Postural Changes and Isosorbide Dinitrate

A Polygraphic Study in Patients with Coronary Artery Disease

Massimo Romano, M.D., Giuseppe Ferro, M.D.,
Massimo Chiariello, M.D., Bruno Ricciardelli, M.D.,
and Mario Condorelli, M.D.

SUMMARY

Sitting or orthostatic positions and trinitrine-like drugs reduce venous return. We focused on the non-invasive assessment of postural-induced cardiovascular stress and isosorbide dinitrate (IDN) induced changes in 8 male patients with coronary artery disease (CAD), using polygraphic recordings by means of a Thermistor Pulse Transducer.

The pre-ejection period (PEP) is sensitive to reduced preload and to the positive inotropic state of the myocardium. In addition, the % diastole (RR interval—electromechanical systole / RR interval) has been recently demonstrated to be correlated to coronary perfusion in CAD patients.

We observed that IDN in clinostatism and the sitting position reduced preload (longer PEP) with increased heart rate (HR) and did not affect % diastole. In orthostatism, while controls showed an increased HR and prolonged PEP, the HR was higher after IDN, with a fall in PEP and a significant decrease in % diastole.

We ascribed this change to adrenergic stimulation by the hypotensive actions of IDN (lowered mean blood pressure) in orthostatism and with a fall in coronary perfusion. Caution should be taken in CAD patients when postural stress could occur during IDN treatment. Moreover, polygraphic studies can be useful to detect individual responses to nitrates and serial recordings could be employed to assess late responses to chronic management with IDN.

Additional Indexing Words:
Systolic time intervals Diastolic time intervals Nitrates Ischemic heart disease

POSTURAL changes from clinostatism to sitting or orthostatic positions induce a decrease in cardiac preload and a rise in heart rate and peripheral...
arteriolar resistance that restores cardiac output.1) Similarly, trinitrine-like drugs induce significant hemodynamic changes like smooth muscle relaxation (which decreases cardiac preload and afterload), and hypotension, which evokes a reflex adrenergic stimulation that, in turn, increases heart rate and peripheral arteriolar resistance.2)

Several previous studies have focused on the non-invasive assessment by systolic time intervals (STI) of the changes in left ventricular function induced by postural variations.3),4) In fact, the pre-ejection period (PEP) provides the most sensitive reflection of changes in preload and inotropic state of myocardium.5) Moreover, it has been recently demonstrated that myocardial perfusion is well correlated with diastolic time (DT) in patients with severe coronary artery disease (CAD).6) This study was planned to assess non-invasively postural-induced cardiovascular stress and hemodynamic changes induced by a widely used antianginal drug, isosorbide dinitrate (IDN), in patients with severe CAD (≥70% stenosis).

**Materials and Methods**

Eight male patients (mean 52±2 years) were enrolled in our study. Informed written consent was obtained. Two of them had previous myocardial infarction (MI) lasting more than 6 months (apical MI in 1 case and inferior MI in the other). All patients had angiographic evidence of at least one critical (≥70%) stenosis of a major coronary artery; 2 had a single vessel disease and 6 a two vessel disease. None of the patients presented congestive heart failure, atrioventricular or intraventricular conduction delay, atrial fibrillation, systemic hypertension or orthostatic hypotension, or any major disease besides CAD. No patient had serious evidence of pathological postural responses of heart rate and blood pressure. All patients had previously received (for a time ranging from 36 to 90 days, mean 42±4 days) chronic treatment with oral IDN (10 mg q.i.d.). This drug regimen had been progressively reduced for 2 days and then discontinued the day before the beginning of the study, when only glyceryl trinitrate was given, if necessary. None of the patients were on digitalis, diuretics and/or beta-blocker treatment.

The study was carried out in the morning, in the postabsorptive state, after an overnight fast. After a 20 min rest on a radiological bed, the head of which was angled at 35°, the patients were lowered down to supine position (angle 0°) and after 60” a polygraphic recording was performed as described in a previous study from our laboratory.7) The patients were then raised to the sitting position with the head of the bed angled at 70° and after 60” a second polygraphic study was performed. The patients were finally passively raised
to the orthostatic position and after 60″ a third recording was obtained. In each position the blood pressure was measured with a standard cuff manometer, according to the recommendations of the A.H.A. After a 30' recovery in the resting position the polygraphic tracings were repeated with same protocol, starting 10 min after sublingual administration of 5 mg of IDN.

