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Identification of Patients with Coronary Artery Disease by Assessing Diastolic Abnormalities during Isometric Exercise

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Summary

Background: Previous clinical studies using invasive and noninvasive methods have shown handgrip-induced diastolic abnormalities in patients with coronary artery disease (CAD).

Hypothesis: The study was undertaken to determine the utility of Doppler echo- and pressocardiography during handgrip in discriminating patients with coronary artery disease (CAD) and in those with normal coronary arteries.

Methods: Both methods were obtained in 96 patients with suspected CAD within 24 h before coronary angiography. An abnormal handgrip-Doppler was defined by an early (E) to late (A) transmitral flow velocities ratio (E/A) < 1 during handgrip and a positive handgrip pressocardiographic test (HAT) by an abnormal increase in the A wave/total excursion or prolongation of the absolute or relative (heart-rate corrected) total relaxation time during isometric exercise.

Results: Of the 96 patients studied, 23 had normal coronary arteries and 73 showed CAD. In patients with normal coronary arteries, handgrip-Doppler showed an abnormal average E/A at rest and during handgrip, whereas all variables of HAT were within normal limits. In patients with CAD, handgrip-Doppler showed only a moderate handgrip-induced increase in average A (+ 19%, $p < 0.001$), whereas HAT showed a significant ($p < 0.001$) increase in mean A wave/total excursion (+ 60%) and decrease in the relative total relaxation time (− 17%). Furthermore, handgrip-Doppler and HAT were abnormal in 15 of 23 (65%, specificity 35%) and the HAT in 5 of 23 (22%, specificity 78%) patients with normal coronary arteries, as well as in 57 of 73 (sensitivity 78%) and 69 of 73 (95%) patients with CAD.

Conclusions: Our study demonstrates that these noninvasive stress tests can become a useful new diagnostic modality for detecting patients with unknown or suspected CAD.

Key words: coronary artery disease, diastolic function, Doppler echocardiography, sometric exercise, handgrip-pressocardiographic test

Introduction

The noninvasive assessment of left ventricular (LV) diastolic function at rest and with exercise remains a clinical problem.[1] It has been proved in experimental[2] and clinical studies[3] that coronary occlusion evokes immediate LV mechanical dysfunction followed by electrical abnormalities. Furthermore, diastolic abnormalities appear before systolic dysfunction and much earlier than symptomatic signs of ischemia.[3] Isometric exercise may induce myocardial asynergy without evidence of significant electrocardiographic (ECG) signs or symptomatic changes[5,6] and frequently is associated with dramatic rise in LV pressure.[7,8] The pathophysiologic explanation of the handgrip-induced ischemia was provided by Brown *et al.*,[9] who demonstrated that constriction of diseased epicardial coronary arteries is mainly responsible for the ischemic response to isometric stress, whereas other authors have proved the role of abnormal response of regional circulation[10] and of poor collaterals.[8] Furthermore, it has been reported that isometric exercise induces diastolic dysfunction much more frequently than do wall motion abnormalities.[5,8]

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Until now, there have been two simple noninvasive methods for assessing exercise-induced diastolic abnormalities, namely, Doppler echo-[11–15] and pressocardiography.[16–26] Whereas Doppler transmitral flow velocities reflect predominantly LV filling rate changes, pressocardiographic diastolic variables mainly correspond to changes in LV pressure in early and late diastole.[27–37] No information, however, is available about the relations between Doppler echo- and pressocardiographic diastolic indices during handgrip as well as about their clinical value in detecting coronary artery disease (CAD).

This study was undertaken to evaluate the usefulness of assessing diastolic abnormalities during handgrip exertion by Doppler echo- and pressocardiography for detecting patients with suspected CAD and to compare their utility in separating patients with normal from those with stenotic coronary vessels.

Methods

Study Population

A group of 99 patients with suspected CAD were included in this study. Patients were considered eligible for study if (1) the underlying rhythm was sinus and the heart rate < 100/min at rest and during handgrip exercise, (2) they had no only slight valvular disease, and (3) no overt heart failure.

Technically adequate Doppler echo- and pressocardiographic tracings could not be obtained during isometric handgrip exercise in three and two patients, respectively; consequently, our study cohort consisted of 96 patients, in whom both stress tests were obtained within 24 h prior to angiography. All cardioactive medication was withdrawn at least 48 h prior to isometric exercise. Informed consent was obtained from each person.

Patients with Coronary Artery Disease

In all, 73 patients (70 men and 3 women) with an age rang from 35 to 75 years (mean 56 years) had CAD. Of these, 42 had a history of prior infarction (17 inferior, 18 anterior, 7 both), 34 a history of hypertension, 15 diabetes mellitus, and 35 a typical angina on effort. The ejection fraction was < 40% in 40 patients. No ventricular wall aneurysm was present.

