Invasive and Noninvasive Assessment of Exercise-induced Ischemic Diastolic Response Using Pressure Transducers

Jan Manolas*

Mobile Unit for Diastolic Stress Test, Department of Check Up, Diagnostic & Therapeutic Center of Athens, Hygeia Hospital, Erythrou Stavrou 4 and Kifissias Ave. Maroussi, Athens 151 23, Greece

Abstract: Left ventricular (LV) pressure curve shows early high-magnitude changes in the presence of induced ischemia. A dramatic rise in LV and left atrial end-diastolic pressures occurs within seconds to minutes in the presence of ischemia induced by dynamic or handgrip exercise as well as pacing of 38 to 183% and during short coronary balloon occlusion of 32 to 208% of baseline. Changes in relaxation or volumetric filling rate or ejection fraction were significantly less pronounced.

Similar end-diastolic abnormalities occurring mainly in patients with coronary artery disease (CAD) have been shown in noninvasive recordings obtained by pressure transducer placed over the point of maximal LV beat (pressocardiograms). Specifically, the amplitude of the A wave to total excursion of pressocardiogram showed a high-magnitude increase after dynamic or handgrip exercise in average by 60 to 142% of baseline; however, changes in pressocardiographic relaxation time indexes were only slightly abnormal. A well-defined “ischemic pattern” of pressocardiographic diastolic changes with handgrip, showed a high prevalence in CAD patients.

The assessment of diastolic changes in the presence of handgrip-inducible ischemia using noninvasive pressure transducers might provide after further studies a simple complementary diagnostic tool to assist in identification of patients with atypical or asymptomatic CAD.

Keywords: Coronary artery disease, diastolic dysfunction, diagnostics, end-diastolic pressure, isometric handgrip exercise, left ventricular dysfunction, myocardial ischemia, stress testing.

INTRODUCTION

Based on catheterization data, it has been shown that significant changes of LV diastolic function occur in the presence of induced ischemia. Patients with CAD have shown a dramatic increase in LV end-diastolic pressure (LVEDP) in the presence of ischemia induced by exercise [1-8] as well as by pacing [9, 10] or short coronary balloon occlusion [11-14].

Diastolic changes in the LV pressure (LVP) curve have been noted for decades and can be noninvasively evaluated by “pulse” pressure recordings, termed now pressocardiograms, which can be obtained by placing an external pressure transducer transthoracically over the left ventricle. It has been shown that these recordings reflect unidirectionally corresponding temporal and amplitude changes of the LVP curve both at rest [15-23] and during exercise [24-26]. A high-magnitude increase of the pressocardiographic relative/“pulse” A wave amplitude has been shown with exercise [24-35] in CAD patients, which was very similar to the corresponding dramatic LVEDP rise in the presence of ischemia.

Since both the noninvasive detection of LV diastolic dysfunction [36, 37] as well as CAD [38, 39] remains an unresolved problem, this “diastolic mechanocardiographic stress test” might become a complementary tool for detecting for CAD in clinical practice.

The aim of this review is to highlight the characteristics of an “ischemic diastolic behavior” and its potential clinical value in daily practice by: 1. Comparing the assessment of LV diastolic behavior using micromanometers vs. other angiographic volumetric measures in the presence of induced ischemia, and 2. Comparing these findings with corresponding exercise-induced pressocardiographic diastolic changes in CAD patients.

INVASIVE ASSESSMENT OF LV DIASTOLIC BEHAVIOUR USING PRESSURE TRANSDUCERS IN PRESENCE OF INDUCED ISCHEMIA

LVP measures both in early and late diastole are generally accepted and used as the gold standard for evaluating any novel noninvasive diastolic variable. LV hemodynamics and specifically diastolic function have been explored during handgrip [1-4] or dynamic [5-8] exercise as well as with pacing [9, 10] and during short coronary occlusion [11-14].

a) Ischemic Changes in End-diastole

Handgrip Exercise

It has been shown that low level handgrip exercise causes a rapid and significant increase in systolic and diastolic blood pressure and might be useful in evaluating LV hemodynamic reserve and distinguishing healthy subjects from patients with heart disease. The LVEDP rises and the rela-
tionship of LVEDP with stroke work index is steep in normals and flat in heart disease [1].

