Diastolic Handgrip Stress Test Using an External Pressure Transducer: on the road for a New Initial Screening Test for Preclinical Coronary Artery Disease?

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ABSTRACT
The initial screening of asymptomatic coronary artery disease (CAD) can be done mainly out of hospitals, where sophisticated techniques cannot and should not be applied widely. This great diagnostic problem could be potentially solved by applying widely a diastolic handgrip stress test by placing an external pressure transducer over the left ventricular (LV) impulse transthoracically and recording a pressocardiogram (Presso Test). Pressocardiogram reflects in time, slope and pulse amplitude LV pressure curve at rest and exercise and some diastolic indexes correlate significantly with corresponding standard diastolic measures of LV pressure. During handgrip, above the pressocardiographic A wave shows in CAD a dramatic increase that corresponds the dramatic rise in LV end-diastolic and atrial pressures in presence of induced ischemia. A high prevalence of these typical and exactly definable “ischemic diastolic changes” have been found in patients with or without symptoms who subsequently showed in angiography significant or non-obstructive CAD. Thus, Presso Test could become a useful diagnostic tool for indentifying even asymptomatic patients in daily practice.

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Key words: Coronary Artery Diseases; Diastolic function; Diastolic Stress Test; Isometric Handgrip Exercise; Left ventricular Function


INTRODUCTION
Although numerous sophisticated techniques are now available and are widely applied for diagnosing and following up patients with coronary artery disease (CAD), the initial screening for asymptomatic/subclinical CAD represents still today one of the greatest diagnostic problems worldwide. Despite our numerous highly developed diagnostic tools, more than 60% of those hospitalized with acute coronary syndrome or dying suddenly have not be identified before these tragic events[1]. There are many factors contributing to this obviously existing screening failure in identifying patients with “silent CAD”.

First, “healthy feeling-and-looking” persons are not usually coming to us in tertiary Hospitals for being examined by our experts using sophisticated diagnostic techniques. Second, most of our modern noninvasive methods are often neither sufficiently cost-effective nor appropriate for applying them for screening asymptomatic intermediate or low risk persons representing the greatest part of CAD patients. Third, all combinations of our current expertize needing tools have been proved in some more recent extensive and thorough studies to have a too low average sensitivity (<70%) and an unacceptable low average specificity (<50%)[2-4]. For all these reasons, the identification of most persons with potential subclinic CAD is still today failing both in our hospitals and in private practice in the early asymptomatic stage.

We should, therefore, realize that by developing further only our sophisticated noninvasive techniques being useful for evaluating patients with known CAD, we cannot improve our initial screening ability. What is still needed for improving our screening for “silent CAD” and prevent early enough its progression, is to develop simple, fast, not expertize needing and widely applicable techniques that might be applied widely as screening tools. In general, a suitable screening test should have a proved firm pathophysiologic basis and also be safe and convenient for any patient and, therefore, widely applicable above out-of-hospitals. Specifically in CAD, we know now that physiologically as well as for the management of CAD patients, the degree of flow-limitation and inducible ischemia are of
greater clinical importance than the degree of anatomic stenosis per se. Consequently, an ideal screening tool for CAD should be a safe, fast and low level exercise modality for detecting latent exercise-inducible ischemia before applying more sophisticated diagnostic “anatomic” techniques – like coronary artery calcification or computer tomographic angiography.

**ISOMETRIC HANDGRIP EXERCISE AND LV PRESSURE DIASTOLIC CHANGES**

The most widely applied exercise modality is dynamic exercise using bicycle or treadmill, which cannot be performed by every subject due to obesity or physical disability or even lack of desire. A low level handgrip exercise testing could represent an almost ideal exercise mode, especially in the out-of-hospital setting. Above, a low level (40% of maximal voluntary contraction) and short (2 min) isometric handgrip exercise represents a fast, safe and most convenient for everyone exercise testing.

However, this short and safe exercise mode has hitherto neither further explored nor widely applied in clinical practice. The most probable cause is that it represents a too short and low level exercise with significantly less heart rate and blood pressure increase, which is obviously not sufficient for producing detectable ischemic ECG changes or specific echocardiographic abnormalities. On the other hand, it has been shown that low level handgrip exercise is associated with significant and early occurring LV pressure (LVP) curve diastolic changes – above a dramatic LV end-diastolic pressure (LVEDP) rise in CAD as well as in several other cardiovascular disease states. Interestingly, this slight handgrip test has been shown to induce in CAD patients significant endothelial dysfunction and great vasospasm diagnosed angiographically in significantly stenosed coronary arteries as well as ischemia even in non-significant CAD.