Patients with Normal Coronary Arteries

These 23 patients (19 men and 4 women) were catheterized because of suspected CAD. Their age ranged from 30 to 65 years (mean 52 years). Of these, 11 had a history of typical angina pectoris, 9 a history of hypertension, whereas 12 showed a positive stress ECG using Bruce protocol (ST depression > 2 mm).

Coronary Angiography

Using Judkins techniques, all patients underwent LV and selective right and left arteriography. Cineangiograms were interpreted without knowledge of the results of the two noninvasive handgrip tests. Multiple views of each coronary artery, including craniocaudal view, were obtained. After visual inspection of the coronary arteries, significant coronary stenosis was defined as > 70% reduction in the luminal diameter. Single-, double-, and triple-vessel disease implied significant coronary stenosis confined to one, two, or three of the major epicardial vessels or their major branches. Coronary arteriography demonstrated significant stenosis in one or more vessels in 73 patients, whereas 23 patients had normal coronary arteries (no stenosis and no diffuse arteriosclerotic changes). Of the 73 patients with CAD, 29 had single-vessel disease (11 left anterior, 9 circumflex, and 9 right CAD), 21 had double-vessel disease, and 23 had triple-vessel disease.

Handgrip-Echocardiography and Measurements

All patients were examined in the left lateral position by precordial M-mode, two-dimensional, and Doppler echocardiography using a commercially available Doppler echocardiography unit (Hewlett-Packard 2500 - ATL 9, Agilent Technologies, Andover, Mass., USA) with a 2.5 MHz duplex imaging transducer. Mitral flow velocities were recorded using an apical four-chamber view, placing a 0.5 to 1.0 cm pulsed-wave Doppler sample volume between the tips of the mitral valve leaflets (Figs. 1A and 2A). Maximal flow velocity was recorded at rest as well as during 1 min and 2 min handgrip exercise.

Handgrip—Pressocardiography and Calculations

Pressocardiograms were recorded on a 12-channel Hellige (Freiburg, Germany) direct writing recorder (Multiscriptor EK 512 P) or on a CU12 Schwarzer (Munich, Germany) recorder. For obtaining optimal recordings, modified EK512P and CU12 recorders were used, whereas for the latter the newly developed MANO-HAT software with automatic calculation and evaluation of all diastolic indices was used. The pressocardiographic tracings were recorded simultaneously with phonocardiogram and ECG at a paper speed of 100 mm/s (Figs. 1B and 2B). The pressocardiographic tracings were recorded by placing the pressure transducer over the maximal cardiac impulse and phonocardiograms by the microphone that was placed near the transducer, both being held in place by an elastic strap.[18–26] The handgrip-pressocardiographic test (HAT) was obtained with the patient in the left lateral position and deep expiration and the patient was advised to avoid a Valsalva at the deep expiration. Handgrip was performed with a balloon dynamometer as described previously, with each squeezing the balloon with the right hand and sustaining his or her grip at 40% of maximal voluntary contraction for 2 min.

As shown in Figures 1B and 2B, the following measurements were made from three consecutive beats thought to be technically best:

- The relative A wave to total (systolic and diastolic) pressocardiographic amplitude (A/H);[35]
- the relative A wave to total diastolic amplitude of the pressocardiogram (A/D);[35]

