Assessment of a New Non-Invasive Index of Cardiac Performance for Detection of Dobutamine-Induced Myocardial Ischemia

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Abstract

Background: Electrocardiography has a very low sensitivity in detecting dobutamine-induced myocardial ischemia.

Objectives: To assess the added diagnostic value of a new cardiac performance index (dP/dt^{ejc}) measurement, based on brachial artery flow changes, as compared to standard 12-lead ECG, for detecting dobutamine-induced myocardial ischemia, using Tc99m-Sestamibi single-photon emission computed tomography as the gold standard of comparison to assess the presence or absence of ischemia.

Methods: The study group comprised 40 patients undergoing Sestamibi-SPECT/dobutamine stress test. Simultaneous measurements of ECG and brachial artery dP/dt^{ejc} were performed at each dobutamine level. In 19 of the 40 patients perfusion defects compatible with ischemia were detected on SPECT. The increase in dP/dt^{ejc} during infusion of dobutamine in this group was severely impaired as compared to the non-ischemic group. dP/dt^{ejc} outcome was combined with the ECG results, giving an ECG-enhanced value, and compared to ECG alone.

Results: The sensitivity improved dramatically from 16% to 79%, positive predictive value increased from 60% to 68% and negative predictive value from 54% to 78%, and specificity decreased from 90% to 67%.

Conclusions: If ECG alone is used for specificity, the combination with dP/dt^{ejc} improved the sensitivity of the test and could be a cost-savings alternative to cardiac imaging or perfusion studies to detect myocardial ischemia, especially in patients unable to exercise.

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Of all the non-invasive tests for the inducement and detection of myocardial ischemia, the most widely available and least expensive is exercise stress test electrocardiography [1]. The value of ECG is limited, however, in patients for whom physical exercise is difficult. In patients unable to exercise maximally, pharmacologic stressors are an increasingly used alternative [2]. Among these, dobutamine is one of the most popular [3,4]. Because ECG alone has very low sensitivity in detecting dobutamine-induced ischemia, this technique is usually combined with two-dimensional echocardiography [5,6] or scintigraphy perfusion imaging [7].

In previous studies [8-10] it was demonstrated that cardiac contractility decreases with a subsequent decrease in left ventricular dP/dt and arterial dP/dt during acute ischemia. The current study suggests that an additional channel of physiological information related to aortic dP/dt response during dobutamine infusion could provide additional diagnostic value for the detection of pharmacologic-induced myocardial ischemia. The information would be provided by a new non-invasive device.

The goal of the present study was to assess the added diagnostic value of a new cardiac performance index (dP/dt^{ejc}) as measured by a newly developed non-invasive device (CardioWatch, Matam Advanced Technology Center, Haifa, Israel), when compared to standard 12-lead ECG, for detecting dobutamine-induced myocardial ischemia, using Tc99m-Sestamibi single-photon emission computed tomography as the standard of comparison.

Patients and Methods

The study group consisted of 40 non-consecutive patients referred for routine dobutamine stress Tc99m sestamibi, SPECT and myocardial scintigraphy for evaluation of coronary artery disease. Only one patient had a previous history of myocardial infarction. The group comprised 25 men and 15 women, mean age 65 ± 11. The Hospital Internal Review Board approved the protocol and all patients signed informed consent. A new non-invasive cardiac performance index (dP/dt^{ejc}) was obtained at baseline and during each level of dobutamine infusion.

Dobutamine stress test

Dobutamine was administered intravenously, starting at a dose of 10 µg/kg/min for 3 minutes (T10), then 20 µg/kg/min for 3 minutes (T20), increasing by 10 µg/kg/min every 3 minutes up to a maximum dose of 40 µg/kg/min (T40). Blood pressure, heart rate and ECG were monitored continuously. Test endpoints were achievement of target heart rate (85% of maximum age-predicted heart rate), horizontal or down sloping ST segment depression of > 2 mm, ST segment elevation of > 1 mm in patients without previous myocardial infarction, severe angina, systolic blood pressure fall of > 40 mmHg, blood pressure of > 240/120 mmHg, or significant arrhythmia.

