Activation of Sympathetic Tone During Dipyridamole Test*

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Cardiac imaging with dipyridamole infusion has been proposed as an exercise-independent tool for the diagnosis of coronary artery disease. Dipyridamole acts through the accumulation of adenosine, which reduces sympathetic tone in vasomotor nuclei of the brainstem and inhibits norepinephrine release in noradrenergic neurons but also activates arterial chemoreceptors. The aim of this study was to assess whether dipyridamole administration (up to 0.84 mg/kg over 10 minutes, a dosage commonly employed for diagnostic testing) may modulate sympathetic activity either directly or indirectly through blood pressure reduction or myocardial ischemia, which may be evoked by dipyridamole infusion and represent two recognized sympathetic stimuli. Twenty patients were studied with infusion combined with two-dimensional echocardiography and 12-lead ECG monitoring. Blood pressure was recorded each minute by a cuff sphygmomanometer. In all patients, we obtained venous blood samples for epinephrine (an index of adrenergic catecholamine release) and norepinephrine (an index of neuronal activity) both in resting conditions and at peak dipyridamole, ie, at the first minute after termination of dipyridamole infusion in negative cases or in the presence of obvious ischemia in positive cases (ie, as soon as a regional ventricular dyssynergy or an ST segment depression >0.1 mV appeared). Epinephrine and norepinephrine determinations were made by a high performance liquid chromatography (HPLC) method. After dipyridamole, there was a significant rise in norepinephrine, while epinephrine did not change significantly. Dipyridamole-induced percentage variations of norepinephrine from baseline were not significantly correlated with mean blood pressure changes (r = .13, p = ns) and were of a similar extent in patients with (n = 10) and without (n = 10) dipyridamole-induced ischemia (+68 vs +73 percent, p = ns). Dipyridamole administration provokes an activation of sympathetic tone which can be detected even in the absence of myocardial ischemia and is not related to blood pressure changes. The increased catecholamine release appears to be of neuronal rather than adrenergic origin.

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HPLC = high performance liquid chromatography; 2D echo = two-dimensional echocardiography

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Cardiac imaging combined with dipyridamole infusion is a widely employed exercise-independent method for the diagnosis of coronary artery disease. The mechanism of action of dipyridamole is mostly attributed to accumulation of myocardial adenosine and stimulation of adenosine receptors. Therefore, dipyridamole infusion might interact with sympathetic tone regulation. In fact, adenosine is a negative feedback inhibitor of the stimulatory actions of catecholamines, reducing sympathetic tone in discrete vasomotor nuclei of the brainstem, as well as acting both presynaptically by reducing the release of norepinephrine from nerve terminals and postsynaptically by attenuating the positive chronotropic actions of the catecholamines. On the other hand, adenosine triggers excitatory cardiopulmonary chemoreceptors. Furthermore, dipyridamole infusion can indirectly modify sympathetic tone through the possible induction of systemic arterial hypotension or myocardial ischemia or both, which represent recognized excitatory stimuli of sympathetic efflux through baroreflex activation and stimulation of cardiac reflexes respectively. The net effect of intravenous dipyridamole testing on sympathetic tone remains unknown to date, although this information might be of pathophysiologic and potential clinical interest. The aim of this study was to evaluate whether dipyridamole administration may modulate sympathetic activity either directly or indirectly through blood pressure reduction or myocardial ischemia or both. We measured epinephrine and norepinephrine by peripheral venous sampling both in resting conditions and after dipyridamole infusion, which was combined with 12-lead ECG and two-dimensional echocardiography (2D echo) following the protocol of high dose echo test, in order to have very sensitive objective markers of myocardial ischemia.

**MATERIALS AND METHODS**

**Selection of Patients**

We studied 20 hospitalized patients (14 men and 6 women, age range 35 to 65 years) undergoing dipyridamole echocardiography test for diagnostic purposes. All patients met the following inclusion criteria: (1) a history of chest pain; (2) not receiving antianginal therapy (nitrates and/or calcium antagonists) for at least 72 h (no patient was receiving beta-blockers); (3) good acoustic window in resting conditions, allowing echocardiographic monitoring; and (4)
overall left ventricular function within normal limits.

All patients performed a dipyridamole echocardiography test, approximately at the same hour of the day. Intravenous sampling was made in resting conditions (after 30 min rest in the supine position) and after dipyridamole, either at peak ischemia (just before aminophylline infusion, in positive cases) or at 1 min after the end of the infusion.

