

The New England Journal of Medicine

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VOLUME 342

MARCH 23, 2000

NUMBER 12



ABNORMAL MYOCARDIAL PHOSPHORUS-31 NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY IN WOMEN WITH CHEST PAIN BUT NORMAL CORONARY ANGIOGRAMS

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ABSTRACT

Background After hospitalization for chest pain, women are more likely than men to have normal coronary angiograms. In such women, myocardial ischemia in the absence of clinically significant coronary-artery obstruction has long been suspected. Most methods for the detection of the metabolic effects of myocardial ischemia are highly invasive. Phosphorus-31 nuclear magnetic resonance (^{31}P -NMR) spectroscopy is a noninvasive technique that can directly measure high-energy phosphates in the myocardium and identify metabolic evidence of ischemia.

Methods We enrolled 35 women who were hospitalized for chest pain but who had no angiographically significant coronary-artery obstructions and 12 age- and weight-matched control women with no evidence of heart disease. Myocardial high-energy phosphates were measured with ^{31}P -NMR spectroscopy at 1.5 tesla before, during, and after isometric handgrip exercise at a level that was 30 percent of the maximal voluntary grip strength. We measured the change in the ratio of phosphocreatine to ATP during exercise.

Results Seven (20 percent) of the 35 women with chest pain and no angiographically significant stenosis had decreases in the phosphocreatine:ATP ratio during handgrip that were more than 2 SD below the mean value in the control subjects without chest pain. There were no significant differences between the two groups with respect to hemodynamic variables at rest and during handgrip, risk factors for ischemic heart disease, findings on magnetic resonance imaging and radionuclide perfusion studies of the heart, or changes in brachial flow during the infusion of acetylcholine.

Conclusions Our results provide direct evidence of an abnormal metabolic response to handgrip exercise in at least some women with chest pain consistent with the occurrence of myocardial ischemia but no angiographically significant coronary stenoses. (N Engl J Med 2000;342:829-35.)

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ACCORDING to data from the Coronary Artery Surgery Study, more than half of all women with chest pain who are referred for coronary angiography do not have angiographically significant coronary stenosis, as compared with only 17 percent of men.¹ Data from the Duke Data Bank² and Kaski et al.³ indicate a similarly low prevalence of angiographically significant coronary stenosis among women with a syndrome of chest pain. Although noncardiac causes can be responsible for the chest-pain syndrome, myocardial ischemia in the absence of angiographically significant coronary stenoses has long been a suspected cause.^{4,5}

One strategy for the detection of ischemia in patients with chest pain and no angiographically significant coronary stenoses has focused on an evaluation of metabolic markers, including measurements of lactate production⁶ and the oxygen saturation of blood from the coronary sinus.⁷ Both these methods are invasive and subject to sampling errors.⁸ Phosphorus-31 nuclear magnetic resonance (^{31}P -NMR) spectroscopy can be used to measure the myocardial high-energy phosphates phosphocreatine and ATP and to determine the ratio of phosphocreatine to ATP. Calculation of the ratio has been useful in identifying ischemia in animals^{9,10} and humans with coronary stenoses.¹¹⁻¹⁶

We designed a multicenter study — the Women's

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Ischemia Syndrome Evaluation — to investigate new and innovative techniques for the detection of ischemic heart disease in women. A specific aim of the study was to investigate the prevalence and pathophysiology of myocardial ischemia in the absence of angiographically significant stenoses. Accordingly, we used the results of ^{31}P -NMR spectroscopy during low-level isometric handgrip exercise as a metabolic marker for myocardial ischemia in women with chest pain and no angiographically significant stenoses.