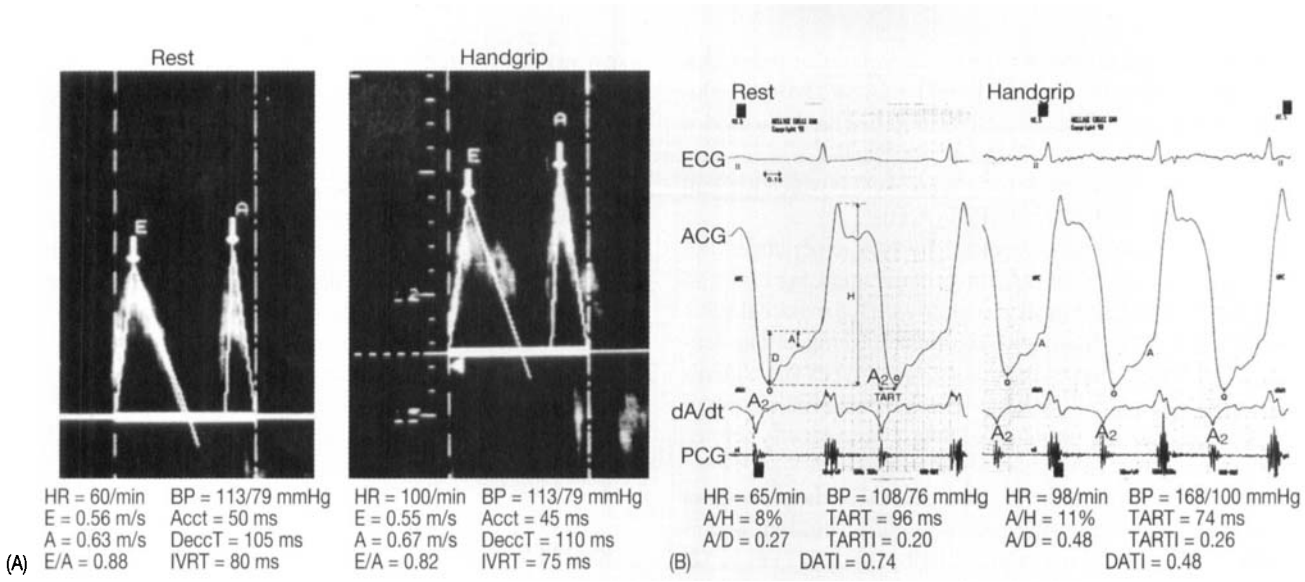

FIG. 1 Graphs from a 54-year-old patient with normal coronary vessels. (A) Pulsed Doppler echocardiogram at rest (left panel) and during handgrip exercise (left panel) showing an abnormal result. At rest E/A is abnormal (< 1) and decreases further during handgrip exercise. A = atrial transmitral flow velocity, AccT = acceleration time, BP = systolic and diastolic blood pressure, DeccT = deceleration time, E = early flow velocity, HR = heart rate, IVRT = isovolumic relaxation time. (B) Simultaneous tracings of left (apex) pressocardiogram (ACG), phonocardiogram (PCG), and ECG (lead II) at rest (left panel) and during handgrip (right panel). During handgrip there was a significant increase in A/D and less of A/H and TARTI, as well as a decrease of TART and DATI ; all these changes, however, were within normal limits. The method of measurements of pressocardiographic variables are given at rest. A = height of the A wave, A_2 = onset of aortic component of second heart sound, D = total diastolic amplitude, H = total (systolic and diastolic) height of pressocardiogram, O = nadir of pressocardiographic tracing.