Dipyridamole-Echocardiography Test

Two-dimensional echocardiographic and 12-lead ECG monitoring was performed in combination with dipyridamole infusion: 0.56 mg/kg over 4 min followed by 4 min of no dose and then 0.28 mg/kg in 2 min. The cumulative dose was therefore 0.84 mg/kg over 10 min. Aminophylline, which promptly reverses the effects of dipyridamole, was readily available. During the procedure, blood pressure values (by cuff sphygmomanometer) and a 12-lead ECG were recorded each minute. Two-dimensional echocardiograms were continuously recorded during and up to 10 min after dipyridamole administration. In the baseline studies, all standard echocardiographic views were obtained when possible. During the test, new areas of abnormal wall motion were looked for on multiple views (mainly parasternal, long and short axis, and apical, four and two chamber views) by rapidly moving the ultrasound transducer through various positions. A commercially available, wide-angle, phased array imaging system (Hewlett Packard, model 77020, 2.5 and 3.5 MHz transducers) was used. The ECG and echo tracings were judged by one experienced observer blind to clinical, angiographic and humoral data.

The test was considered positive for myocardial ischemia when there was a horizontal or downsloping ST segment shift of at least 0.1 mV, 0.08 s after the J point compared with baseline and/or when a new transient dyssynergy, which was absent or of a lesser degree in the baseline study, appeared after dipyridamole.

Norepinephrine and Epinephrine Blood Sampling

Throughout the study, an intravenous cannula was placed in the forearm vein for dipyridamole infusion as well as for blood withdrawal for measurement of plasma norepinephrine and epinephrine concentrations. Venous blood samples were obtained in resting conditions, just before starting dipyridamole infusion, and after dipyridamole, either at peak ischemia (just before aminophylline administration, in positive cases) or at 1 min after the end of the infusion.

Norepinephrine and epinephrine determinations were made by an HPLC method, previously described in detail. Replicate analysis of a plasma pool gave a coefficient of variation for norepinephrine of 8.5 percent and for epinephrine of 19.7 percent.

Statistical Analysis

Data are given as means ± SD. Intragroup and intergroup differences were tested for significance by means of Student's t-test for paired and unpaired values. Linear regression analysis was employed. A p value lower than 0.05 was considered statistically significant.

Results

After dipyridamole, there was a significant rise in plasma norepinephrine (rest = 235 ± 127 vs dipyridamole = 366 ± 210, p<0.01), while epinephrine did not change significantly (rest = 50 ± 38 vs dipyridamole = 69 ± 81, p = ns). Ten patients developed dipyridamole-induced echocardiographic (n = 6) and/or electrocardiographic (n = 9) signs of ischemia (group 1). The time lag between the onset of ischemia (echocardiographically or electrocardiographically assessed) and venous sampling was 3 ± 1.5 min. The remaining ten patients did not show any evidence of ischemia during the test (group 2). The dipyridamole dose administered was 0.70 ± 0.15 mg/kg in group 1 and the full dose of 0.84 mg/kg in each patient of group 2 (p<0.01). In group 1, heart rate went from 76 ± 18 (rest) to 89 ± 14 (dipyridamole, p<0.01), and mean blood pressure went from 108 ± 22 (rest) to 105 ± 21 (dipyridamole, p = ns). In group 2, heart rate went from 67 ± 11 (rest) to 93 ± 12 (dipyridamole, p = <0.01), and mean blood pressure went from 99 ± 17 (rest) to 94 ± 13 (dipyridamole, p = ns). Chest pain occurred in four of ten patients in group 1 and in none of group 2. In resting conditions, the two groups showed similar values of both epinephrine and norepinephrine (Fig 1 and 2). Epinephrine values did not change significantly after dipyridamole in either group (Fig 1). At peak dipyridamole, there was a significant increase in norepinephrine over resting values in both groups, while no significant intergroup differences were detected (Fig 2). The percentage changes of norepinephrine were not significantly correlated with mean blood pressure changes (r = .1, p = ns) (Fig 3).

Discussion

Our data show that dipyridamole administration provokes an activation of sympathetic tone. The in-

![Figure 1](http://journal.publications.chestnet.org/pdftoasx?url=/data/journals/chest/21652/)
creased catecholamine release appears to be of neuronal rather than adrenomedullary origin. In fact, the circulating concentration of norepinephrine, which is directly correlated with sympathetic neuronal activity, represents a balance between the amount of norepinephrine released by sympathetic nerve terminals and eliminated by excretion and metabolism. The plasma concentration of epinephrine represents a balance between adrenomedullary release, excretion, and metabolism.