METHODS

Study Population

The population consisted of 35 women (age range, 31 to 72 years; mean [\pm SD], 57 ± 10) who were admitted to the University of Alabama at Birmingham Medical Center with chest pain and no coronary luminal stenoses of more than 20 percent in any epicardial coronary artery according to an evaluation by the angiographic core laboratory at Rhode Island Hospital. These women underwent magnetic resonance studies of cardiac function, magnetic resonance perfusion imaging, and radionuclide myocardial perfusion imaging in addition to coronary angiography as part of the study protocol.¹⁷ A reference population was recruited to determine the response to stress induced by isometric handgrip exercise, as measured by the phosphocreatine:ATP ratio, among 12 healthy age- and weight-matched women (age range, 39 to 70 years; mean, 51 ± 8) who had no evidence of heart disease on the basis of exercise stress testing and risk-factor analysis according to the National Cholesterol Education Program guidelines.¹⁸ A third group with stenosis of at least 70 percent in the left anterior descending coronary artery was also studied and consisted of four women and seven men. These patients ranged in age from 52 to 74 years (mean, 64 ± 9). The angiograms of these patients were evaluated in a blinded fashion by the members of the Department of Cardiovascular Disease at the University of Alabama at Birmingham. All subjects provided informed consent, and their physicians approved their participation.

^{31}P -NMR Spectroscopy

All subjects underwent ^{31}P -NMR spectroscopy (Gyrosan ACS, Philips, Best, the Netherlands) at 1.5 tesla in the supine position. A 10-cm surface coil for transmission and receiving was placed over the precordium and secured with a Velcro strap to minimize respiratory artifacts. Heart rate and blood pressure were monitored throughout the procedure. After tuning and matching the surface coil, "scout" proton images were obtained in the transverse and sagittal orientations with use of a standard spin-echo technique (echo time, 28 msec). A volume of 160 to 200 cc, including the anterior wall and apex of the left ventricle but excluding the chest-wall muscle, was defined from the scout images. Appropriate adjustments were made to optimize the proton signal. We confirmed the position of the coil by identifying on the images a small vial containing phenylphosphonate located at the coil's center. This vial was also used to calibrate the 180-degree pulse. The localization technique used was image-selected *in vivo* spectroscopy (ISIS). Studies of phosphate solutions showed that the signal from within the designated area (voxel) accounted for 90 percent of the total signal, indicating excellent localization. The center frequency was set approximately 100 Hz up field from the phosphocreatine peak (midpoint in the spectral range). A cardiac-gated spectrum was obtained with the subject at rest with the use of adiabatic half-passage pulses. The adiabatic pulses ensure that excitation is uniform throughout the voxel. The spectral acquisition variables were as follows: repetition time, 3 seconds; 1024 points; sweep width, 2000 Hz; and 128 averages. The time required for a single spectrum ranged from 7.5 to 9 minutes, depending on the heart rate. Additional spectra were obtained during and after isometric handgrip exercise. In some

cases, the heart was far enough from the coil (≥ 7 cm) that a coronal ISIS plane (3 to 3.5 cm thick) was used instead of a cubic voxel to increase the available signal-to-noise ratio. Location within the ISIS plane was based on the coil's sensitivity profile, which decreases in geometric fashion as the distance from the coil's center increases.

Under these conditions, it is probable that lung and liver tissue will be included in the voxel. However, lung tissue has no appreciable ^{31}P -NMR signal *in vivo*, and the amount of blood contained within the lung tissue is corrected for during data processing. Liver has a strong ^{31}P -NMR signal from ATP and monophosphates and diphosphates; however, liver has no phosphocreatine. Therefore, any measurable phosphocreatine signal must come from the myocardium. Although the recorded phosphocreatine:ATP ratio of the voxel will be lower because of the liver's contribution to the ATP signal, the relative change in the ratio as a result of stress testing will not be affected, since any change primarily reflects changes in myocardial phosphocreatine.