SPECT-Tc99m Sestamibi

Tc99m sestamibi, 25 mCi (925 MBq), was injected at rest and stress-flushed with 10 ml saline in a 2 day protocol. Image acquisition began approximately 1 hour after resting and stress injection. SPECT imaging was performed on a SP6 GAMMA CAMERA (Elscint, Israel). For each Tc99m Sestamibi acquisition, 32 projection images (30 seconds per projection) were obtained

SPECT = single-photon emission computed tomography

in a 180° circular orbit beginning from the 45° right anterior oblique to the 45° left posterior oblique projection. Projection images were obtained with a large-field-of-view scintillation camera equipped with 37 photomultiplier tubes and a sodium iodide crystal 0.375 inch (0.96 cm) thick, coupled with a low energy high resolution parallel-hole collimator. Images were stored on a 64 x 64 16-bit matrix. Transaxial reconstruction was performed after filtered back projection (Butterworth filter, with a 0.4 cutoff and an order of 3.5). Reconstructed slices were reoriented into the short, horizontal long and vertical long axes.

dP/dt^{ejc} measurements

The rationale and technical details of the new non-invasive technique for dP/dt^{ejc} measurements have been described in previous publications [10,11], and will be discussed here only briefly.

The device

The ascending limb of aortic pressure (dP/dt^{ejc}) was measured non-invasively with a newly designed computer-controlled device (CardioWatch). This device consists of three components: a sphygmonometric arm cuff attached to an air pressure unit, an array of proprietary sensors attached to the arm at the antecubital space [Figure 1] over the brachial artery, and a computerized monitoring system.

By applying occlusive pressure over the brachial artery during systole using a non-inflatable cuff, a temporary standing fluid column is created, whereby the rising intraaortic pressure is transmitted to the periphery with minimal distortion. This standing column of blood may be regarded as though it were a virtual manometric tube installed directly into the aortic arch.

The time intervals required for the aortic pressure wave to overcome a given occlusive brachial pressure applied by a sphygmomanometer on the arm are equal to the times needed to reach the same pressure in the central aorta plus the propagation time to the brachial point, which is constant in the same patient throughout the measurements. Time intervals are measured from the onset of flow breakthrough at the first sensor to the breakthrough reached at successive sensors [Figure 2].

Applying multiple successive occlusive pressures on the brachial artery from peak systole to diastole and plotting the values against time intervals described above results in the reconstruction of the central aortic pressure curve; we can calculate the dP/dt^{ejc}, the index used in the present study, from the ascending arterial pressure waveform. Non-invasive systolic pressure waveforms are generated by measuring the time delay between the first sensor on the array serving as a reference sensor and the onset of brachial artery flow in the subsequent sensors during controlled upper arm deflation. The delay decreases with falling cuff pressure so that the plot of pressure versus time delays yields the ascending portion of the arterial waveform. Previously, ECG was used as a reference point instead of the first sensor [11]. However, since the delay between onset of R-wave on ECG and the first sensor on the arm is constant in a given patient

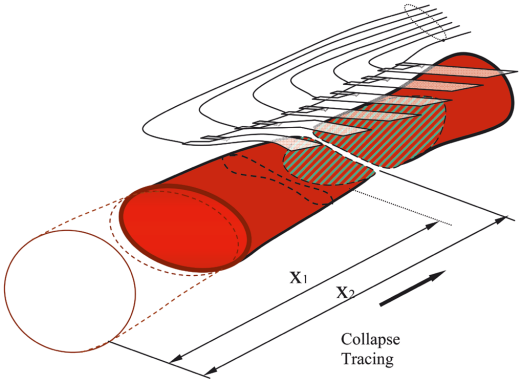

Figure 1. Detailed view of the new sensor system for measuring dP/dt^{ejc} and artery with the collapsed region under the cuff. X1 represents time from QRS to the first sensor serving as reference, X2 is the time from QRS to the second sensor.