The stimulation of the sympathetic nervous system increases the release of catecholamines into the circulation without a corresponding increase in removal from the circulation.\(^4\)

There are several potential mechanisms of dipyridamole-induced sympathetic activation as follow: (1) baroreflex stimulation due to arterial hypotension; (2) myocardial ischemia; and (3) chemo reflex activation.

Arterial hypotension, due to the systemic arteriolar vasodilating effects of adenosine, might provoke baroreflex activation.\(^11\) However, we found only a slight mean blood pressure decrease at peak dipyridamole, in good agreement with the extensive clinical experience with the test.\(^12,13\)

Further evidence against the possible role of baroreflex activation was the lack of any significant correlation between percentage changes of norepinephrine and percentage changes of blood pressure in the population under study. It is also possible that there is indeed a baroreflex activation releasing norepinephrine which then modulated a change in blood pressure so that the measured blood pressure is not the blood pressure that stimulates the baroreceptor.

Myocardial ischemia is a recognized potent stimulus to sympathetic drive, probably via the activation of mecanoreceptors sensing the increase in cavitary pressure provoked by ischemia.\(^7\)

It has been shown previously that echocardiographically assessed dipyridamole-induced ischemia is usually associated with a marked rise in end-diastolic pressure\(^12\) which represents an appropriate stimulus for sympathetic activation.\(^7\) However, the relative contribution of this mechanism to the detected increase in sympathetic activity appears to be relatively minor. In fact, there was no difference in circulating catecholamines between the ischemic and nonischemic group. A possible explanation is that the technique employed for evaluating sympathetic tone might have missed the burst of sympathetic activity due to ischemia. In fact, the average time lag between the onset of ischemia and venous sampling was 3 ± 1.5 min. The lack of significant norepinephrine increase in ischemic vs nonischemic patients probably reflects the brevity of sympathetic discharge, which does not persist long enough to permit accumulation of norepinephrine to apparent steady state concentrations. As the half-life of norepinephrine is 1 to 2 min, any increased level of neurotransmitter output will not be reflected by a new steady state until more than 4 min have elapsed (assuming that 90 percent of steady state levels would be achieved in three to four half lives).\(^10\) Another factor might have obscured a possible difference of sympathetic activation between ischemic and nonischemic patients. The administered dose of dipyridamole was
lower in the ischemic group, since the test protocol requires the scalar administration of the dose and the detection of obvious dysrhythmia in an absolute end point of the test. The administration of the higher dose in patients who were already positive after the lower dose would have been unsafe, and therefore, unethical. It has been demonstrated that sympathetic stimulation due to intravenous adenosine infusion is dose-dependent, and it is conceivable that the same might be true for dipyridamole infusion, which acts through adenosine accumulation. Therefore, myocardial ischemia did not significantly contribute to the recorded increase in norepinephrine, but this obviously does not imply that it does not activate sympathetic tone. Methods evaluating sympathetic tone with a greater temporal resolution, such as microneurography or heart rate spectral analysis, are required to address this point.

Finally, in conscious normal human subjects, adenosine activates reflex mechanisms, probably through a direct stimulation of cardiovascular chemoreceptors. In fact, initial increases in heart rate and blood pressure seen after adenosine intravenous bolus injection in normal volunteers were abolished in patients with autonomic failure and were not seen when adenosine was injected into the descending aorta in patients undergoing diagnostic catheterization. Adenosine also may directly activate myocardial chemoreceptors (afferent fibers) that result in sympathetic activation. These excitatory effects apparently override the possible negative modulatory effect of adenosine on sympathetic tone, due to an inhibitory action on discrete vasomotor nuclei on the brainstem as well as on norepinephrine release in noradrenergic neurons. The net effect of these complex actions is a positive modulation of sympathetic outflow.

Some limitations of the present study should be acknowledged. Although intravenous sampling was made at baseline after 30 min rest in the supine position, an aspecific sympathetic arousal due to the anxiety of the stressing procedure rather than to the dipyridamole itself cannot be discarded. Measurements of plasma norepinephrine from an antecubital vein is influenced to a large degree by forearm release and metabolism of norepinephrine. Arterial norepinephrine is a better indication of "systemic" sympathetic tone but requires an intrarterial catheter.

We conclude that dipyridamole appears to be a definite sympathetic stimulus. However, the extent of sympathetic activation (evaluated as the percent increment of plasma norepinephrine) is much lower than that occurring with other stresses, such as treadmill or cold pressor test, which reportedly increase norepinephrine by 243 and 167 percent, respectively, while the average increase of norepinephrine that we found after dipyridamole was 70 percent.

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REFERENCES