RADIOCARDIOGRAPHIC ASSESSMENT OF DOBUTAMINE AND ISOSORBIDE DINITRATE THERAPY IN PATIENTS WITH MITRAL STENOSIS AND PULMONARY CONGESTION

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Simultaneous hemodynamic and radioangiographic measurements were performed on 10 patients with mitral stenosis and pulmonary congestion for evaluating the acute effects of dobutamine (DB, 5 μg/kg/min), isosorbide dinitrate (ISD, 10 mg sublingually) or a combination of the two. DB alone produced a significant increase of the cardiac index (CI) from 2.9 ± 0.1 to 3.7 ± 0.2 L/min/m² (p < 0.01), but a modest increase in pulmonary artery diastolic pressure (PAPD) and in pulmonary blood volume by approximately 15%, respectively. ISD alone caused a decline in PAPD from 26 ± 2 to 18 ± 1 mmHg (p < 0.001), in right heart volume from 300 ± 36 to 215 ± 18 ml/m² (p < 0.05) and in left heart volume from 321 ± 28 to 248 ± 20 ml/m² (p < 0.05), but no change in the CI. Combined administration of the two agents resulted in favorable alterations in both hemodynamic variables: PAPD decreased from 26 ± 2 to 20 ± 1 mmHg (p < 0.01) and the CI increased from 2.9 ± 0.1 to 3.3 ± 0.1 L/min/m² (p < 0.05).

Thus, DB alone had a tendency to aggravate pulmonary venous congestion in our patients, while ISD is effective in reducing the congestive manifestations of heart failure due to its venodilating effects but less beneficial in increasing the CI. The combined therapy of DB and ISD appears to be extremely effective in restoring an adequate cardiac output and in relieving the symptoms of pulmonary vascular congestion in the presence of mitral stenosis.

PATIENTS with severe heart failure generally have a reduced cardiac output and an increased pulmonary and systemic venous pressures. Therapy should aim to increase cardiac output and to relieve the symptoms of pulmonary vascular congestion. Currently two kinds of pharmacological means to augment cardiac output have become available for the treatment of congestive heart failure: inotropic drugs and vasodilating agents. In treating congestive heart failure, therefore, a choice of drugs, inotropic drug, vasodilating drug or a combination of these, must be done for each patient. Among the newer drugs, dobutamine (DB), a beta adrenergic stimulant, has received attention because of its potent inotropic activity with minimal chronotropic and vascular effects1–7. Conversely, sublingually or orally administered isosorbide

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dinitrate (ISD) appears to have its predominant effect on venous capacitance vessels, producing a significant reduction of the left ventricular filling pressure\(^{8-10}\).

Radioangiograms (RCG), the precordial recording of radionuclide dilution curves using \(^{131}\)I-human serum albumin (RIHSA) are quite useful in evaluating patients with congestive heart failure, because both the cardiac output and the circulating blood volume can be easily determined by a simple technique. In 1967, Kuwashara et al\(^{11}\) have reported a new method for analyzing the RCG by an analog computer simulation technique, which enables the quantification of the right and the left heart volumes, the pulmonary blood volume and the blood volume of the other parts of the circulatory system (body blood volume) in addition to cardiac output. Using this radiocardiographic technique we evaluated the acute effects of dobutamine infusion, sublingual isosorbide dinitrate and a combination of these in patients with mitral stenosis and pulmonary congestion.

**MATERIALS AND METHODS**

Studies were performed on 10 hospitalized patients with symptomatic heart failure in class III or IV according to the classification defined by the New York Heart Association. Four were female and 6 male, ranging in age from 32 to 72 years (mean: 53 years). The underlying heart diseases were mitral stenosis with regurgitation in 8, 6 of which combined aortic valve lesions, and solitary mitral stenosis in 2. Two patients had recurrent heart failure after open heart surgery. Eight patients were in atrial fibrillation and the others were in normal sinus rhythm. Digitalis and diuretics were discontinued for 24 hours before the study and informed consent was obtained from each patient prior to the study.