Electrocardiogram (usually lead II), phonocardiogram and indirect carotid pulse tracings were recorded on a photographic multichannel polygraph (Electronics for Medicine DR 8), at a paper speed of 100 mm/sec. The phonocardiogram and indirect carotid pulse tracings were recorded by means of Rentsch's thermistor pulse transducer, the characteristics of which have been previously described.8)

From the above mentioned tracings, the following STI were calculated: electromechanical systole (EMS), left ventricular ejection time (LVET); pre-ejection time (PEP), calculated subtracting LVET from EMS.9) Diastolic time (DT) was obtained by subtracting the EMS from the RR interval and finally % diastole was calculated by dividing the DT for the RR interval.10) The triple product was calculated by the following formula: (heart rate (HR) × systolic blood pressure × LVET). Statistical comparison was performed by Student's t-test for paired observation in assessment of changes of body position, while the effect of drug was evaluated by Duncan's test of analysis of variance for paired samples. Data are expressed as mean±SEM.11)

**RESULTS**

*Control conditions:* The HR and mean blood pressure (MBP) significantly increased in orthostatism as compared to the supine position (p<0.001 and p<0.01, respectively), while the triple product (TP) decreased with changes from clinostatism to a sitting position. It showed a further significant decrease in orthostatism (Table I). The PEP gradually increased from clinostatism to orthostatism. The EMS decreased significantly in orthostatism (as the

<table>
<thead>
<tr>
<th>Table I. Values (mean±SEM) of Heart Rate (HR), Mean Blood Pressure (MBP) and Triple Product (TP) in the Three Different Postures</th>
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<tbody>
<tr>
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<tr>
<td>HR (b/min)</td>
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<tr>
<td>MBP (mmHg)</td>
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<td>TP (×10⁹)</td>
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</tbody>
</table>

C=clinostatism; S=sitting position; O=orthostatism. n=8.
Statistical analysis was performed by Student's t-test for paired observations.
* p<0.001 vs C, ** p<0.01 vs C, § p<0.01 vs S.
Table II. Values (mean±SEM) of Pre-ejection Period (PEP), Electromechanical Systole (EMS) and %Diastole (%D) in the Three Different Postures

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>S</th>
<th>O</th>
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<tbody>
<tr>
<td>PEP (msec)</td>
<td>96±5</td>
<td>103±4.4**</td>
<td>113±7.2*§</td>
</tr>
<tr>
<td>EMS (msec)</td>
<td>392±7.6</td>
<td>362±7.2</td>
<td>331±6.4*§§</td>
</tr>
<tr>
<td>%D</td>
<td>53±4.1</td>
<td>51±3.1**</td>
<td>48±1.2*§</td>
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</table>

C=clinostatism; S=sitting position; O=orthostatism. n=8.

Statistical analysis as in Table I.
* p<0.001 vs C,  ** p<0.01 vs C,  §§ p<0.001 vs S,  § p<0.01 vs S.

Table III. Values (mean±SEM) of Heart Rate (HR), Mean Blood Pressure (MBP) and Triple Product (TP) in the Three Different Postures

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<tr>
<th></th>
<th>C</th>
<th>S</th>
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<tbody>
<tr>
<td>HR (b/min)</td>
<td>87±3</td>
<td>95±4.2**</td>
<td>111±5.4*§</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>91±7.2</td>
<td>91±6</td>
<td>90±4.3**</td>
</tr>
<tr>
<td>TP (×10⁹)</td>
<td>2455±330.5</td>
<td>2536±317.5</td>
<td>234±262</td>
</tr>
</tbody>
</table>

C=clinostatism; S=sitting position; O=orthostatism after isosorbide dinitrate (IDN) (5 mg s.l.). n=8.

Statistical analysis as in Table I.
* p<0.001 vs C,  ** p<0.01 vs C,  § p<0.01 vs S.

Table IV. Values (mean±SEM) of Pre-ejection Period (PEP), Electromechanical Systole (EMS) and %Diastole (%D) in the Three Different Postures

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>S</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP (msec)</td>
<td>107±8.1</td>
<td>112±5**</td>
<td>95±10*§</td>
</tr>
<tr>
<td>EMS (msec)</td>
<td>349±6.4</td>
<td>327±6.1**</td>
<td>293±8.2*§</td>
</tr>
<tr>
<td>%D</td>
<td>49±2</td>
<td>48±1</td>
<td>45±1.1*§</td>
</tr>
</tbody>
</table>

C=clinostatism; S=sitting position; O=orthostatism after isosorbide dinitrate (IDN) (5 mg s.l.). n=8.

Statistical analysis as in Table I.
* p<0.001 vs C,  ** p<0.01 vs C,  § p<0.01 vs S.

sum of prolonged PEP and shorter LVET) (p<0.001 vs the other two positions). Finally, the % diastole (%D) shows a statistically significant decrease with changes from clinostatism to the sitting position and from the latter to orthostatism (Table II).