As shown in Table 1, Krayenbuehl et al. [2] have found that no or only minimal LVEDP rise occurs with handgrip exercise in healthy persons as well as in patients without significant volume or pressure overload and no inducible ischemia (Fig. 1a).

In contrast, a dramatic increase in average LVEDP of 38% over baseline value occurred in patients with CAD (Fig. 1b). However, a similar LVEDP rise was also found in patients with severe aortic stenosis or hypertrophic non-obstructive cardiomyopathy at 30% and 61% of baseline, respectively [2]. In both these groups, however, an inducible ischemia could contribute significantly to the great LVEDP rise.

Table 1. Ischemia-induced end-diastolic pressure changes in CAD.

| Inducing Modality | Patients Group | LVEDP rest | LVEDP stress | LVEDP Change to rest |
|-------------------|----------------|------------|--------------|----------------------|
| Krayenbuehl et al., Eur J Cardiol 1974 | Handgrip | n = 21 | 16 | 22 | +38% |
| Flessas et al., Circulation 1976 | Handgrip | n = 30 | 14 | 23 | +64% |
| Sigwart et al., Am J Cardiol, 1982 | Bicycle | n = 7 | 12 | 34 | +183% |
| Caroll et al., Circ., March 1983 | Bicycle | n = 15 | 22 | 38 | +73% |
| Hess et al., Circulation 1992 | Bicycle | n = 15 | 17 | 33 | +94% |
| Barry et al., Circulation 1974 | Pacing | n = 7 | 12 | 29 | +142% |
| Mann et al., Circulation 1979 | Pacing | n = 26 | 17 | 30 | +76% |
| Bertrand et al., J Am Coll Cardiol 1988 | Balloon Occlusion | n = 16 | 20 | 34 | +70% |
| Sigwart et al., Am J Cardiol 1990 | Balloon Occlusion | n = 32 | 12 | 37 | +208% |
| Gbrib and Sigwart in Serruys, Simon R, Beatt KJ(eds), Dordrecht 1990 | Balloon Occlusion | n = 30 | 15 | 22 | +47% |
| Serruys et al. in Serruys, Simon R, Beatt KJ(eds), Dordrecht 1990 | Balloon Occlusion | n = 14 | 22 | 29 | +32% |
| Duval-Moulin, J Am Coll Cardiol 1997 | Balloon Occlusion | n = 16 | 14 | 28 | +100% |

Abbreviations: Mean LVEDP = left ventricular end-diastolic pressure; n = number of study patients with coronary artery disease.

Fig. (1). Left ventricular and aortic high-fidelity pressure curves in a healthy subject (A) and in a patient with coronary disease (B). AoP = aortic pressure; dP/dt = first derivative of left ventricular pressure; EDP = left ventricular end-diastolic pressure; LVP = left ventricular pressure. TORET = total relaxation time. Handgrip leads in A to a small decrease of end-diastolic pressure from 8 to 6 mmHg. In contrast, there is a dramatic EDP rise in B from 26 to 41 mmHg - increase by 58% (modified Krayenbuehl HP, Eur J Cardiol 1974).
Flessas et al. have shown a marked increase in LVEDP in average of 64% over baseline in CAD patients with poor collaterals, who also showed new asynergies [3]. Alternatively, Brown et al. first demonstrated an angiographically significant handgrip-induced narrowing at the site of stenosed coronary arteries due to vasospasm [4].

**Dynamic Exercise**

Sigwart et al. [5] have shown an extensive LVEDP rise during bicycle exercise in CAD patients before percutaneous transluminal coronary angioplasty that is significantly reduced after this procedure in average at 183% and 46% of baseline, respectively. Caroll et al. [6] found that CAD patients with normal LV ejection fraction showed a mean LVEDP rise of 73% over baseline, whereas those with prior infarction and great akinetic area showed a rise of only 24% above rest value.

An active vasoconstriction with narrowing of coronary artery stenoses was also found with dynamic exercise in CAD patients, whereas patients with angina showed a higher pulmonary arterial pressure rise than those pretreated with nitroglycerin [8]. It appears, thus, that a vasospasm in site of atheromotic coronary arteries represents an important mechanism causing ischemia and LVEDP rise both with handgrip and dynamic exercise.