The nuclear magnetic resonance technique that we used differed from that used by either Weiss et al.¹⁵ or Yabe et al.,¹⁶ who used one-dimensional chemical shift imaging and depth-resolved spectroscopy, respectively. All three techniques use surface coils whose sensitivity is subject to the weighting of the measured signals according to their distance from the coil. This approach leads to a greater sensitivity to spectra generated from anterior myocardium than to spectra generated from posterior myocardium. Accordingly, the focal area in our study and the previous studies was the anterior wall (generally, the left anterior descending coronary artery). The use of a surface coil to transmit the radio frequency also causes a non-uniform excitation through the area of interest. The use of adiabatic pulses in our study ensured that excitation was uniform; however, it still did not allow adequate sampling of the posterior wall, because of the distance of the wall from the coil. Although we used a larger voxel than was used in the previous studies, a large portion of the volume included the ventricular chamber and tissue outside the myocardium, so the effective myocardial content was not greater than in the previous studies. With the elimination of skeletal muscle from the voxel, there was no potential auxiliary source of phosphocreatine.

Isometric Handgrip Exercise

A hand dynamometer (Smedley, Stoelting, Wood Dale, Ill.) was modified for use inside the whole-body magnet. Metal components that could affect the results were replaced with brass, and the spring was replaced with Tygon silicone tubing (Norton, Akron, Ohio). Calibration of the handgrip was linear over the ranges of grips obtained. To allow output to be monitored continuously without compromising the radio-frequency-shielded enclosure of the scanner, we mounted the handgrip at one end of an 8-ft (2.4 m) wooden beam and connected the handgrip to a slide potentiometer mounted at the opposite end. The output was monitored by computer (Biopac Systems, Santa Barbara, Calif.), with measurements obtained three times per second. Before entry into the whole-body magnet, the maximal voluntary grip strength of each subject was determined. During stress testing, handgrip output was maintained at 30 percent of the maximal voluntary grip strength. If the output dropped below 20 percent, the subject was asked to squeeze harder to achieve a level of 30 percent. If the heart rate and blood pressure did not return to resting levels approximately 10 minutes after testing, the subject was monitored for 10 additional minutes. The entire procedure took 65 to 75 minutes from the time the subject entered the magnet.

Among the 58 subjects, only 1 (2 percent) was unable to complete the exercise regimen and 2 (3 percent) reported mild chest pain during testing that disappeared after testing was completed. None of the subjects had ST-segment changes during testing.

Statistical Analysis

Studies and data processing were conducted with the researchers unaware of the heart disease status of the subjects. Data obtained during ^{31}P -NMR spectroscopy were transferred to a computer work-

station (Sparc 10, Sun Microsystems, Mountain View, Calif.) for processing with Sunspec and Fitmasters software (Phillips), with peak positions known. The data were summed and fitted automatically after frequency offset and estimates of the starting phase had been entered. The fit of the summed data was used for processing individual spectra. The ratio of the areas of phosphocreatine and ATP were adjusted for both blood volume within the left ventricular cavity and differences in T_1 between phosphocreatine and ATP. We calculated the standard deviation of the phosphocreatine:ATP ratio using the Cramér-Rao lower bound,^{19,20} which estimates the quality of the fit on the basis of the noise of the measurement. This value ranged from 10.6 to 16.4 percent of the ratio for all the measurements obtained. The phosphocreatine:ATP ratio and hemodynamic measurements obtained during exercise were compared with the average of the ratios obtained at rest.

We determined the variability in the results of spectrometry by making six consecutive measurements of the resting phosphocreatine:ATP ratio in a single setting in a 27-year-old man. The mean phosphocreatine:ATP ratio of all six measurements was 1.63 ± 0.19 , with the standard deviation of any individual measurement ranging from 10.6 to 13.3 percent. The reproducibility of the results of exercise stress testing was assessed in a single subject who was tested five times over a two-week period. The changes in the phosphocreatine:ATP ratio ranged from a decrease of 10 percent to an increase of 10 percent (mean, $+0.6 \pm 11$ percent). The threshold for an abnormal phosphocreatine:ATP ratio in response to stress testing was -22.6 percent, 2 SD below the mean value for the reference population; lower values were considered abnormal.