**Hemodynamic Studies**

All patients were studied in the supine position and a Swan-Ganz catheter was advanced to the pulmonary artery from the right antecubital vein. Pressure was recorded using a Statham P23Db transducer with a baseline at the mid-thoracic level. Arterial blood pressure was obtained by standard cuff technique, and the mean arterial pressure (MAP) was calculated as follows:

\[
\text{MAP} = \left(\text{systolic blood pressure} + 2 \times \text{diastolic pressure}\right)/3
\]

**Radiocardiographic Studies**

Details of this method and its validity and reproducibility have been reported previously\(^{12-14}\). Three scintillation counters were placed over the subclavian vein, the heart and the left sternal border of the second intercostal space (2LIS). Approximately 50\(\mu\)Ci of \(^{131}\)I-labelled human serum albumin (RISA) was injected as a bolus into the antecubital vein followed by 10 ml of saline flush, and 3 time-activity curves (the input curve, RCG and 2LIS-RCG) were recorded on a strip chart for one min. Seven min after the tracer injection, the equilibrium state was again recorded at the same geometry and the blood was sampled to calculate circulating blood volume. Heart rate and systemic blood pressure were also obtained at this time. The RCG thus obtained was placed on the half-mirror apparatus attached to high-speed analogue computer. The simulated RCG, displayed on the CTR, was fitted to the original RCG tracing by adjusting the potentiometers of the computer. When the best fitted curve was obtained, mean transit time of the right heart (MTTr), lung (MTTp), left heart (MTTI) and body (MTTb) was measured from the values of the potentiometer. Cardiac output (F) was calculated from the 2LIS-RCG in order to exclude background activity from tissues other than the heart. The mean blood volume (ml) of the right heart, lung, left heart and the body were calculated by the following equations:

- right heart volume (RHV) = MTTr × F
- pulmonary blood volume (PBV) = MTTp × F
- left heart volume (LHV) = MTTI × F
- Body blood volume (BBV) = MTTb × F

**Protocol**

After a control RCG was performed, DB was administered intravenously for 10 min with a rate of 5 \(\mu\)g/kg/min, after which the second RCG was obtained. After a 30-min convalescence period, 10 mg of ISD was administered sublingually and the third RCG was obtained 15 min later. Immediately after completing the third RCG, DB infusion was restarted at the same rate as in the second study and the 4th RCG was completed. Pulmonary artery pressure and electrocardiogram were monitored during these studies. The radiocardiographic study of combined DB and ISD was not completed in 2 of the patients for technical reasons. All values were analyzed by a paired t-test and expressed as mean ± SEM.

TABLE I  HEMODYNAMIC RESULTS OF DOBUTAMINE, ISOSORBIDE DINITRATE AND THE COMBINATION OF THESE

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dobutamine</th>
<th>Isosorbide dinitrate</th>
<th>Isosorbide dinitrate + Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>66±4</td>
<td>84±7*</td>
<td>75±6</td>
<td>87±8*</td>
</tr>
<tr>
<td>Systemic artery pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic (mmHg)</td>
<td>126±5</td>
<td>141±6*</td>
<td>106±5*</td>
<td>126±3</td>
</tr>
<tr>
<td>diastolic (mmHg)</td>
<td>68±4</td>
<td>67±4*</td>
<td>63±4</td>
<td>70±3</td>
</tr>
<tr>
<td>mean (mmHg)</td>
<td>88±4</td>
<td>92±4*</td>
<td>77±4</td>
<td>89±3</td>
</tr>
<tr>
<td>Pulmonary artery pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic (mmHg)</td>
<td>46±3</td>
<td>52±3*</td>
<td>31±3*</td>
<td>36±3*</td>
</tr>
<tr>
<td>diastolic (mmHg)</td>
<td>26±2</td>
<td>30±1*</td>
<td>18±1*</td>
<td>20±1*</td>
</tr>
<tr>
<td>mean (mmHg)</td>
<td>33±3</td>
<td>39±2*</td>
<td>23±2*</td>
<td>28±2</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.9±0.1</td>
<td>3.7±0.2*</td>
<td>2.8±0.2</td>
<td>3.3±0.1*</td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>46±5</td>
<td>46±4</td>
<td>40±4</td>
<td>40±4</td>
</tr>
<tr>
<td>Total pulmonary resistance (dynes·sec·cm⁻⁵)</td>
<td>615±49</td>
<td>584±56</td>
<td>455±48*</td>
<td>450±41*</td>
</tr>
<tr>
<td>Total systemic resistance (dynes·sec·cm⁻⁵)</td>
<td>1639±130</td>
<td>1369±133</td>
<td>1514±163</td>
<td>1452±113</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. *p < 0.05