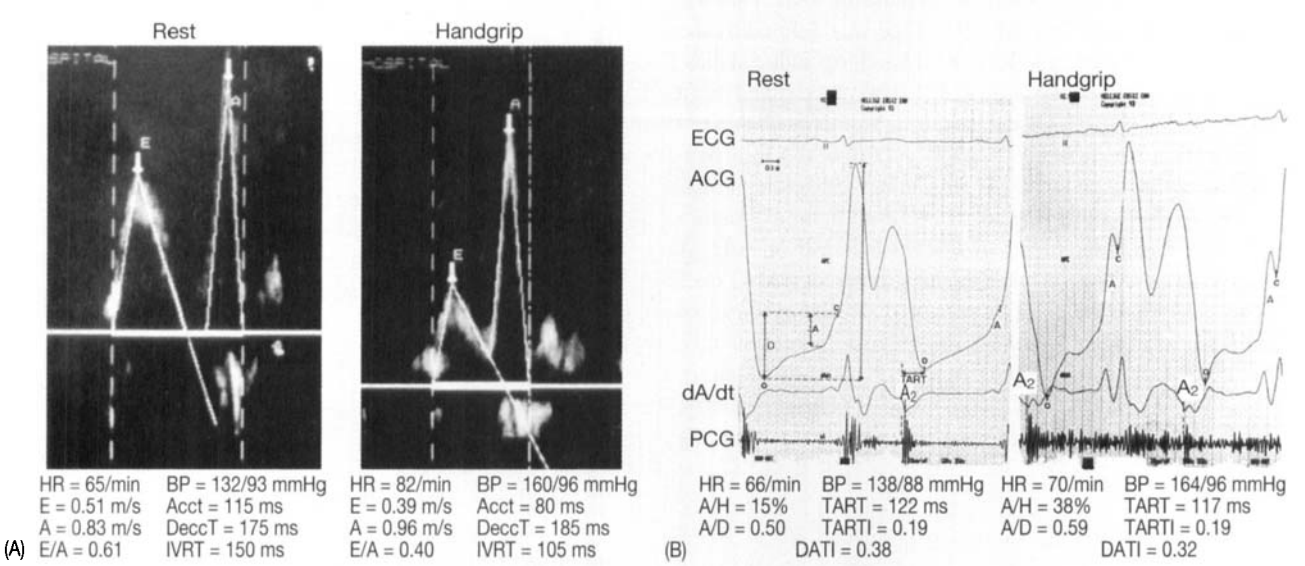

FIG. 2 Graphs from a 61-year-old patient with double-vessel coronary artery disease showing an abnormal Doppler echocardiogram (A) both at rest (left panel) and during handgrip (right panel) as well as an abnormal handgrip pressocardiographic test (HAT) (B) result. In handgrip-Doppler, there is a significant decrease in E, AccT, and IVRT, as well as an increase in A. Left pressocardiogram shows normal variables at rest, but during handgrip there is a typical dramatic increase in A/H and less of A/D as well as a decrease in TART and DATI. This patient shows a typical "ischemic" pattern of diastolic response assessed by the HAT characterized by an abnormal and more than double increase in A/H, whereas in Doppler the corresponding diastolic changes in flow velocities profile are less pronounced. Same variables as in Figure 1.

- the total (apex) pressocardiographic relaxation time (TART) measured from the onset of the aortic component of the second heart sound (A2) in the phonocardiogram to the protodiastolic nadir (0) of the pressocardiogram;[34, 36]

- the duration of the diastolic period, measured from A2 to the onset of the systolic upstroke (C point) of the pressocardiogram which has been found to be coincident with that of the LV pressure curve;[36]

- the total (apex) pressocardiographic relaxation time index (TARTI) given by the formula TARTI = $\sqrt{A2\text{-}C}$/TART; the index represents a modified Bazett formula that has been used to correct temporal variables for heart rate;[36] and
- the diastolic amplitude time index (DATI) which was calculated as follows: DATI = TARTI/(A/D).[37]

All measurements were made by two experienced observers blinded to the other findings of the study. For each value, three independent measurements with the maximal value observed at rest and during handgrip were averaged. The definitions of criteria of positivity as well as of types and patterns of diastolic abnormalities were based on data from our previous studies, whereas normal values have been exactly defined in a large cohort of normals.[19–25]

Accordingly, a positive HAT was defined by the presence of at least one of the following exercise-induced diastolic abnormalities: (1) A/H during or/and after handgrip > 21%, or (2) TART during handgrip > 143 ms or/and TARTI during handgrip < 0.14, or (3) DATI during handgrip < 0.27.

These definitions are now established as standard diagnostic criteria for assessing diastolic function, as defined by Paulus *et al.*[37] for the European Society of Cardiology.

A "compliance" (C) type of diastolic variables response to handgrip was defined by the presence of an isolated abnormal elevation of the A/H during and/or after handgrip, a "relaxation" (R) type of diastolic response by an isolated abnormal prolongation of TART and/or a decrease in TARTI during handgrip, whereas a "mixed" (RC) type was defined by the presence of both the C and R types of handgrip-induced diastolic abnormalities.[22] A fourth DATI type was defined as an isolated abnormal DATI decrease during isometric exercise.[24]

On the other hand, an "ischemic" pattern of diastolic dysfunction was defined by a handgrip-induced absolute or relative prolongation of resting normal relaxation time or pathologic (> 21%) and more than double increase of A/H. A "nonischemic" pattern is present when a pathologic HAT does not fulfill the criteria of an "ischemic diastolic response" of the pressocardiographic indices to handgrip.[23] Consequently, a "nonischemic" pattern is present when (1) A/H shows an abnormal but less than double increase during or after handgrip, or (2) TART or TARTI is abnormal both at rest and during handgrip.[23,25]

Statistical Analysis

Continuous data are expressed as mean value ± 1 standard deviation (SD), and categorical variables are presented as absolute and relative frequencies. The Mann-Whitney or Wilcoxon signed rank test and the Kruskal-Wallis criterion were applied to assess the effects of isometric handgrip exercise on the hemodynamic and diastolic presso- as well as echocardiographic variables. Further univariate analysis was performed based on correlation coefficients and the chi-square test to screen out potential cofactors.

To determine whether the behavior of diastolic variables with exercise was independent of the presence or absence of arterial hypertension or of LV systolic dysfunction or prior myocardial infarction, we performed a multivariate analysis based on a generalized linear regression model in order to evaluate the model's goodness-of-fit. Finally, sensitivity and specificity were calculated to assess the performance of the two noninvasive stress tests. Sensitivity and specificity were defined as the number of true-positive and true-negative detections, respectively, of exercise-induced diastolic abnormalities, as assessed by HAT or handgrip Doppler echocardiography, divided by the total number of patients with CAD and normal coronary arteries, respectively.