Among the women with chest pain and no coronary luminal stenoses of more than 20 percent, women with normal phosphocreatine:ATP ratios during stress testing were compared with women with abnormal responses with the use of t-tests for continuous data and Fisher's exact test for dichotomous data.

RESULTS

The phosphocreatine:ATP ratios in the three study groups are summarized in Figure 1. In the reference population of 12 age- and weight-matched control women, the phosphocreatine:ATP ratio decreased by a mean of 2.6 ± 10.0 percent in response to stress testing, a response that is similar to changes previously reported in other studies.^{15,16} Among the patients with stenosis of the left anterior descending coronary artery of at least 70 percent, the decrease in the phosphocreatine:ATP ratio was significantly greater (19.6 ± 10.7 percent, $P=0.001$).

The response among the 35 women with chest pain and coronary-artery stenosis of no more than 20 percent spanned the range of results. Seven women in this group (20 percent) had an abnormal response during stress testing; the average decrease in the phosphocreatine:ATP ratio was 28.7 ± 5.1 percent. Two other women had decreases that were just above the threshold. Figure 2 shows the results of ³¹P-NMR spectroscopy for 2 of the 35 women in this group. The woman whose results are shown in Figure 2A had a 27 percent decrease in the phosphocreatine:ATP ratio in response to stress testing, whereas the woman whose results are shown in Figure 2B had a decrease of 1 percent. In both examples, it is evident that the decrease in the ratio was mostly due to a decline in phosphocreatine, since the ATP level tended to remain stable. The phosphocreatine:ATP ratio typically returned to pretesting values within 10 minutes after

testing and returned to pretesting levels in all subjects within 20 minutes.

We examined a number of risk factors — resting hemodynamic variables, hemodynamic response to stress testing, ejection fraction, thickness of the left ventricular wall, the results of radionuclide myocardial perfusion studies during stress testing, and response of brachial flow to stress testing — to gain further insight into the seven women with an abnormal decrease in the phosphocreatine:ATP ratio in response to stress testing (Table 1). There were no significant differences between this subgroup and the subgroup with a normal decrease in the phosphocreatine:ATP ratio in response to stress testing in any of the variables other than the phosphocreatine:ATP ratio. In addition, there was no correlation between the increase in the product of the heart rate and systolic blood pressure (rate–pressure product) and the change in the phosphocreatine:ATP ratio during stress testing.

DISCUSSION

Our results provide direct evidence of a myocardial metabolic change in women with chest pain and no angiographically significant coronary stenoses. One fifth of these women had an abnormal decrease in the myocardial phosphocreatine:ATP ratio during mild handgrip exercise. Interestingly, the magnitude of this decrease was equal to or greater than that in patients with stenosis of the left anterior descending coronary artery of at least 70 percent.

These results suggest that among women with chest pain but without coronary stenoses, a subgroup has metabolic evidence of myocardial ischemia during mild stress testing. The threshold we set for an abnormal response was 2 SD below the mean value for the reference population. Assuming a gaussian distribution, we estimate that 1 of 40 measurements (2.5 percent) should be below this threshold. Twenty percent of our patients had abnormal results. Since we measured the phosphocreatine:ATP ratio on a continuous scale, the threshold value can be adjusted after further refinement and verification. This may cause the threshold to shift upward, which would then shift the two patients with borderline results into the subgroup with abnormal responses, increasing the percentage of abnormal responses. Ultimately, with long-term follow-up, the prognostic value of this measurement can be assessed and compared with the value of other methods of identifying ischemia.