RESULTS

Hemodynamic Changes

The hemodynamic effects of dobutamine infusion, sublingual isosorbide dinitrate and combination of these are presented in Table I.

Dobutamine or Isosorbide Dinitrate: Mean systemic artery pressure (MAP) was 88 ± 4 mmHg during the control, increased slightly to 92 ± 4 mmHg (+5%) during DB infusion and fell moderately to 77 ± 4 (−12%) with ISD. Pulmonary artery systolic pressure, pulmonary artery mean pressure and pulmonary artery diastolic pressure (PADP), which averaged 46 ± 3, 33 ± 3 and 26 ± 2 mmHg, respectively, during the control, increased to 52 ± 3 (+15%), 39 ± 2 (+20%) and 30 ± 1 mmHg (+16%) during infusion of DB and fell significantly to 31 ± 3 (−31%, p < 0.005), 23 ± 2 (−29%, p < 0.005) and 18 ± 1 mmHg (−30%, p < 0.001) with ISD, respectively.

The cardiac index (CI), averaging 2.9 ± 0.1 L/min/m² during the control, increased significantly to 3.7 ± 0.2 (+28%, p < 0.01) during DB infusion, but remained essentially unchanged with ISD, averaging 2.8 ± 0.2 (−2%). Heart rate (HR), averaging 66 ± 4 beats/min during the control, increased significantly during DB to an average of 84 ± 7 (+27%, p < 0.05), and increased slightly to 75 ± 6 (+13%) with ISD. The stroke index (SI) averaging 46 ± 5 ml/beat remained unchanged (±4%) with DB and fell to 40 ± 4 (−12%) with ISD. Total systemic resistance (TSR) dropped from 1639 ± 130 to 1369 ± 133 dynes·sec·cm⁻⁵ (−16%) with DB, and to 1514 ± 163 (−8%) with ISD. Total pulmonary resistance (TPR) averaging 615 ± 49 dynes·sec·cm⁻⁵ during the control fell to 584 ± 56 (−7%) during DB and fell further to 455 ± 48 (−26%, p < 0.05) with ISD.

Combination of Dobutamine and Isosorbide Dinitrate: With combined administration of DB and ISD, MAP was unchanged from the control level. PADP fell by 19% (p < 0.01) and the rise of PADP with DB alone was suppressed (+16%). The CI increased significantly from the control level (+20%, p < 0.05) although it was lower than DB alone, but contrasting to the slight decrease of the CI with ISD alone. HR rose significantly by 34% (p < 0.05) from the control level. The SI slightly decreased by 8%. TSR and TPR decreased by 14 and 25% (p < 0.025), respectively.

