinephrine levels were not measured. These authors concluded that the occurrence of angina selectively enhances the cardiac sympathetic response to exercise, and that in the absence of angina, patients with coronary artery disease and normal control subjects have similar sympathetic response to exercise.[36]

An analogous situation occurred in our study, since group IIB showed a significantly higher increase in plasma epinephrine with exercise as compared with groups IIA and I (norepinephrine levels at peak exercise were also higher in group IIB, but the difference was not statistically significant). Epinephrine itself can produce myocardial ischemia by mechanisms (predominantly a marked increase in contractility) distinct from those of exercise-induced ischemia (predominantly increased heart rate and rate-pressure product).[37]

The limited ability to detect differences, if they exist, is a problem in studies with small samples. In our study the problem is further compounded by the variability in the peak values. Therefore, conclusions concerning the non-significant findings must be interpreted cautiously, as differences may exist which this study could not detect. This and the lack of hemodynamic data to further support our interpretation of the results are the main limitations of this study.

In summary, this study shows that plasma ANF increases with exercise, and that this elevation does not correlate with rises in plasma catecholamines. Patients with well-documented coronary artery disease have higher exercise-induced elevations of ANF than do patients without coronary disease. Among the patients with coronary artery disease, the presence of exercise-induced myocardial ischemia, as documented by tomographic thallium scans, does not produce further release of ANF, suggesting that the cause for ANF release is not ischemia per se, but possibly, as demonstrated in previous studies, exercise-induced left ventricular dysfunction leading to increases in intracardiac pressures. Further studies are needed to clarify the role of myocardial ischemia on ANF release.

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