There are several potential physiologic and metabolic mechanisms for an abnormal decrease in the phosphocreatine:ATP ratio in response to stress testing in the absence of coronary stenoses, including microvascular coronary artery disease, coronary vasospasm, and elevation of left ventricular diastolic pressure (i.e., lusitropy). Microvascular coronary artery disease is usually assessed clinically by intracoronary Doppler ultrasonography, which shows an inadequate

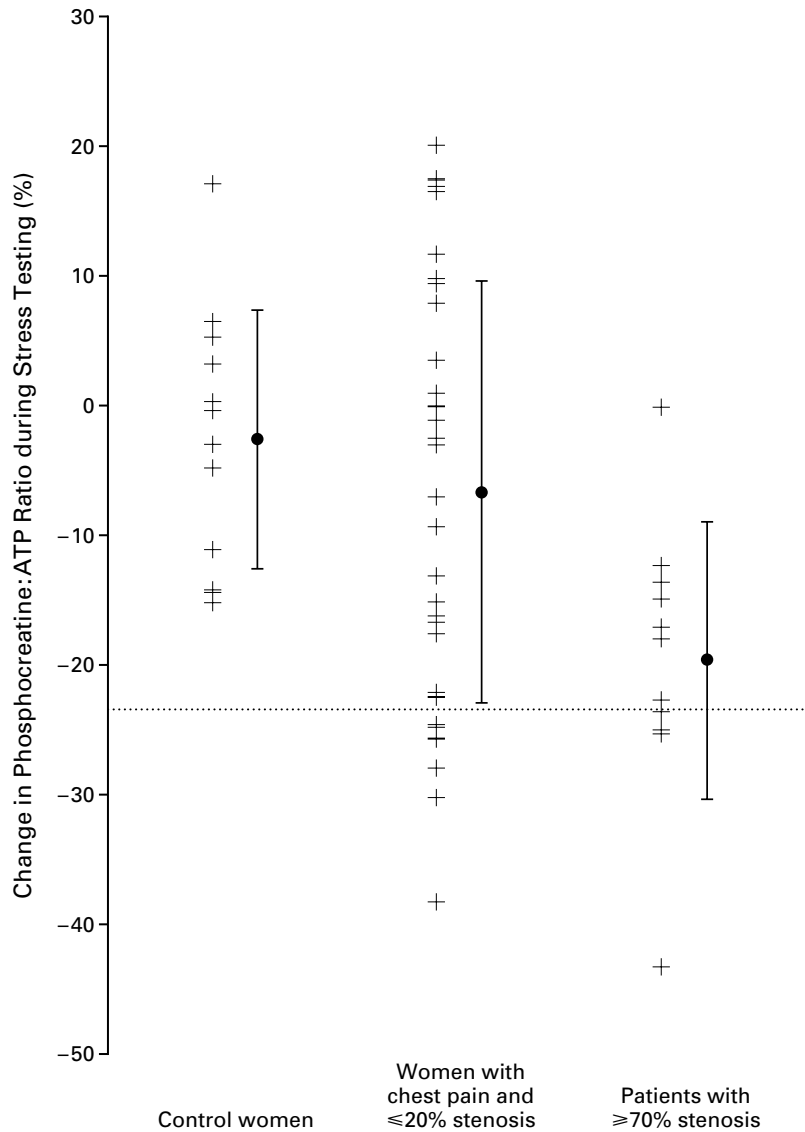


Figure 1. Mean (\pm SD) and Individual Changes in Phosphocreatine:ATP Ratios during Handgrip Stress Testing in 35 Women with Chest Pain and Coronary-Artery Stenosis of 20 Percent or Less, 12 Age- and Weight-Matched Control Women with No Evidence of Heart Disease, and 11 Patients with Stenosis of at Least 70 Percent.

The mean decrease in the phosphocreatine:ATP ratio was 6.6 ± 15.5 percent among the women with chest pain, 2.6 ± 10.0 percent among the control women, and 19.6 ± 10.7 percent among the patients with stenosis of at least 70 percent. The dotted line marks the threshold for an abnormal response (-22.6 percent), a value that was 2 SD below the mean value for the normal subjects; results below this value were considered abnormal.