Radiocardiographic Changes in Blood Distribution

Table II shows radiocardiographic changes in the 10 patients. Total circulating blood volume
TABLE II  RADIocardioGRAPHIC RESULTS DURING DOBUTamine, ISOSORBIDE dINITRATE AND THE COMBINATION OF THESE

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dobutamine</th>
<th>Isosorbide dinitrate</th>
<th>Isosorbide dinitrate + Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood volume (L/m²)</td>
<td>3.35±0.18</td>
<td>3.39±0.19</td>
<td>3.42±0.23</td>
<td>3.30±0.13</td>
</tr>
<tr>
<td>Body blood volume (ml/m²)</td>
<td>2293±100</td>
<td>2323±111</td>
<td>2513±166</td>
<td>2409±121</td>
</tr>
<tr>
<td>Pulmonary blood volume (ml/m²)</td>
<td>440± 56</td>
<td>503± 68</td>
<td>442± 53</td>
<td>390± 31</td>
</tr>
<tr>
<td>Right heart volume (ml/m²)</td>
<td>300± 36</td>
<td>216± 17*</td>
<td>215± 18*</td>
<td>208± 20*</td>
</tr>
<tr>
<td>Left heart volume (ml/m²)</td>
<td>321± 28</td>
<td>341± 28</td>
<td>248± 20*</td>
<td>291± 28</td>
</tr>
<tr>
<td>Central blood volume (ml/m²)</td>
<td>1061± 97</td>
<td>1060± 96</td>
<td>904± 76</td>
<td>889± 58</td>
</tr>
<tr>
<td>Body blood volume/central blood volume</td>
<td>2.3±0.2</td>
<td>2.3±0.1</td>
<td>2.9±0.2*</td>
<td>2.8±0.2</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. *p < 0.05

(TBV), averaging 3.35 ± 0.18 L/m² during the control, remained essentially unchanged by the administration of DB, ISD or combination of the two. Body blood volume (BBV) increased from 2293 ± 100 to 2513 ± 166 ml/m² (+9%) with ISD, and to 2409 ± 121 (+8%) with DB and ISD combined, the increase of which is considered to be insignificant. Pulmonary blood volume (PBV), averaging 440 ± 56 ml/m² during the control, increased by 14% with DB but remained unchanged with ISD alone or combination of DB and ISD. With DB, ISD, or DB and ISD combined, right heart volume (RHV) decreased by 25% (p < 0.05), 24% (p < 0.05) and 26% (p < 0.05), respectively. Left heart volume (LHV) decreased significantly by 22% (p < 0.05) with ISD but remained practically unchanged with DB or DB and ISD combined. The ratio of BBV to central blood volume (CBV = RHV + PBV + LHV), averaging 2.3 ± 0.2 during the control, increased significantly to 2.9 ± 0.2 with ISD alone or DB and ISD combined, but remained unchanged with DB alone.

Correlations between the CI and PADP are illustrated in Fig. 1. ISD resulted in a significant reduction of PADP with little or no changes in the CI. DB, on the other hand, produced a substantial increase of the CI but PADP was also increased. Combined therapy with DB and ISD produced a decrease in PADP as well as an increase of the CI, resulting in a significant improvement of cardiac function.

Adverse Effects

No serious adverse effects resulted from the study. In 4 patients, chest discomfort of undetermined cause occurred during DB infusion. Although arrhythmias were uncommon, some patients appeared to have an increased frequency of ventricular premature beats during administration of DB. ISD administration demonstrated a subjective improvement of dyspnea in 8 of 10 patients but produced no marked hypotension in any of them.
DISCUSSION

The most rational and effective therapy for patients with valvular heart disease is the radical operation of the valvular lesions. There are, however, some patients for whom surgical therapy would involve a prohibitively high risk and should be deferred, while other patients develop acute deterioration in cardiac function as a result of sudden valvular insufficiency. In such patients, pharmacological support of cardiac function may be required temporarily to tide the patients over during a crisis or to buy time for diagnostic studies and/or surgical preparations.

Although previous studies have shown that dobutamine was a potent and relatively selective inotropic agent with only minor chronotropic effect\(^3\)–\(^7\) and that isosorbide dinitrate was useful to improve pulmonary congestion\(^8\)–\(^10\) few data are available concerning the effect of these drugs in patients with mitral stenosis. This study extends these findings to a group of patients with mitral stenosis and pulmonary congestion.