However, Krayenbuehl has found a great handgrip-induced LVEDP rise also in patients with severe aortic stenosis or non-obstructive hypertrophic cardiomyopathy at 36% and 60% from baseline value, respectively. In CAD patients without associated valvular disease, LVEDP increased at 38% over the baseline value. Interestingly, this characteristic LVEDP rise was not associated with any ECG changes or symptoms, which all occurred in later phases.

**ISCHEMIC DIASTOLIC CHANGES OF LVP CURVE**

In absence of structural cardiac disease, Krayenbuehl found a dramatic average LVEDP rise from 16mmHg to 22 mmHg (38% of rest value) and Brown et al. from 15mmHg to 24 mmHg (60% increase from baseline). Interestingly, Flessas et al. found that an increase of LVEDP from 14 to 23 mmHg (64% of rest value) was associated with new wall motion abnormalities in those patients without collateral vessels. Similar significant LVP abnormalities in end and also in early (relaxation) diastole have also been found in presence of angina pectoris with dynamic exercise. We termed these characteristic for the presence of CAD high-magnitude diastolic LVP abnormalities in absence of ECG or systolic or volumetric changes an “ischemic diastolic response”. Figure 1 left panel,

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**Figure 1** Left ventricular (LVP) and aortic (AoP) pressures pressure at Rest and during 2 min of 40% isometric handgrip exercise in a patient with CAD showing an “ischemic diastolic response” (left panel) and a patient with non-obstructive hypertrophic cardiomyopathy showing a “non-ischemic diastolic response” (right panel). Left Ventricular end-diastolic pressure (LVEDP) increases in the former from 14 to 38 Hg (171%) and in the latter from 27 to 43mmHg (59%); dP/dt: first time derivative of LVP; ECG: electrocardiogram (modified from Manolas J, Hel J Cardiol 1994).
shows the diastolic LVP curve changes in a patient with significant 1 vessel CAD with a dramatic handgrip-induced increase of LVEDP from 14 to 38mmHg (171% rise from baseline value) without ECG changes. In contrast, figure 1 right panel shows that in a patient with non-obstructive hypertrophic cardiomyopathy and dyspnea on effort, the LVEDP was already at rest increased and raised further from 27 to 43 mmHg (59% of rest value); whereas this significant end-diastolic change could also be partly induced by structural changes within the LV wall –like myocardial disarray and fibrosis, in presence of normal coronary arteries.

We have postulated that a noninvasive technique that could accurately detect these dramatic and characteristic handgrip-induced ischemic LVP changes in diastole, might be helpful for improving the initial screening patients without or with only atypical symptoms with inducible ischemia, especially those without any structural cardiac disease[12].

**USE OF PRESSOCARDIOGRAPHY FOR ESTIMATING LVP DIASTOLIC CHANGES**

It has been proved that recordings obtained by an optimal external “pulse”-pressure transducer placed on the thorax over the maximal left ventricular (LV) pulse reflects in time and slope and “pulse” amplitude at rest[13-18] (Figure 2) and with exercise[19-21] to corresponding LV pressure curve diastolic changes. Figure 2 shows the similarity in slopes and coincidence of onset of systolic rise (C point) with the corresponding onset of LVP rise and pressocardiogram as well as mostly also of lowest point of pressure decay of the LV curve in early diastole. Further, the 1st time derivatives of both curves are very similar.

Alternatively, the relative A wave to total pressocardiographic height (A/H) (Figure 3) has been found to correlate with LVEDP and left atrial pressure as well as specific LV stiffness measures at rest[15- 18] as well as with exercise[19-21]. Moreover, the total relaxation time (TORET) measured from the aortic valve closure to lowest point of these pressure transducer-derived recordings as well as TORET corrected for diastolic length-termed TORET index (TORETI) have been shown to correlate significantly with invasive LV relaxation measures[14,18]. Thus, the term “pressocardiogram” reflects better than the older term “apex- or vibro-cardiogram” the true genesis of these tracings, which do not represent just some “precordial vibrations” or are obtained from the apical part of the LV pulse of the heart -but from the middle part of the left ventricle[22].

**PRESSOCARDIOGRAPHY DURING HANDGRIP EXERCISE**

Figure 4 demonstrates the first recordings of Presso test in 1985 in an office in Athens, Greece; whereas the A/H shows a more than double increase from baseline with 2 min handgrip exercise in a patient with atypical symptoms, who has subsequently shown in angiography a significant stenosis in left coronary artery.