increase in flow in response to a direct-acting vasodilator such as adenosine or an endothelium-dependent vasodilator such as acetylcholine. Hasdai et al. recently reported that 20 subjects (10 of them women) with recurrent chest pain but no angiographically significant coronary stenoses had abnormal responses to acetylcholine.²¹ One third of these subjects had a reduced response of coronary blood flow to acetylcholine on Doppler ultrasonography, findings that cor-

related with independently assessed results of radio-nuclide perfusion studies. Other groups have reported similar impairments in coronary-artery responses to acetylcholine in patients with chest pain and normal coronary arteries, although none have directly measured coronary microvascular flow or provided metabolic evidence of myocardial ischemia in response to this abnormality.²²⁻²⁴

Coronary vasospasm is an uncommon response to

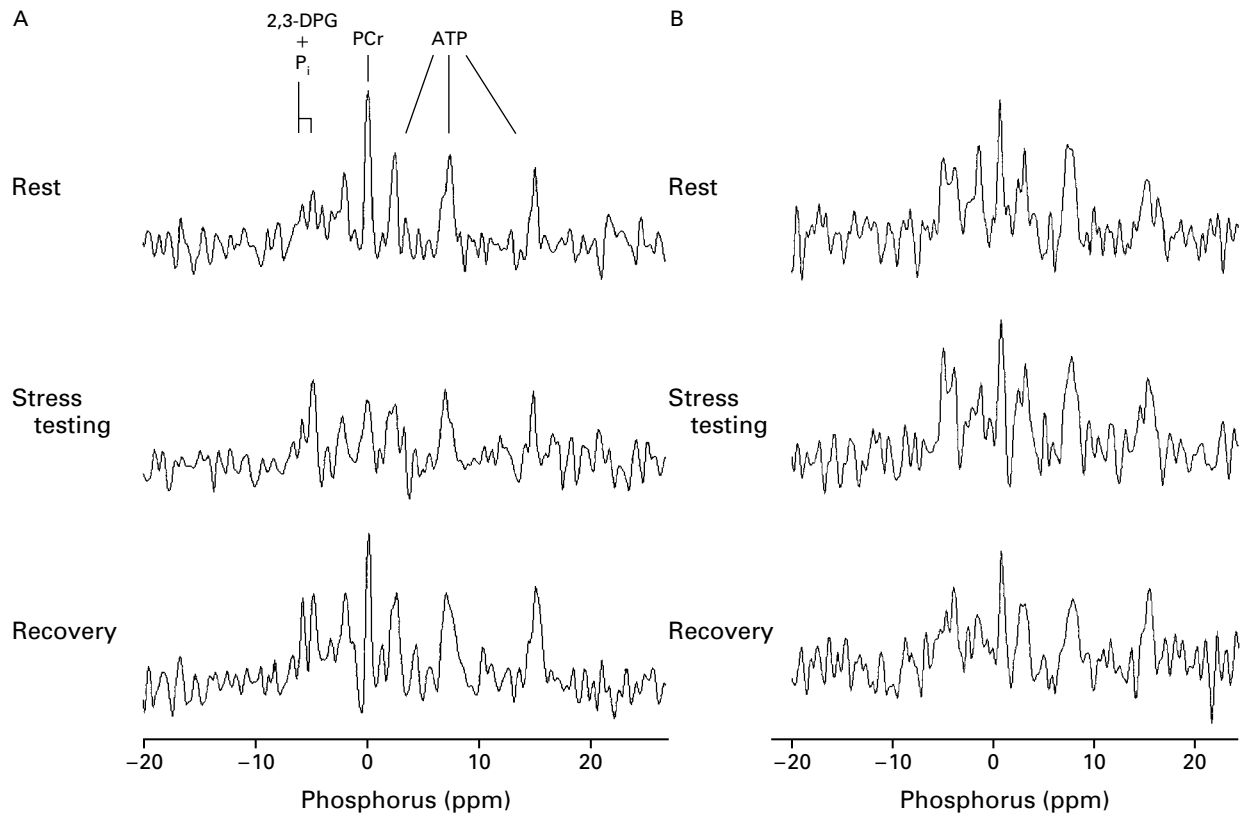


Figure 2. Results of ^{31}P -NMR Spectroscopy in Two Women with Chest Pain and Coronary-Artery Stenosis of 20 Percent or Less. The woman whose results are shown in Panel A had a significant decrease (27 percent) in the phosphocreatine:ATP ratio during stress testing, whereas the woman whose results are shown in Panel B did not (decrease of 1 percent). The peaks of phosphocreatine (PCr), ATP, and inorganic phosphate (P_i) plus 2,3-diphosphoglycerate (2,3-DPG) are identified in Panel A. In Panel B, there is little change in the phosphocreatine:ATP ratio from period to period and only minor spectral variations in the amount of 2,3-diphosphoglycerate. The presence of this substance reflects the amount of red cells from the ventricular chamber within the area analyzed.

exercise and is likely to be associated with chest pain and ST-segment elevation. Only two subjects (3 percent) in our study reported chest pain during stress testing. Lusitropy causes insufficient myocardial perfusion as a result of elevated left ventricular diastolic pressure. However, we found no significant difference in the prevalence of hypertension or the thickness of the left ventricular wall between the women with a normal decrease in the phosphocreatine:ATP ratio in response to stress testing and those with an abnormal decrease. Given the concordance between our results and those of others,²¹⁻²⁴ the presence of microvascular coronary artery disease may best explain why the phosphocreatine:ATP ratio was abnormal during stress testing in women with chest pain but no angiographically significant coronary stenoses.

