ORIGINAL ARTICLE

Adenosine provokes diastolic dysfunction in microvascular angina

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Adenosine stress echocardiography was performed in nine patients (58 ($\pm$ 3) years, eight women) with documented microvascular angina. Global ventricular function was assessed by Tc^{99m} blood pool imaging and Doppler, whereas longitudinal ventricular function was assessed by simultaneous tissue Doppler echocardiography of the lateral mitral annulus. Adenosine was infused incrementally to onset of chest pain in all patients. There was no significant change in global or longitudinal systolic function. Adenosine induced global diastolic dysfunction, demonstrated by blood pool imaging and by Doppler of the transmitral flow. All patients had long axis diastolic dysfunction at peak adenosine, revealed by a ratio of early to late diastolic velocity of lateral mitral annulus <1 , which was absent at rest. Adenosine, as a stress agent, provokes regional and global diastolic dysfunction in microvascular angina, which may be a consequence of subendocardial ischaemia. Long axis diastolic dysfunction can be easily revealed by tissue Doppler of the lateral annular motion.

The term "microvascular angina" is used to identify patients who present with typical exertional angina pectoris, ST-segment depression on exercise, and a normal coronary arteriogram.¹ It is associated with normal resting left ventricular systolic function,² but patients with microvascular angina may have diffuse subendocardial ischaemia,³ and possibly subendocardial dysfunction. The ventricular subendocardial fibres are predominantly longitudinal in orientation and connected to the mitral annulus, and therefore, they can be studied by recording longitudinal motion of the mitral annulus.

Tissue Doppler echocardiography is an ultrasonic modality that records systolic and diastolic velocities within the myocardium, and it has been used for the assessment of subendocardial function by measuring mitral annular velocities.^{4,5}

Previous stress echo modalities have not demonstrated myocardial ischaemia in patients with microvascular angina. Studies with dobutamine have shown no changes in wall motion,^{6,7} but this may have been possibly because the stress modality or the measurements were insensitive.

Adenosine, by stimulating maximal cardiovascular reserve, may reveal the inability of microvasculature to dilate and increase flow to the myocardium, with the hypothetical consequence of subendocardial ischaemia in microvascular angina.⁸ If this is the case, motion of the inner myocardial layers may be reduced, and because subendocardial fibres are attached to the mitral annulus, abnormal mitral annular motion might be used for the diagnosis of subendocardial ischaemia. We therefore used tissue Doppler adenosine echocardiography, obtained simultaneously with a radionuclide blood pool study, in order to assess if it could reveal any functional consequences of ischaemia in patients with microvascular angina.

METHODS

Patients

Nine patients (58 (3) years, eight women) with documented microvascular angina (typical anginal pain, positive electrocardiography on exercise with ST-segment depression >1 mm, abnormal perfusion scans, normal coronary arteriography) were assessed at rest, and then during an infusion of adenosine through a peripheral vein (50 μ g/kg/min, then 100 μ g/kg/

min, and then 140 μ g/kg/min, each for six minutes). The infusion was stopped in all patients due to the onset of chest pain. All patients were in sinus rhythm. All drugs were stopped 24 hours before the study. The protocol was approved by the locally appointed ethics committee and the informed consent was obtained from all subjects.

Radionuclide angiography

At rest and peak stress, global left ventricular function was assessed by ^{99m}Tc blood pool imaging, using an Elscint Gamma Camera. Best septal separation views (40° left anterior oblique) were obtained for 10 million counts/frame, in list mode. Images were formatted with 32 frames/cardiac cycle. The left ventricular region of interest was drawn semiautomatically but checked individually, with atrial filling indicated manually.

Echocardiography

Images were obtained during two minutes, at the end of each stage, using an apical four chamber view (Vingmed System 5, 2.5 MHz transducer). All echocardiographic data were obtained and processed by one investigator, blinded to the radionuclide data.

Global diastolic function was assessed by pulsed wave Doppler of the transmitral flow. The sample volume was placed at the tips of the mitral leaflets and peak early (E) and atrial (A) velocities were measured. E/A velocity ratio was calculated.