In a group of healthy subjects, we could define for the 1st time the normal limits of pressocardiographic diastolic changes and the “positivity criteria” of this “handgrip pressocardiographic stress test” - now termed Presso Test[23]. These positivity criteria show a high sensitivity and normalcy in patients with myocardial disease. Subjects without evidence of cardiovascular diseases showed no or only slight changes in diastole within these normal limits (Figure 5) and patients with significant CAD with or without symptoms showed a typical dramatic increase in the A/H ratio (Figure 6) or an absolute (TORET) and relative prolonged relaxation time (TORETI) (Figure 7) or both[24-27]. The Presso Test’s definitions and criteria have been included in the guidelines of European Society of Cardiology[28].

Most importantly, by comparing the LV diastolic behaviour as assessed by Presso Test in patients with CAD without prior myocardial infarction with those with hypertrophic cardiomyopathy,
we could for the 1st time define exact differentiation criteria separating an “ischemic” from a “non-ischemic” diastolic pattern with isometric exercise[25].

The high-magnitude of the handgrip-induced pressocardiographic diastolic changes-above of at end-diastole were very similar-if not identical-with those found in cath lab using micromanometer in left ventricle in CAD patients with inducible ischemia. Specifically, in outpatients without myocardial infarction and without drugs, a high-magnitude increase of A/H has been found at 67-100% over the baseline value within just 1 to 2 minutes of a 2 min low level isometric handgrip exercise[25-26]. It should also be emphasized that when compared with the A wave changes[19-21,23-27], an impaired relaxation - defined by TORET prolongation and/or TORETI decrease - was less pronounced than the A/H increase, ranging from 16 to 22% of baseline value[25-27].

The prevalence of an “ischemic pattern” has been shown to be higher in outpatients[26] then in hospitalized patients with CAD without prior infarction[27]. This could be caused by a decrease in adrenalin secretion with handgrip due to bed rest as well as medical treatment in the latter[27]. Further, hospitalized patients with prior myocardial infarction showed less frequently an ischemic diastolic response than those without (52% vs 61%, respectively)[27]; this could be explained by the fact that necrotic and scared “non-viable” myocardial tissue is not producing a significantly increase of exercise-induced “ischemic LV stiffness”.

An handgrip-induced ischemic diastolic response, as assessed by Presso Test, has been found to occur less often in hypertension or cardiomyopathies[29,30]. In these patients, an ischemia can be the result of structural changes within the LV wall associated with fibrosis or myocardial disarray as well as endothelial dysfunction or microvascular disease.

**CONCLUSIONS**

According to findings in catheterization studies using identical micromanometers in and over the left ventricle for obtaining high-fidelity pressure and pulse-pressure recordings, respectively, it has been shown that the latter - termed pressocardiograms- reflect diastolic changes of the LVP curve in time and amplitude, both at rest and exercise.

The dramatic diastolic LVP changes –above in end-diatole- that have been found in presence of induced ischemia in CAD patients correspond to those high-magnitude diastolic changes –above of A wave- of pressocardiogram found with short/low level isometric handgrip exercise in CAD patients. Thus, in absence of other non-CAD structural diseases-like cardiomyopathies or aortic valvular diseases, handgrip-pressocardiographic stress test might become useful as a complementary diagnostic modality above in out-of-hospital setting- for identifying those patients, who potentially suffer from subclinical/silent CAD. This simple and safe stress test might serve somehow as a “Pre-test” for separating those patients who might need more sophisticated and expertize diagnostic techniques.
Figure 6 Preso Test with an “ischemic pattern” due to A wave increase in a patient with 3 vessels CAD. The HR increases from 86/min to 94/min during and after handgrip. The A/H increases from 12% at rest up to 38% during and 46% after handgrip; thus, showing a maximal increase of 283% over the rest value. The relaxation time shows a slight decrease. Abbreviations as in figure 2. (modified from Manolas, Cardiology 1995).

Figure 7 Preso Test with an “ischemic pattern” due to relaxation prolongation in an asymptomatic patient with 2 vessels CAD. The A wave amplitude does not change significantly. Whereas HR increases from 60/min to 76/min, TORET prolongs from 141ms to 170ms during handgrip (19% over rest value) and TORETI (= √A2-C/TORET) decreases from 0.17 to 0.12. In contrast, the A wave amplitude shows only insignificant changes with handgrip (modified from Manolas, Cardiology 1995).
CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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