Myocardial ^{31}P -NMR spectroscopy is a sensitive method of identifying ischemia and ischemic damage in a number of diseases.¹³⁻¹⁵ Bottomley et al. were the first to demonstrate that the resting phosphocreatine:ATP ratio was decreased in patients with myocar-

dial infarction.¹³ Neubauer et al. found that the resting phosphocreatine:ATP ratio correlated with the clinical severity of myocardial dysfunction and that it increased after pharmacologic treatment.¹⁴ Weiss et al. reported a significant decrease in the phosphocreatine:ATP ratio during isometric handgrip exercise in patients with coronary stenoses of at least 70 percent.¹⁵ This ratio did not change significantly during exercise in either normal subjects or patients with nonischemic heart disease. In addition, of five patients with coronary stenoses of at least 70 percent and an abnormal decrease in the phosphocreatine:ATP ratio during isometric exercise, all had normal values during exercise after undergoing revascularization.

Yabe et al.¹⁶ reported a reduction in the phosphocreatine:ATP ratio during handgrip exercise among patients with ischemia but not among those without ischemia, with the use of thallium redistribution imaging as the standard for identifying ischemia. Thus, the body of literature on ^{31}P -NMR spectroscopy to date strongly supports the hypothesis that decreases

TABLE 1. CHARACTERISTICS OF WOMEN WITH A NORMAL RESPONSE TO STRESS TESTING AND WOMEN WITH AN ABNORMAL RESPONSE.*

CHARACTERISTIC	WOMEN WITH A NORMAL RESPONSE (N=28)	WOMEN WITH AN ABNORMAL RESPONSE (N=7)
Decrease in phosphocreatine:ATP ratio (%)	1.3±12.1	28.7±5.1†
Age (yr)	56.6±10.7	59.0±10.4
Resting heart rate (beats/min)	66±15	59±25
Resting systolic pressure (mm Hg)	130±21	122±15
Resting diastolic pressure (mm Hg)	74±14	68±11
Thickness of left ventricular wall (mm)	10.2±1.9	9.4±1.6
Left ventricular ejection fraction (%)	65.0±10.2	66.1±10.2
History of hypertension (% of women)	79	71
Response to stress testing		
Increase in heart rate (%)	13.1±8.8	10.6±8.1
Increase in systolic pressure (%)	14.0±7.1	14.9±10.9
Increase in diastolic pressure (%)	15.8±8.9	19.2±7.6
Increase in rate–pressure product (%)‡	29.3±15.0	25.9±11.3
Results of radionuclide perfusion studies (no. of women)		
Normal	21	3
Abnormal	7	4
Brachial-flow response (no. of women)§		
Abnormal (<4)	8	3
Normal (≥4)	9	2

*Plus–minus values are means ±SD. A normal response was defined as a decrease in the phosphocreatine:ATP ratio of no more than 22.6 percent during stress testing.