**Drug administration:** After IDN, the HR progressively increased with changes to clinostatism and to orthostatism, the MBFP decreased only in the orthostatic posture (p<0.01) and the TP was unaffected (Table III). The PEP was significantly greater in the sitting position than in clinostatism (p<0.01) but significantly decreased in orthostatism (p<0.001 vs clinostatism and p<0.01 vs sitting posture). The EMS decreased progressively from clino-
statism to orthostatism, while the %D showed a significant decrease only in orthostatism (p<0.001 vs clinostatism and p<0.01 vs sitting position) (Table IV).

**IDN vs control:** IDN administration induced a statistically significant increase in HR and a decrease in MBFP in all three postures, when compared to control values. The TP was unchanged (Fig. 1). The PEP values increased after IDN in clinostatism (p<0.01) and the sitting position (p<0.05) and decreased in orthostatism (p<0.01). The EMS and %D were significantly reduced by IDN in all three postures (Fig. 2).

**DISCUSSION**

Trinitrine-like drugs, such as isosorbide dinitrate (IDN) induce venodilation and blood pooling. This results in a reduction in preload with a reflex adrenergic response that induces a rise in heart rate and peripheral arteriolar resistances to restore failing cardiac output. On the other hand, STI are a well established, non-invasive technique for the study of left ventricular function. In particular, the PEP has been demonstrated to represent the most
sensitive index of changes in cardiac preload and myocardial inotropic status. Moreover, recent reports have focused on diastolic time interval, which is well correlated with myocardial perfusion in patients with severe coronary artery disease. In particular, it has been recently proposed that % diastole is a useful measure that is non-linearly correlated to HR and EMS changes. Therefore, we focused on changes in HR, mean blood pressure, PEP and % diastole to assess the hemodynamic response to IDN in three different postures.

Polygraphic recordings were simplified by means of TPT, which has been demonstrated to be particularly useful in the study of the STI changes during exercise or postural stress.

According to previous observations in normal subjects, we observed in our patients, in control conditions, a progressive increase of HR and BP passing from clinostatism to orthostatism. The reduction of the preload induced an increase in the PEP and a decrease in LVET. The EMS, as the sum of PEP plus LVET, decreased in orthostatism. IDN administration induced an enhancement of the physiological response to postural changes. The IDN-induced reduction in preload evoked, in orthostatism, a significant fall in BP
with a consequent increase of the adrenergic reflex response, as demonstrated by the higher HR and the diminished PEP value as compared to control condition.

PEP/LVET ratio has been found in previous studies to be inversely correlated to the ejection fraction in resting and supine positions. The PEP/LVET ratio usually rises when cardiac preload decreases and, vice versa, decreases when myocardial inotropic positive changes occur. In this study, we excluded the ratio because, during an adrenergic positive inotropic effect, as in orthostatic responses to IDN, both PEP and LVET decrease with different slopes.

It is reported that high HR or prolonged EMS decrease DT and % diastole. A reduction in cardiac preload induces an increase of HR and a decrease of EMS. As a consequence of these effects, with greater influence of HR, % diastole shows a marked reduction, mainly in the orthostatic position. IDN administration induced in our patients tachycardia and a decrease in EMS, with a resulting significant fall in % diastole.

Our results suggest that, in orthostatism, IDN induces a fall in BP and, as a consequence, an adrenergic stimulation occurs with tachycardia and a decrease in PEP. The TP, an indirect index of O₂ consumption, was not modified by IDN, while the % diastole decreased. This observation may reflect a slight decrease of myocardial perfusion. On the other hand, our group of patients represented a homogenous population with stable resting BP values and they had previously received oral IDN. This may have reduced the effect of IDN administration. It is, therefore, noteworthy that a marked fall of BP (after IDN) could be obviously dangerous in patients with CAD. Indeed, the combined administration of IDN and hydralazine was found to be dangerous in patients with congestive heart failure during postural stress. It is reported that these subjects change poorly in preload when postural variations occur. Thus, caution should be used in acute administration of nitrates to patients with severe CAD when sudden postural changes might occur, since there are largely different individual hemodynamic responses to vasodilator drugs. These individual drug responses should be tested in each patient before initiating treatment and polygraphic studies seem to represent a useful, non-invasive and reproducible technique to evaluate these hemodynamic responses.

REFERENCES

2. Hirshleifer I: A clinico-pharmacological comparison of the nitrites. Western Med 4: 263,