Left ventricular long axis function was assessed by tissue Doppler of the lateral mitral annulus. A 6 mm pulsed sample volume was placed within the lateral mitral annulus in systole. Every effort was made to align the pulsed wave cursor so that the Doppler angle of incidence was as close to 0° as possible to the direction of motion of the lateral mitral annulus. From the spectral traces we measured peak systolic velocity, and peak diastolic velocities during early filling (E_{TDE}) and atrial contraction (A_{TDE}). E_{TDE}/A_{TDE} ratio was calculated.

Abbreviations: E/A, early/atrial; E_{TDE} , diastolic velocity during early filling; A_{TDE} , diastolic velocity during atrial contraction

Table 1 General resting echocardiographic characteristics of the study group (in mm)

Parameter	Mean (SD)
Aortic root diameter	30 (3)
Left atrial diameter	36 (5)
End diastolic ventricular septal thickness	11 (1)
End diastolic left ventricular diameter	48 (6)
End diastolic posterior wall thickness	10 (1)
End systolic left ventricular diameter	31 (4)
Right ventricular diameter	20 (2)

Statistical analysis

Statistical analysis was performed with SPSS software (version 9.0). Results are presented as mean (SD). The change of parameters from baseline to peak adenosine was compared by paired samples *t* test or by Fisher's exact test for proportions. A *p* < 0.05 for a two tailed test was considered significant.

RESULTS

General resting echocardiographic characteristics of the study group are given in table 1.

Seven patients completed two stages and two patients all three stages of the adenosine stress protocol. Heart rate increased from a 81 (7) beats/min at baseline to 113 (11) beats/min at peak adenosine (*p* < 0.01). Blood pressure did not change significantly during adenosine infusion: 156 (15)/87 (8) mm Hg at rest, and 150 (16)/82 (7) mm Hg at peak stress.

There were no significant changes in global or regional systolic function (table 2). Adenosine induced global diastolic dysfunction, demonstrated by ^{99m}Tc blood pool imaging (first third filling) and by conventional Doppler of the transmitral flow (E/A ratio).

All patients had long axis diastolic dysfunction at peak adenosine, revealed by the development of a ratio of early-to-late diastolic velocity of the lateral mitral annulus of < 1 (fig

1). Reversal of the E_{TDE}/A_{TDE} ratio (which decreased by 35%) was due mainly to an increase of the A wave velocity (by 47%), rather than a decrease of the E wave velocity (which fell by 11%).

DISCUSSION

In nine patients with microvascular angina adenosine provoked regional and global diastolic dysfunction. This may have been a consequence of subendocardial ischaemia, which is suggested by abnormal left ventricular long axis function assessed by tissue Doppler imaging.

Definition of microvascular angina

There is no accepted definition of this condition. We have employed two main criteria: (1) arteriographically entirely normal coronary arteries; and (2) evidence of reduced perfusion. Some authors accept a diagnosis of microvascular angina in patients with non-flow limiting stenosis (that is, less than 50%).⁹ However, since data from intravascular ultrasound studies suggest that the degree of stenosis might be underestimated angiographically,¹⁰ we have selected only those patients with entirely normal arteriograms. We used clinical and electrocardiographic markers of ischaemia, combined with a positive myocardial perfusion scan.

Adenosine in microvascular angina

Microvascular angina is associated with patchy perfusion abnormalities.¹¹ No single underlying basis has been defined. Small vessel coronary artery disease, abnormal coronary vascular resistance, and subendocardial ischaemia, have each been invoked as a possible mechanism, although none is universally accepted. Several reports suggest that adenosine may cause myocardial ischaemia in microvascular angina, probably as a result of an increase in the regional inhomogeneity of flow.⁸ Ischaemia provoked by adenosine might be localised to the subendocardial layers, causing only diastolic dysfunction with preserved systolic function. All investigated patients demonstrated subendocardial diastolic dysfunction. We did