**Pacing**

Barry et al. [9] and Mann et al. [10] have found in patients with CAD a large rise in LVEDP during pacing-induced angina of 142% and 76% over the baseline, respectively.

**Balloon Occlusion**

As shown in Table 1, several authors have found a LVEDP rise of 32 to 208% of baseline in presence of acute transient ischemia induced by a short percutaneous transluminal occlusion of proximal left anterior descending artery [11-14]. Specifically, an increase in mean LVEDP as well as LA mean and “pulse” pressures at 208%, 164% and 63% over baseline values have been found at 30 sec of coronary occlusion, whereas the LV pressure-volume curve was shifted upward and to the left, indicating a significant change in LV stiffness [12].

b) Ischemic Changes in Relaxation & Volumetric Measures

In contrast to the dramatic changes in end-diastolic pressure measures, LVP decay as well as volumetric diastolic measures and ejection fraction were less pronounced and showed a variable pattern of not always unidirectional changes in presence of induced ischemia.

The time constant of LV relaxation was increased with pacing by 35% over baseline [10] and during coronary occlusion by 24 to 55% over baseline [11, 14, 15]. The isovolumic relaxation time was only slightly prolonged in the early phase of occlusion at 13 to 17% above baseline [12, 14], but it shortened after 30 sec [12].

Min dP/dt was either decreased with pacing induced ischemia associated with angina by 11% [10] or increased with dynamic exercise by 34% above rest value [5]. Finally, the early LV filling was not blunted in CAD patients, but was maintained during dynamic exercise-induced ischemia, whereas late filling was restricted [6].

On the other hand, LV ejection fraction decreased in CAD with handgrip or pacing 21% below rest value [3] and showed with dynamic exercise a 13 to 19% decrease [5-7]. A significantly more pronounced decrease in ejection fraction of 31 to 38% from baseline was found during coronary occlusion [11, 12, 14]. LV end-diastolic index varied greatly in presence of ischemia, showing either a decrease or a significant increase [3, 5-7, 9, 11, 12, 14].

Thus, the most consistent changes in presence of induced ischemia were the high-magnitude rise in LVEDP of 32 to 208% and in LA pressure of 164 to 185% over baseline values, whereas LV relaxation and volumetric indexes showed less pronounced and variable changes. We termed these typical diastolic LVP changes in presence of ischemia an “ischemic diastolic response”.

**NONINVASIVE ASSESSMENT OF ISCHEMIC DIASTOLIC RESPONSE USING EXTERNAL PRESSURE TRANSDUCER**

**Relations of Pressocardiogram with LVP (Figs. 2 and 3):** By obtaining simultaneously high-fidelity recordings using almost identical internal and external pressure transducers, the relations between LVP and pressocardiographic curves have been studied [15-23]. As shown in Figs. 2 and 3, the onset and lowest points as well as the slopes and 1st time derivative of the pressocardiographic and LVP curves have been found to be very similar. In (Fig. 3) from a patient with heart failure, the pressocardiographic relative A wave to total height (A/H) is highly elevated corresponding to the analogous A wave rise of left atrial and LV pressures and the total relaxation time (TORET) of LVP and Pressocardiogram prolonged.

It has been proved that the pressocardiogram reflects in time, slope and “pulse” amplitude the LVP curve at rest [15-23] and with exercise [24-26]. Specifically, the TORET, measured from the aortic component of the 2nd heart sound in phonocardiogram to the lowest pressocardiographic 0 point, was almost identical with that of LVP curve Figs. 2 and 3. TORET and the TORET index (TORETI), representing a modified Bazett formula for heart rate correction, correlated significantly with min dP/dt [19, 23]. Alternatively, the A/H showed a significant correlation with LVEDP and more sophisticated LV stiffness indexes ranging from 0.57 to 0.87 [15, 16, 20-23]; above, Voigt et al. found a close correlation of A/H to corresponding LVP curve measure of “LA pulse wave” of 0.81 [16]. Thus, the term “pressocardiography” reflects better the true genesis of these recordings.