A value of $p < 0.05$ was considered significant. The level of significance was determined using Statistical Package for Social Sciences (SPSS) statistical software (SPSS, Inc., Chicago, Ill., USA).

Results

Isometric Handgrip Exertion and Hemodynamic Changes

The low-level handgrip test could be performed easily and with convenience by all patients. No patient developed angina or ST-segment changes during handgrip, although antianginal treatment was discontinued in all patients. In three patients, premature ventricular ectopic beats were provoked by handgrip stress, and reverted spontaneously after cessation of exercise.

As shown in Tables I and II, systolic and diastolic blood pressure increased significantly during handgrip in both groups of patients, whereas the heart rate increased significantly only in patients with CAD. There was no difference in blood pressure (systolic and diastolic) or heart rate both at baseline and during exercise between patients with and without CAD as well as between the two stress tests. Alternatively, since there was no great effect of handgrip on heart rate, and patients with tachycardia at baseline or with handgrip had been excluded from our study, no fusion of echocardiographic E and A waves or of the pressocardiographic rapid filling and A waves occurred (Figs. 1 and 2).

Doppler Echocardiographic Findings with Handgrip Exercise

Table I shows the mean value ± 1 SD of transmitral flow velocity indices in patients with normal coronary arteries (control group) and those with CAD at baseline and during handgrip exertion. In the control group, average A at rest was higher than E and E/A was slightly abnormal (< 1). All transmitral flow velocities indices showed no significant change during isometric exercise. An abnormal E/A (< 1) during handgrip exercise was found in 15 of 23 (65%) patients. In patients with CAD, from all variables only average A at rest was significantly higher than in controls; furthermore, there was a handgrip-induced significant increase in A and a shortening in deceleration time. Compared with the control group, mean A in the CAD group was significantly higher, E/A was lower, and the isovolumic relaxation time was longer during handgrip exercise. Furthermore, E/A < 1 during handgrip was found in 57 of

TABLE I Summary of handgrip-doppler echocardiogram data

	Control group	CAD group	p#
Rest			
HR (beats/min)	64 ± 9	57 ± 10	NS
SBP (mm Hg)	129 ± 13	138 ± 16	NS
DBP (mm Hg)	78 ± 9	82 ± 11	NS
E (m/s)	0.56 ± 0.10	0.54 ± 0.15	NS
A (m/s)	0.56 ± 0.11	0.65 ± 0.15	<0.01
E/A (−)	0.99 ± 0.25	0.87 ± 0.33	NS
AT (ms)	64 ± 17	65 ± 19	NS
DT (ms)	153 ± 38	162 ± 50	NS
IVRT (ms)	96 ± 24	101 ± 22	NS
Handgrip			
HR	77 ± 17	83 ± 15	NS
p*	NS	<0.01	
SBP	160 ± 15	166 ± 17	NS
p*	<0.001	<0.001	
DBP	92 ± 11	98 ± 13	NS
p*	<0.001	<0.001	
E (m/s)	0.57 ± 0.12	0.55 ± 0.19	NS
p*	NS	NS	
A (m/s)	0.64 ± 0.18	0.76 ± 0.17	<0.01
p*	NS	<0.001	
E/A (−)	0.94 ± 0.28	0.83 ± 0.48	<0.05
p*	NS	NS	
AT (ms)	54 ± 14	65 ± 19	NS
p*	NS	NS	
DT (ms)	143 ± 58	141 ± 52	NS
p*	NS	<0.01	
IVRT (ms)	85 ± 22	106 ± 32	<0.005
p*	NS	NS	

P values were obtained by paired and unpaired Student's tests.

Abbreviations: P* = p value between handgrip exercise and rest measurements, p# = p value between patients with normal coronary arteries and coronary artery disease (CAD), NS = not significant ($p > 0.05$), A = atrial transmitral flow velocity, AT = acceleration time, DBP = diastolic blood pressure, DT = deceleration time, E = early transmitral flow velocity, E/A = E to A ratio, HR = heart rate, IVRT = isovolumic relaxation time, SBP = systolic blood pressure.

73 (78%) of these patients, whereas 4 of 73 (5%) had E/A > 2. Furthermore, patients with prior myocardial infarction showed a significant higher prevalence of E/A < 1 (Table III).

Pressocardiographic Findings with Handgrip Exercise

As shown in Table II, in the control group the mean values of all diastolic variables were within normal limits at rest and during handgrip; whereas only DATI showed a significant decrease during handgrip exercise. A positive HAT result was observed in 5 of 23 (22%) of the patients with normal coronary arteries. In the CAD group, there was a significant handgrip-induced increase in mean A/H and A/D as well as a decrease in TARTI and DATI. During handgrip, A/H and A/D were significantly higher and DATI lower in CAD patients, whereas at rest all diastolic variables showed no significant difference between the two groups.