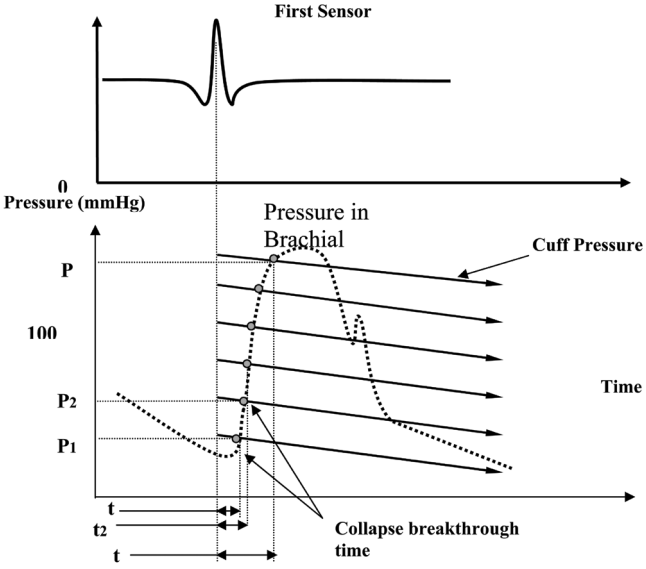

Figure 2. Measurements of the time delay between the first sensor on the array serving as a reference sensor and the onset of brachial artery flow in the subsequent sensors during controlled upper arm deflation. The plot of pressure vs. time delays yields the ascending portion of the arterial waveform.

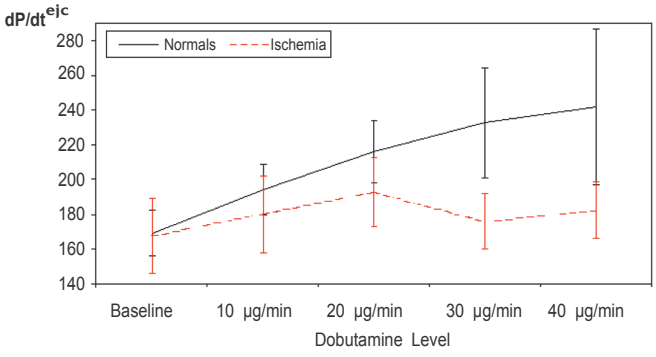

Figure 3. dP/dt^{ejc} changes during dobutamine infusion in normal patients and ischemic patients based on results of Tc99m Sestamibi-SPECT

(130 ± 17 msec), we can use the first sensor instead of ECG. The pressure wave thus generated is identical to the pressure wave generated utilizing the ECG reference system with constant delay. These waveforms were validated previously with simultaneously obtained invasive ascending aortic pressure, and a correlation coefficient of $r = 0.98$ was found [11].

Statistical analysis

Data were expressed as average ± standard deviation. Comparisons between groups were performed using the Student's one-tailed *t*-tests. Statistical significance was achieved at the 5% level ($P < 0.05$)

Results

Perfusion defects compatible with ischemia were detected on SPECT in 19 of 40 patients. The increase in dP/dt^{ejc} during infusion of dobutamine in this group was severely impaired as compared with the non-ischemic group [Figure 3]. The dP/dt^{ejc} outcome was combined with the ECG results, providing an ECG-enhanced value and compared to ECG alone.

Comparing normal and ischemic patients on Δ dP/dt^{ejc}

In order to decide on the criterion for determining normal/ischemia by dP/dt^{ejc} on negative ECG patients, we referred to the differences in dP/dt^{ejc}: T20-T10, T20-baseline and T10-baseline.

One-tailed *t*-tests were performed to test the one-sided hypothesis, which claims that there is a specific difference between the two groups, since we are interested only in one direction of difference on $\Delta dP/dt^{ejc}$ between normal and ischemic patients at increasing stages of dobutamine infusion. $\Delta dP/dt^{ejc}$ was found to be significantly greater in normal patients compared to ischemic patients. The most significant difference in $\Delta dP/dt^{ejc}$ between normal and ischemic patients was found at T20-baseline ($P = 0.0079$). The average increase was 48.7 (SD = 34.2) in normal patients and only 22.6 (SD = 24.7) in ischemic patients.