Table 2 Global and longitudinal systolic and diastolic function at rest and during adenosine; values are mean (SD) unless stated otherwise

Parameter	Rest	Peak adenosine	p Value
Ejection fraction (%)	56 (8)	60 (6)	NS
Peak systolic velocity LMA (cm/s)	8.8 (2.1)	11.4 (3.2)	NS
First third filling (% ED counts)	50.4 (10)	17.9 (12)	<0.05
E wave (cm/s)	70 (11)	77 (17)	NS
A wave (cm/s)	73 (15)	93 (21)	<0.05
E/A ratio < 1 (%)	35	75	<0.05
E_{TDE} velocity (cm/s)	12.4 (2.1)	10.7 (1.3)	NS
A_{TDE} velocity (cm/s)	11.1 (2.3)	15.3 (3.3)	<0.05
E_{TDE}/A_{TDE} LMA < 1 (%)	0	100	<0.001

ED=end diastolic; LMA=lateral mitral annulus.

Figure 1 Examples of tissue Doppler traces of the lateral mitral annulus, at baseline (left) and peak dose of adenosine (right). Systolic velocity was unchanged. The patient had long axis diastolic dysfunction at peak adenosine, revealed by a ratio of early-to-late diastolic velocity < 1, which was absent at rest.

Learning points

- The term “microvascular angina” is used to identify patients who present with typical exertional angina pectoris, ST-segment depression on exercise, and a normal coronary angiogram.
- Adenosine may provoke subendocardial ischaemia and dysfunction in microvascular angina, probably as a result of an increase in the regional inhomogeneity of flow.
- Tissue Doppler echocardiography, by measuring mitral annular velocities in the long axis, can diagnose subendocardial dysfunction, subendocardial fibres being aligned longitudinally and connected to the mitral annulus.
- Long axis diastolic dysfunction assessed by tissue Doppler of lateral mitral annular motion may be a useful diagnostic test to differentiate patients with microvascular angina from those with non-cardiac chest pain.

not have a control group, but it has been reported that in normal subjects adenosine infusion induces increases in early filling and E/A ratio, as assessed by Doppler of the transmitral flow.¹²

We used the protocol described because, in our experience, patients with microvascular angina are particularly sensitive to this form of stress, often experiencing their normal chest pain at a lower infusion rate. Moreover, there are now extensive data suggesting that maximal coronary vasodilatation is achieved at 140 µg/kg/min, heart rate–systolic blood pressure product being less important than the selective effect on the coronary vasculature.¹²

Diagnosis of subendocardial dysfunction by tissue Doppler

The subendocardial fibres are aligned longitudinally and connected to the mitral annulus. Long axis contraction and relaxation result in its displacement, which can be measured by the new method of tissue Doppler echocardiography, in terms of velocity. There are three distinct velocity waves during each cardiac cycle: a systolic wave, starting just after the QRS complex, an early diastolic wave (E), and a late diastolic wave (A), starting after the P wave. A ratio of early-to-late velocities of mitral annular motion of <1 has good sensitivity and specificity (>70%) for detecting diastolic dysfunction, even in patients with a pseudonormal E/A ratio.¹³

The method of recording velocities of the mitral annular motion has been reported before.¹⁴ We used the apical window because it provides the best alignment of the Doppler beam for both transmitral flow and mitral annular movement. The intraobserver and interobserver variability of both acquiring and measuring the tissue Doppler velocities of the lateral mitral annular motion were ≤16% and ≤20%, respectively.¹⁴

CONCLUSION

Long axis diastolic dysfunction revealed by tissue Doppler of lateral mitral annular motion was present at peak adenosine in nine investigated patients with microvascular angina.

We have described a small, but very homogeneous group of patients. These patients are difficult to identify, resulting in limited numbers in most studies. This pilot study shows that adenosine tissue Doppler stress echocardiography might be useful as a diagnostic test for microvascular angina, if confirmed in large series of patients and in comparison with control subjects; it also demonstrates a possible mechanism for the chest pain in patients with normal coronary arteries.

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