**Pressocardiography with Exercise:** In early 60s, Benchimol and Dimond in La Jolla, California [24] have first shown a significant increase by 52% over the rest value of the average pressocardiographic relative A wave to total excursion (A/H) in 25 patients with ischemic heart disease and no change in 32 controls [25]. Using simultaneous LVP and pressocardiogram recordings in a patient with inductible ischemia, these authors reported first that the A/H increased post exercise by 113% and the LVEDP by 100% over the
rest value [25]. Ginn et al. showed an exercise-induced A/H rise of 79% from baseline in CAD and a fair interobserver reproducibility [27]. Aronow et al. also found after dynamic exercise an A/H increase of 72% over rest value, showing to be of equal importance as ECG changes, since it enabled in asymptomatic patients an improved prediction of subsequent CAD [28].

Siegel et al. in Emory University reported for the first time a dramatic increase of average A/H of 75% of rest value during short low level handgrip [29]. Since 1985, we have applied a “presso- and phonocardiographic handgrip stress test”—termed now presso test—safely and successfully in >8,000 patients without any life-threatening complications.
To provide a safer and more convenient exercise protocol for all patients, we have chosen an only 2 min handgrip exercise protocol at 40% of maximal voluntary contraction with one hand. Recordings were made with a small pressure sensor placed directly on the thoracic wall (without fluid or air coupling) over the maximal LV beat and a heart sounds microphone near it, both held in place by an elastic strap [30-35]. A valid presso test could be obtained in all but 5-8% of the population studied and no life threatening or irreversible complications have been hitherto reported.

We have for the 1st time defined the normal limits of both A wave amplitude and relaxation indexes at rest and with handgrip exercise as well as the magnitude of their changes (Table 2) in a large cohort of controls [30-35]. These criteria are partly included in the guidelines of ESC [40]. In controls, all these indexes were within normal limits in all phases of handgrip (Fig. 4). As shown in Table 2, a positive presso test is defined by the presence of one of the following 3 “diastolic types” at rest or/and with handgrip [33]: the “relaxation or R-type”, the “compliance or C-type” and the “mixed or RC-type”. Patients with a C-type presso test result showed the worst, those with R-type the most favorable and those with RC-type an intermediate outcome [33]. Therefore, the transmission from R- to RC- and C-type

### Table 2. Definition of positivity, types and patterns of presso test.

| i. Diastolic Types & Positivity |
|--------------------------------|
| A positive test is defined by the presence of one of following diastolic types in one of the exercise steps: **Relaxation (R-)** type: Rest: TORET > 159 ms or TORETI < 0.16; During Handgrip: TORET > 155 ms or TORETI < 0.14; **Compliance (C-)** type: in all steps A/H > 21%; Mixed or RC- or Mixed type: in all steps both R- and C-type criteria present in the same beat. A positive test result is defined by the presence of one these types during and/or after handgrip. The transmission of R-→RC→C type is termed deterioration and the opposite improvement of type. |

| iii. Grading of Diastolic Dysfunction |
|--------------------------------------|
| Slight: TORET < 181 ms and/or A/H < 35%; Moderate: at HG or post HG: TORET > 180 ms and < 210 ms and/or A/H > 30% and < 41%; Severe: TORET > 210 ms and/or A/H > 40% |

| iii. Diastolic Patterns |
|-------------------------|
| Defined according to the HG-induced change in % from baseline value: **Ischemic Pattern:** Abnormal TORET prolongation of > 10-20% or/and A/H increase of > 25-70% of resting values depending on baseline values. **Non-ischemic Pattern:** Positive presso test and absence of the above ischemic criteria. |

Abbreviations: A/H = Relative A wave to total presocardiographic excursion; C-type = Compliance type; C-type = Compliance type; R-type = Relaxation type; RC= Relaxation and Compliance or Mixed type; TORET = total relaxation time; TORETI = TORET index and is defined by the following formula: TORET = √A2/C/TORET

Fig. (4). Healthy subject showing a “Normal diastolic response”: Simultaneous recordings of electrocardiogram (ECG), PCG (medium and low frequencies) and presocardiogram (Presso) at rest and during handgrip. All variables are at rest and during handgrip within normal limits with a shortening of TORET and no change in A/H with handgrip exercise. The A/H and TORET are increasing, but remain within normal limits. HR = heart rate; R-type = relaxation type; TORETI = total relaxation index. Other abbreviations as in (Fig. 2).
is defined as a “deterioration of type”. The test’s positivity was defined by the presence of one of these diastolic types during or after handgrip exercise.