†P<0.001.

‡The rate–pressure product is the product of the heart rate and systolic blood pressure.

§This measure was assessed in 17 women with a normal response and 5 women with an abnormal response.

in the myocardial phosphocreatine:ATP ratio with handgrip exercise (which induces mild-to-moderate stress) provide direct metabolic evidence of the presence of myocardial ischemia.

The decrease in the phosphocreatine:ATP ratio during stress testing in our patients with angiographically significant coronary stenoses (mean decrease, 17.2 percent) was not as great as that reported by Weiss et al., who noted an average decrease of 35 percent among similar patients.¹⁵ Several factors in our technique might minimize such decreases. We averaged the measurements over a period of approximately eight minutes. A delay in the response of high-energy phosphates to stress would result in an artifactually larger phosphocreatine:ATP ratio. It is also possible that the mild exercise test we used did not generate enough stress to induce an abnormal metabolic response. This explanation is unlikely, since there was no correlation between the increase in the rate–pressure product and the decrease in the phosphocreatine:ATP ratio. Thus, we may have underestimated the true prevalence of myocardial ischemia among women without angiographically significant coronary stenoses.

A major limitation of our approach was the inability to assess the phosphocreatine:ATP ratio in regions other than the anterior wall of the heart because of decreased sensitivity of the surface coil at depths of more than 10 cm. Hence, our results are relevant only with respect to the metabolic status of the anterior wall of the heart. A second limitation was the inability to measure inorganic phosphate accurately in vivo. Measurements of inorganic phosphate can provide a means of assessing pH on the basis of the chemical shift of the inorganic phosphate peak relative to that of phosphocreatine. With use of a magnetic field of 1.5 tesla, inorganic phosphate cannot be reliably measured, because of the overlap of the two peaks arising from the presence of 2,3-diphosphoglycerate in red cells. We plan to perform these experiments in a system with a stronger magnetic field. The improved spectral resolution of such a system will allow pH to be monitored and will identify the acidosis associated with ischemia.

A final limitation of our study was the lack of provocative coronary-vasospasm testing in our subjects, since primary epicardial coronary vasoconstriction is another possible mechanism of the abnormal phosphocreatine:ATP response. We believe that this explanation is unlikely, since none of our patients had ST-segment elevations typical of the presence of variant angina and previous studies in similar populations of patients with chest pain and no coronary stenoses have shown this pathophysiologic mechanism to be infrequent.²¹⁻²⁴

In conclusion, we found that at least 20 percent of women who were undergoing coronary angiography to evaluate chest-pain syndromes in the absence of angiographically significant coronary-artery stenoses had evidence of altered myocardial metabolism on stress testing combined with ³¹P-NMR spectroscopy, suggesting the presence of ischemia. The concordance of our work with the findings of others using Doppler measurements of coronary-artery flow suggests that microvascular coronary artery disease is a likely mechanism for myocardial ischemia in the absence of angiographically significant stenoses. A non-invasive nontraumatic method to identify a metabolic abnormality in this subgroup of women with chest-pain syndromes may facilitate the development of treatment for this ubiquitous disease.

Supported by contracts (N01-HV-68161, N01-HV-68162, N01-HV-68163, and N01-HV-68164) with the National Heart, Lung, and Blood Institute, by a General Clinical Research Center grant (MO1-RR00425) from the National Center for Research Resources, and by grants from the Gustavus and Louis Pfeiffer Research Foundation, the Women's Guild of Cedars–Sinai Medical Center, the Ladies Hospital Aid Society of Western Pennsylvania, and QMED.

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