TABLE II Summary of handgrip-pressocardiographic data

	Controls	Patients with CAD	p#
Rest			
HR	68 ± 9	60 ± 11	NS
SBP	133 ± 14	141 ± 17	NS
DBP	79 ± 9	81 ± 10	NS
TART (ms)	115 ± 19	127 ± 27	NS
TARTI (−)	0.20 ± 0.05	0.18 ± 0.04	NS
A/H (%)	12 ± 5	15 ± 8	NS
A/D (−)	0.40 ± 0.15	0.48 ± 0.16	NS
DATI	0.70 ± 0.37	0.47 ± 0.30	NS
Handgrip			
HR	80 ± 16	86 ± 14	NS
p*	NS	<0.01	
SBP	156 ± 15	163 ± 23	NS
p*	<0.001	<0.001	
DBP	94 ± 9	100 ± 12	NS
p*	<0.001	<0.001	
TART (ms)	118 ± 24	145 ± 47	NS
p*	NS	NS	
TARTI (−)	0.20 ± 0.06	0.15 ± 0.03	NS
p*	NS	<0.001	
A/H (%)	16 ± 8	24 ± 10	<0.001
p*	NS	<0.001	
A/D (−)	0.50 ± 0.10	0.63 ± 0.13	<0.001
p*	NS	<0.001	
DATI (−)	0.40 ± 0.18	0.26 ± 0.11	<0.01
p*	<0.01	<0.001	

Abbreviations: A/H = A wave/total excursion ratio, A/D = A wave/total diastolic excursion ratio, DATI = diastolic amplitude time index, DBP = diasolic blood pressure, HR = heart rate, TART = total (apex) pressocardiographic relaxation time, TARTI = total (apex) pressocardiographic relaxation time index. Other abbreviations as in Table I.

As shown in Table III, there was a significant difference in the distribution of the types of abnormal diastolic response between controls and CAD group, whereas the latter showed a higher prevalence of C and RC types as well as an ischemic pattern. Furthermore, patients with prior myocardial infarction showed a higher prevalence of a positive HAT result.

Relations between Doppler- Echo- and Pressocardiographic Diastolic Variables

No significant correlation was found between Doppler echo- or pressocardiographic indices and the ejection fraction. However, A at rest and with handgrip as well as E/A during handgrip showed poor correlations with age ($r = +0.34$, $p < 0.01$ and $r = -0.23$, $p < 0.05$, respectively). Alternatively, significant, but only very poor correlations were those of A wave/total excursion with isovolumic relaxation time and A ($r = -0.27$ and $r = 0.22$, $p < 0.05$).

TABLE III Distribution of diastolic abnormalities with handgrip exercise in controls and in patients with coronary artery disease (with or without prior myocardial infarction)

	Controls (n = 23)	CAD (n = 73)	p Value	No prior MI (n = 31)	Prior MI (n = 42)	p Value
E/A < 1 (%)	15 (65)	57 (78)	NS	17 (54)	31 (74)	< 0.09
HAT positive (%)	5 (22)	69 (95)	< 0.001	27 (87)	42 (100)	< 0.02
Normal (%)	18 (78)	4 (5)	< 0.001	4 (13)	0 (0)	< 0.02
R-type (%)	2 (9)	17 (23)	NS	8 (26)	9 (21)	NS
C-type (%)	1 (4)	26 (36)	< 0.004	10 (32)	16 (38)	NS
RC-type (%)	0 (0)	21 (29)	< 0.004	8 (26)	13 (31)	NS
DATI-type (%)	2 (9)	5 (7)	NS	1 (3%)	4 (10)	NS
Ischemic (%)	1 (4)	42 (58)	< 0.001	19 (61)	22 (52)	NS
Non-ischemic (%)	4 (18)	27 (37)	< 0.08	7 (23)	16 (38)	NS

Abbreviations: MI = myocardial infarction, C-type = compliance type, DATI-type = diastolic amplitude time index type, RC-type = relaxation and compliance type. Other abbreviations as in Tables I and II.

Multivariate analysis revealed no influence of arterial hypertension and of a decrease in ejection fraction on positivity of HAT or on the pressocardiographic A wave/total excursion when adjusted for age and gender. In contrast, TART was found to be significantly influenced by both arterial hypertension and LV systolic dysfunction ($p = 0.026$ and $p = 0.046$, respectively). On the other hand, E/A was found to be significantly influenced in our study patients by both the presence of prior myocardial infarction (Table III) and LV systolic dysfunction ($p = 0.001$), but not by the presence of arterial hypertension.