A positive presso test was present in an average 7% of a large cohort of healthy volunteers [30-35, 41-44] and in 5% of healthy athletes [43] as well as in 22% of patients with normal coronary arteries in angiography [35]. In patients with angiographically verified CAD, a positive presso test (ischemic or non-ischemic) has been found in 86-93% of outpatients [30-34] and 95% of hospitalized patients with CAD [35]. Moreover, patients with hypertension [41, 42], hypertrophic cardiomyopathy [43, 44] and syndrome X [45] showed a positive presso test in 70%, 95% and 100%, respectively.

Ischemic Diastolic Response Using Presso Test: In patients without inducible ischemia the magnitude of early or/and late diastolic abnormalities with exercise is significantly less pronounced than those found in patients with CAD and inducible ischemia (Figs. 5a and 5b). By applying presso test in hundreds of patients with inducible ischemia, we have observed that characteristic high-magnitude A wave rise with or without relaxation abnormalities occur (Figs. 6 and 7), which were very similar to those found in catheterization studies using micromanometers in left ventricle with handgrip (Fig. 1b) or dynamic exercise [1-8]. Namely, mean A/H increase with handgrip exercise in CAD patients showed a range from 100% to 142% of baseline value in outpatients [30-32, 34] and 60% in hospitalized patients [35]. In contrast, mean TORET prolongation with handgrip exercise in CAD ranged from only 0 to 14% and TORET decrease from to 16 to 22% of baseline [30-32, 34, 35]. These less pronounced and variable changes in pressocardiographic relaxation time indexes are in accordance to those of LVP decay indexes in presence of ischemia induced by exercise or pacing [5, 10], but not with the significantly impaired LV relaxation observed in first sec of coronary occlusion [11, 14, 15].

![Fig. (5). Condt...](image-url)
Fig. (5). a: Asymptomatic patient with hypertension showing a “positive presso test” result and a “non-ischemic diastolic response” of Relaxation (R)-type. TORET is slightly increased at rest. Both TORET and A/H are slightly increasing and TORETI decreasing with handgrip.

b: Asymptomatic patient with hypertension showing a “non-ischemic diastolic pattern” of Compliance (C)-type. All indexes are within normal limits at rest. During handgrip, TORET is shortened and A/H is slightly abnormal. Abbreviations as in (Figs. 2 and 3).

Fig. (6). Pressocardiogram from an asymptomatic 67-year-old man at rest, A/H is slightly increased and TORETI slightly decreased (mixed or RC-type). At handgrip 1 min and 2 min, there is a dramatic increase of A/H (HG1 at 56% and HG2 at 64% of baseline) and a decrease of TORET and TORETI increase. The automated evaluation shows the presence of a “positive” presso test with “severe LV diastolic dysfunction” at exercise and an “RC-type” at rest and “C-type” at exercise as well as a “deterioration of type” due to “RC→C” change resulting to the diagnosis of “ischemic” pattern. Subsequent CTCA showed multiple calcified “mixed” plaques in all coronary vessels without significant stenoses of >50%. Same abbreviations as in (Figs. 2 and 3).
As shown in Table 2, based on magnitude criteria of changes in both A/H and TORET and TORETI, we have introduced an exact definition of an “ischemic” and “non-ischemic” pattern of diastolic response to handgrip exercise [34]. An “ischemic pattern” was found in 72% of outpatients [34] and in 61% of hospitalized patients with at least one significant coronary stenosis (>70%) without infarction [35] and less frequently (52%) in patients with prior myocardial infarction [35]. The lower prevalence of an ischemic pattern in hospitalized patients could be explained by bed rest, less catecholamines, preceding anti-ischemic or other drug treatments. Alternatively, the lower prevalence of high-magnitude A/H increase in patients with prior infarction is in accordance to Caroll et al. who found only a minor increase in LVEDP in patients with prior MI [6].