Arterial systolic pressure increased during DB infusion. Although some investigators\(^2\)–\(^4\) have observed significant increases in MAP with DB, mean and diastolic arterial pressure changed very little in our study. Since the CI increased more than MAP, DB infusion resulted in a 16% reduction of TPR. By our radiocardiographic evaluations, the proportion of BBV to CBV remained unchanged. This result suggests that the fall observed in TPR should not be taken as evidence that DB exerted significant direct vasodilating effects, but it would result from a reduction in compensatory vasoconstriction secondary to improved circulation at dosage of 5 μg/kg/min. The cardiovascular effects of DB which have been found in this study are not necessarily beneficial in the following two aspects: First, the increase of cardiac output would appear to be relatively more dependent on heart rate than stroke volume. Second, DB increased PADP in 8 of the 10 cases (16% of the control value on the average; p < 0.1), although some investigators have reported that PADP decreased significantly\(^5\)–\(^6\) or remained unaltered\(^4\)–\(^7\) at dosages of 4–8 μg/kg/min. In our study, DB decreased RVH significantly and increased PBV by 14%, but LHV remained unchanged. This was probably caused by a shift of the blood to the pulmonary vascular system and to the left atrium from the right side of the heart by an enhancement of the right ventricular emptying due to DB, which would result from a mechanical obstruction to left ventricular filling due to a narrowed mitral orifice. In some of the patients there was a tendency to aggravate pulmonary congestion. These findings emphasize the cautious use of DB in the setting of combined valvular disease with mitral stenosis and/or aortic stenosis.

The observed hemodynamic response to sublingual administration of ISD in our patients was consistent with the previous data in patients with CHF\(^8\)–\(^10\). The heart rate rose, mean systemic and pulmonary arterial pressure dropped and the PADP fell significantly with a 30% reduction in TPR resulting in the relief of the symptoms of pulmonary congestion. The CI decreased slightly but not significantly, and TSR did not change significantly. Thus, sublingual ISD, which principally cause venodilation, reduces ventricular preload and pulmonary congestion, but it lacks consistent effects on systemic impedance.

It has recently been demonstrated that the reduction of mitral regurgitation by vasodilating agents such as nitroprusside was not entirely caused by a decrease in systemic impedance\(^18\)–\(^20\) but by a decrease in the size of the left heart cavity\(^21\)–\(^22\). Therefore, the decrease of the left ventricular chamber size, if achieved, should decrease the severity of mitral regurgitation. Gomes et al.\(^23\) have reported that both the end-diastolic and end-systolic dimensions of the left ventricle measured by echocardiography diminished significantly in response to sublingual ISD. In this study, sublingual ISD decreased RHV and LHV significantly, although RHV or LHV obtained in the present study includes volumes of both the atrium and the ventricle combined, and shifted the circulating blood from the central to the peripheral capacitance vessels due to venodilation and a decreased venous return. This reduction of LHV by ISD should result in at least a partial reduction of mitral regurgitation. Thus, the present study would extend previous observations of the extracardiac vasodilating effects of ISD to the objective clinical demonstration of an increase in the ratio of BBV to CBV (BBV/CBV). The significant reduction of PADP and TPR was induced, but PBV was not altered. These results suggest that the reduction of PADP was due to the pulmonary venous dilatation\(^24\) in addition to the reduction of venous return by ISD.

From the present investigation it was shown that the concomitant administration of DB with
ISD affords extreme benefit from the principal salutary actions of each agent and, thereby, provides a hemodynamic improvement unattainable by either agent alone (Fig. 1). The principal advantage afforded by ISD added to DB as compared to DB administration alone is deemed to be its suppression of the elevation of PADP.

In conclusion, ISD was considered, in general, not to be indicated in valvular heart disease, especially in mitral stenosis. However, our study demonstrates that sublingual ISD is efficacious in reducing the congestive symptoms with no change of the CI, and that the combined therapy of DB and ISD will be beneficial in patients with decreased CI and elevated PADP.

REFERENCES

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