Discussion

The results of the present study indicate that the detection of diastolic abnormalities with isometric handgrip exercise as assessed by Doppler echo- and pressocardiography represents a useful indicator of CAD.

Using exact definitions of an abnormal diastolic response, a high prevalence of exercise-induced diastolic dysfunction as assessed by HAT and handgrip-Doppler echocardiography was found in patients with documented CAD (95 and 78%, respectively). Alternatively, in patients without stenotic coronary vessels, Doppler was abnormal in 65% and HAT in 22%. It appears thus that HAT is both more sensitive and specific than handgrip-Doppler echocardiography and therefore superior as detector of CAD, since it separates better patients with and without stenotic coronary vessels.

These differences between the two simple noninvasive methods might be explained by the fact that handgrip-induced changes in pressocardiographic variables correspond to those in LV filling pressure,[37] which have been shown to be the most accurate indices of diastolic function.[3–7, 8, 39–41] On the other hand, Doppler echocardiography assesses filling rate (volume) changes within the left ventricle that are greatly influenced by multiple factors (heart rate, age, presence of mitral incompetence, etc.) and often show a "pseudonormalized" pattern with increasing filling pressure.[1, 42–45]

Based on extensive experimental and clinical research, it has been proved that altered diastolic properties of the left ventricle are frequently present in CAD. These changes may be in the passive (or "static") diastolic properties of the left ventricle and/or in the "active" processes of relaxation and atrial filling. Many interrelated factors have been found to be responsible for diastolic dysfunction in the acute (angina, acute myocardial infarction) or chronic (hibernating, diffuse fibrosis, scar, congestive heart failure) stage of ischemic heart disease.[1–3, 9, 39, 40]

Using invasive measurements, it has been demonstrated that LV pressure-derived parameters are generally much more altered during ischemia than volume or filling rate variables.[4, 38–42, 45] Furthermore, there is evidence that although impaired relaxation represents a central and very early event during ischemia, the most dramatic alterations are those of pressure at end diastole.[4, 7–9, 39–41] Most of these studies have shown a great rise (double or more) of LV end-diastolic and left atrial pressures, whereas volume variables showed only slight to moderate changes. Specifically, a dramatic rise in LV end-diastolic pressure[4, 7–9, 39, 40] and an upward shift in the pressure-volume curve[41] have been demonstrated during handgrip exercise. Handgrip exercise induces ischemia by increasing blood pressure and heart rate,[5–10, 18–25] resulting in an increase in myocardial oxygen requirement; and the presence of poor collateral circulation and/or vasoconstriction results in a decrease in coronary flow reserve.[5, 6, 9]

On the other hand, Doppler flow indices have been found to show a very variable pattern of changes during transient ischemia. Some authors have reported a decrease in E/A during ischemia, whereas others have demonstrated an increase or no change in E/A.[11–15] These opposite results can be explained by changes of Doppler variables that are not unidirectional in early and late diastole with increasing filling pressure in the presence of ischemia.[1, 42–45] In contrast, an increase in the relative A wave height and a prolongation in relaxation time of the pressocardiogram have regularly been observed by many authors in patients with ischemic heart disease.[16–20, 26] Especially, the alterations at end diastole are unidirectional, and a dramatic

rise in A wave post exercise[16, 17] as well as during isometric exercise[18–23] has been reported as a characteristic finding in patients with CAD.

Handgrip-Doppler Echocardiography and Handgrip Pressocardiographic Test as Predictors of Significant Coronary Artery Disease

Handgrip exercise was not associated with any complications in our study patients. The most important finding of this study is the high prevalence of LV diastolic abnormalities as assessed by Doppler echo- and pressocardiography during low-level isometric handgrip exercise in patients with documented CAD, both tests being obtained within 24 h before coronary arteriography.

According to our present data, it appears that an abnormal handgrip-induced response of diastolic variables derived from pressocardiogram is a more sensitive marker of CAD than that of Doppler-derived indices. The HAT is superior to handgrip Doppler as a predictor of CAD for several reasons. First, both the sensitivity and specificity of HAT are significantly greater than those of Doppler. Second, the handgrip-induced diastolic changes in the pressocardiographic heart rate-corrected relaxation time and mainly in the A wave/total excursion ratio are much greater than those in the corresponding Doppler variables in early and late diastole (Tables I and II). Thus, HAT appears much better to separate patients with suspected CAD with normal from those with significantly stenotic coronary arteries, reflecting more accurately an "ischemic diastolic response," which is characterized predominantly by a dramatic rise in filling pressures at end diastole and less by a prolongation of relaxation time.[4, 18–21, 38–41] As shown in Table III, such a characteristic ischemic pattern of diastolic behavior with exercise occurred > 14 times more often in patients with CAD than in those with normal coronary arteries. In addition, the former appear to be further characterized by the occurrence of a C or a RC type, which only rarely occur in the latter.