A more severe “ischemic diastolic response” with deterioration of diastolic type – termed coronary differential form - has been found in 10% of mildly hypertensives, who subsequently showed in CT angiography in 33% non-obstructive and 44% significant CAD [42]. This finding is in accordance with those of Johnson et al. who using a similar to our handgrip exercise protocol have found a shift towards anaerobic metabolism due to induced endothelial dysfunction and ischemia even in those women without significant stenoses or even those without any atheromatic plaques of epicardial coronary arteries in CT angiography, being associated with worse outcome [46].

As the noninvasive identification of patients with CAD by current techniques and all their combinations still represents a great problem [38, 39], the detection of an “ischemic diastolic response” by presso test - especially when associated with deterioration of type- and in absence of significant valvular cardiac disease or cardiomyopathies, may help us in the daily practice for initiating further more sophisticated examinations for assessing more information about localization, extent of and severity of coronary stenoses.

ASSESSING AN ISCHEMIC DIASTOLIC RESPONSE IN PATIENTS WITHOUT CAD

An ischemic diastolic response is expected to be present also in absence of CAD, since an inducible ischemia may also be found in patients without CAD, which is caused by many other pathophysiological processes included under the term “ischemic heart disease” [47]. Many myocardial structural and functional alterations can contribute in the presence of inducible ischemia on the level of cardiomyocytes and increasing LV stiffness, such as pressure overload states associated with LV hypertrophy (hypertension, aortic stenosis etc) as well as cardiomyopathies and diabetes mellitus, which may be associated with endothelial dysfunction, microvascular disease, interstitial fibrosis, capillary rarefaction, myocardial disarray etc. Some of these states may represent comorbidities in heart failure with preserved ejection fraction (HFpEF) being associated potentially with a “pron-
flammatory state” [48]. According to our clinical experience dyspnea on effort in HfPEF patients may be at least partly the result of considerable inducible ischemia with increasing LV stiffness and rising filling pressures leading to a more forceful left atrial kick (unpublished data), as shown in (Fig. 7), in presence or absence of significant or non-significant CAD.

An ischemic pattern of presso test has been found in 29% of patients with systemic hypertension [40] as well as in 15% of those with hypertrophic cardiomyopathy [41]; whereas the former showed more frequently a slight “non-ischemic” diastolic response with an “R-type” [41, 43, 44] and the latter a characteristic extremely prolonged TORET [43, 44].

Moreover, we have shown that presso test shows some significant differences in diastolic behaviour between patients with hypertension and hypertrophic cardiomyopathy that might be used for their differentiation. Namely, the former usually shows only slight diastolic abnormalities [41, 42] and the latter a characteristic extreme prolongation of TORET [43, 44]. An ischemic pressocardiographic A wave increase has also been found in patients with angina and normal coronary arteries, termed syndrome X [45].

Thus, Presso test may be also useful in evaluating patients without CAD, who may show early occurring “latent”–and “exercise-inducible” ischemic or non-ischemic LV diastolic abnormalities--such as hypertension, cardiomyopathies and even HfPEF.

CONCLUSIONS

Based on cath studies using micromanometers for recording LV pressure in CAD patients, conclusive evidence exists that characteristic high-magnitude changes in diastolic function occur in presence of ischemia induced by exercise or other techniques. Pressocardiograms obtained using specially designed external pressure transducers placed over the LV beat reflect LV pressure curve in time, slope and A wave “pulse” amplitude. Pressocardiograms obtained in CAD patients using low level handgrip exercise show a similar characteristic “ischemic diastolic pattern” with dramatic “pulse” A wave increase as well as a less frequent and pronounced prolongation of total relaxation time.

Based on well-defined defined criteria for positivity and an ischemic pattern, the diastolic handgrip stress pressocardiography may help us in separating healthy and myocardial disease patients as well as identify those with an “ischemic” diastolic response, who may need more sophisticated tests.

With further enlarged studies, this simple, fast, safe and convenient “diastolic stress test”, which has a firm pathophysiologic basis, might become increasingly useful for all physicians without need of special training. Specifically, it might make a complementary screening tool for subclinical CAD, yielding important additional information beyond that available from the ECG or echocardiographic findings.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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