The combined ECG + dP/dt^{ejc} criterion

The combined criterion for determining ischemia was defined as positive ECG or $\Delta dP/dt^{ejc}$ of less than a certain value. A range of values of $\Delta dP/dt^{ejc}$ was examined for the combined criterion. Optimal results were achieved at the cutoff point $\Delta dP/dt^{ejc} = 28$, meaning ischemia is diagnosed when ECG is positive or when dP/dt^{ejc} increases (from baseline to T20) by less then 28 units. The results of this criterion were 79.0% sensitivity, 67% specificity, 68% positive predicted value, and 78% negative predicted value, much better than those of the criterion based on ECG alone (16% sensitivity, 91% specificity, 60% positive predicted value, 54% negative predicted value); as a result, however, there was a loss of specificity.

Discussion

When pharmacologic stress testing is performed with imaging, the electrocardiographic information can usually be overlooked and the image is used fundamentally to determine if a test is positive or negative. Some authors [12] compared the ECG and imaging information for the same patient using pharmacologic stress testing with dobutamine and concluded that imaging is more trustworthy, informative and precise for detecting ischemia than the ECG. Although dobutamine induces ECG changes and anginal pain in patients with coronary artery disease, at the present this test is not accepted unless accompanied by imaging.

While several alternative and often exellent techniques have been developed to allow stress testing and cardiac imaging without exercise in patients with ischemic heart disease – e.g., dypiridamole-thallium test [13], dobutamine sestamibi-SPECT [7], dobutamine echocardiography [4,5] – these tests are generally unavailable at the bedside in internal medicine departments to which most patients with chest pain are admitted. They are usually performed in cardiology units to stratify patients at risk for coronary artery disease.

The present study describes a new non-invasive technology for the measurement of one of the most sensitive indices of myocardial contractility, represented by the rate of increase of intraventricular pressure (left ventricular dP/dt and arterial dP/dt) [14-16].

The technology described here provides a simple alternative that can measure non-invasively the rate of pressure change in the aorta during ejection. The advantage of the combination of non-invasive tests that we have described is that it requires only a 12-lead ECG, which is widely available and inexpensive, and the new device, which is non-invasive and minimally operator-dependent. Potential limitations of this new technique could be found in patients with aortic stenosis, pulmonary vascular disease, in patients with very thick arms, or in the presence of occlusive disease of the arch arteries (where pressure and dp/dt in the brachial artery may differ markedly from the pressure in the arch). The gold standard used in this study is far from being a perfect technique for diagnosing ischemic heart disease. Experience with a much larger and varied group of patients and normal subjects is required before this technique can be recommended for daily clinical use.

Conclusions

We describe our initial experience with a newly developed device for non-invasive detection of ischemia. The device measures the arterial rate of pressure rise during ejection dP/dt^{ejc}. This hemodynamic parameter is substantially affected by ischemia induced during dobutamine infusion. Thus, if ECG alone is used for specificity, the combination with dP/dt^{ejc} improves the sensitivity of the test and could provide an attractive cost savings alternative in patients unable to exercise. Further studies with larger numbers of patients are needed to confirm our initial findings.

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Capsule

Inside B cell germinal central

B cells become effective factories for antibody production only after they have gone through a series of maturation steps that select clones of B cells carrying somatic mutations for high-affinity antibodies. This process takes place in the germinal center, where B cells are also thought to compete vigorously for available antigen. Using intravital microscopy, Allen and team observe that the behavior of germinal center B cells is more consistent with a competition for the attention of helper T cells than for scarce antigen. This finding could prove useful in considering how best to stimulate robust immune responses with vaccines.

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Eitan Israeli

Capsule

Apoptosis Bak and Bax

The proteins Bax and Bak are key mediators of cell death signals that function at the mitochondria to promote apoptosis. There is evidence for multiple modes of regulation of Bax and Bak in cells. Some studies have proposed that other members of the Bcl-2 family of proteins interact with and directly activate Bax and Bak – a scenario in which cell survival seems to be the default state of the cell. However, activity of Bax and Bak is also held in check by interaction with pro-survival proteins, and it may be that relief of this inhibition determines the cell's fate. Willis et al. present evidence that the default state of Bax and Bak would lead to cell death. Cells lacking the direct activators of Bax and Bak still undergo apoptosis in response to over-expression of upstream components of the cell death pathway.

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