Comparing the behavior of diastolic variables of both methods during isometric exercise, HAT showed a more than three times greater increase in average A/H than in the A of Doppler (+60 vs. +19%). In addition, handgrip caused a more pronounced change in the pressocardiographic absolute and relative relaxation time indices (+14 and −17%, respectively) than in E of Doppler (−2%). Furthermore, the most widely used diastolic index of Doppler, namely the E/A, showed an almost identical behavior with handgrip exercise in patients with and without CAD (−5 and −4%, respectively). Moreover, deceleration time decreased significantly and acceleration time remained unchanged during exercise in patients with CAD. These findings are in contrast to those of El-Said *et al.*[11] who recently reported a significant decrease in acceleration time, E, and E/A in 23 patients with single-vessel CAD using dobutamine stress Doppler, and no changes of these indices in controls. However, other authors have found no change or even an increase of E/A during induced myocardial ischemia.[13–15] This great variety of ischemia-induced changes in Doppler indices could be explained by differences in the level of LV filling pressure in a different cohort of patients and the opposite alterations of these variables in early and late diastole resulting in a "pseudonormalized" flow velocities profile with increasing filling pressures within the left heart.[1, 42–45] Furthermore, no close correlations have been found between Doppler and HAT variables, confirming the fact that these two noninvasive methods assess different aspects of LV filling dynamics, the former reflecting volume and filling rate whereas the latter reflect pressure changes within the left ventricle.

In addition, there are some significant differences in LV diastolic behavior with handgrip as assessed by these two noninvasive methods, depending on the presence of prior myocardial infarction (Table III). Patients with prior infarction show a positive HAT result and an abnormal E/A ratio more frequently.

Alternatively, multivariate analysis showed that a positive HAT result as well as the handgrip-induced changes in A wave/total excursion are not significantly influenced by the presence of arterial hypertension or decreased LV ejectional performance when adjusted for age and gender. In contrast, the total relaxation time of both presso- and E/A ratio of Doppler echocardiogram with exercise is significantly influenced by these two factors.

Study Limitations

There are some technical and theoretical limitations with Doppler echo- and pressocardiography during isometric exercise in the present study. Technically acceptable recordings of pressocardiogram could not be obtained with handgrip in 105 of 1,558 (7%) and of Doppler echocardiography in 12 of 108 (12%) patients in our laboratory.

Theoretical limitations in the present study are that treadmill ECG and single-photon emission computed tomography data were not available in all patients and that no direct comparison was made with pressure-volume curves derived from catheterization data. However, the relations of both Doppler echo- and pressocardiographic variables with pressure have been examined sufficiently by many authors using simultaneous noninvasive and LV pressure tracings.[1, 42, 44] Specifically, the relations of pressocardiogram with LV pressure have also been studied during handgrip exercise.[37]

Finally, it should be mentioned that our control group of patients with angiographically normal coronary arteries cannot be regarded as a "healthy" group, since all these patients had either hypertension and/or a positive exercise ECG. However, the selection of all our patients was random, as it was done prospectively before angiography and there was no significant difference in the prevalence of hypertension between our control and CAD groups (39 vs. 47%).

Conclusions

Our study shows for the first time the usefulness of detecting exercise-induced diastolic abnormalities as assessed by use of Doppler echo- and pressocardiography with handgrip

in patients with suspected coronary artery disease. Both methods show a high prevalence of diastolic abnormalities in patients with subsequently proved significantly stenotic coronary arteries. This high sensitivity of these two noninvasive stress tests as indicators of CAD could be of clinical value and potentially become a new modality for identifying such patients in everyday practice. However, HAT shows significantly higher sensitivity as well as specificity and reflects better the characteristic exercise-induced dramatic end-diastolic alterations and, thus, appears to be more useful in distinguishing patients with normal from those with stenotic coronary vessels in clinical practice.

Although multicenter studies with follow-up data from quite a large number of patients are needed before introducing the assessment of handgrip-induced diastolic abnormalities as a routine diagnostic tool for identifying patients with significant coronary stenoses, we do believe that these two "diastolic handgrip stress tests," in the present stage of development, can also become helpful as additional tools in evaluating patients in this clinical setting.

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