CARDIOVASCULAR EFFECTS OF DIBUTYRYL CYCLIC AMP IN PATIENTS WITH CONGESTIVE HEART FAILURE

—Comparison with Dobutamine and Captopril—

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To assess the effect of dibutyryl cyclic AMP (DBcAMP) on patients with congestive heart failure (CHF) in comparison with dobutamine and captopril, these three agents were administered to 9 patients with CHF. DBcAMP was infused at a rate of 0.2 mg/kg/min for 30 min, dobutamine was infused at a rate of 8 μg/kg/min and captopril 25 mg was administered orally. Hemodynamic and echocardiographic studies were performed before and after administration of each agent. Systolic arterial pressure (SAP) fell with DBcAMP and captopril but rose with dobutamine. Cardiac output (CO) rose and systemic vascular resistance (SVR) fell with each agent but the magnitude of the change was greater with DBcAMP than with the other two agents. Left ventricular end-systolic dimension decreased and percent fractional shortening increased with all these drugs. Comparing DBcAMP and captopril, although the degree of change in CO was closely correlated with that in SVR by captopril, the degree of increase in CO by DBcAMP was more than that expected from the degree of the decrease of SVR. Comparing DBcAMP and dobutamine, SAP and pressure rate product increased with dobutamine, but the former fell and the latter was not changed by DBcAMP. Arrhythmia was not increased by DBcAMP, though it was markedly increased by dobutamine.

In conclusion, the magnitude of positive inotropic and vasodilator effect of DBcAMP was equal to or greater than that of dobutamine or captopril. So DBcAMP is thought to be useful for the treatment of CHF.

DIBUTYRYL cyclic AMP (DBcAMP), a derivative of cyclic AMP, has been shown to penetrate the cell membrane more easily than cyclic AMP, while having the same effect.1-3 It has a positive inotropic and vasodilator effect4 and has been thought to be beneficial in patients with congestive heart failure. This study was designed to compare the effect of DBcAMP with dobutamine5 and captopril6 and to evaluate its efficacy in patients with congestive heart failure.

METHODS

Subjects: Eight men and one woman with chronic congestive heart failure and average age of 60 ± 9 years (range 47 to 76) were studied. All patients had left ventricular dilation and impaired contractility. The etiology of congestive heart failure was dilated cardiomyopathy in 7 patients, old myocardial infarction in one and aortic regurgitation in one. Four of 9

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Japanese Circulation Journal Vol. 52, June 1988 503
patients had class II, 3 had class III and 2 had class IV congestive heart failure as defined by the New York Heart Association. The left ventricular end-diastolic dimension measured by echocardiography was more than 54 mm (mean ± SD, 69 ± 9 mm, range 54 to 80) and percent fractional shortening (FS) was less than 30% (mean ± SD, 19 ± 5% range 10 to 29). All patients had been treated with digitalis and diuretics, six patients had received antiarrhythmic agents and three patients had also received a vasodilator. The digitalis, diuretics and antiarrhythmic agents were continued on a daily basis throughout the study period, but vasodilators were withheld for at least three days before this study.

**Hemodynamic study:** In 9 patients a Swan-Ganz balloon-tipped catheter was inserted via the antecubital or femoral vein and advanced into the right or left pulmonary artery. Pulmonary artery systolic (PASP) and diastolic (PADP) pressure and right atrial pressure (RAP) were recorded. Cardiac output (CO) was measured by thermodilution techniques with the use of ice-cold normal saline solution. Systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) were obtained with a standard mercury sphygmomanometer. The mean arterial pressure (MAP) was estimated from the following formula:

\[
\text{MAP} = \frac{\text{DAP} + (\text{SAP} - \text{DAP})}{3}
\]

Systemic vascular resistance (SVR) and pressure rate product (PRP) were calculated as follows:

\[
\text{SVR} = \frac{80(\text{MAP} - \text{RAP})}{\text{CO}(\text{dyne}\cdot\text{s}\cdot\text{cm}^{-5})}
\]

\[
\text{PRP} = \text{SAP} \times \text{heart rate}
\]

**Echocardiographic study:** In all 9 patients echocardiographic study was performed at the same time as the hemodynamic study. The M-mode echocardiogram (Toshiba SSH 40A) was recorded by line scan recorder with 50 mm/sec paper speed, and left ventricular end-diastolic (Dd) and end-systolic (Ds) dimensions were measured. Percent fractional shortening (FS) and mean Vcf (mVcf) were calculated using the following formula:

\[
\%\text{FS} = \frac{(\text{Dd} - \text{Ds})}{\text{Dd} \times 100}
\]

\[
\text{mVcf} = \frac{(\text{Dd} - \text{Ds})}{(\text{Dd} \times \text{ejection time})}
\]

**Drug administrations**

Dobutamine administration: After the measurement of baseline hemodynamic and echocardiographic parameters at bed rest, dobutamine was administered by intravenous infusion at incremental rates until a dose of 8 µg/kg-min was reached. After this stable infusion rate had been maintained for 5 min, hemodynamic and echocardiographic measurements were repeated and then the infusion of dobutamine was discontinued. In previous studies the response to dobutamine was demonstrated to be dose-dependent but adverse effects such as tachycardia, hypertension and increasing of ventricular arrhythmia occurred frequently at large doses. In this study the infusion rate of 8 µg/kg-min of dobutamine was selected because Maskin indicated the optimal rate of dobutamine infusion averaged 7.8 µg/kg-min, and Leier et al also suggested the optimal rate was 7.3–7.7 µg/kg-min.

**DBcAMP administration:** Six hours or more after the dobutamine was discontinued and the hemodynamic values returned to baseline levels, the hemodynamic and echocardiographic values were re-measured. The 9 patients then received intravenous infusion of DBcAMP at a rate of 0.2 mg/kg-min for 30 min. The hemodynamic and echocardiographic measurements were repeated 10, 20 and 30 min after the start of the infusion, and 10 min after terminating the infusion. Yamada and Ahrén reported that DBcAMP exerts its hemodynamic effects in a dose-dependent fashion. But in large doses lactic acidosis may occur or vulnerability to ventricular fibrillation is thought to be increased. In the clinical setting, DBcAMP is usually administered in a dose of 0.025–0.2 mg/kg-min. In our study a dose of 0.2 mg/kg-min was chosen and no serious adverse effects occurred with this dose.

Captopril administration: After a 24-hour period and return of hemodynamic values to baseline levels, 7 patients received a single dose of 25 mg of captopril orally. Hemodynamic and echocardiographic measurements were performed before and 30, 60 and 120 min after the administration. The hemodynamic effect of captopril is thought to be dose-independent; the effects occurred at the dose of 25 mg and no further effect was achieved by increasing the dose. In many reports, captopril was administered at a dose of 25 mg in patients with congestive heart failure, so we administered at this dose in this study.

**Statistical analysis:** The hemodynamic and
TABLE 1  HEMODYNAMIC AND ECHOCARDIOGRAPHIC DATA BEFORE AND AFTER DBcAMP, DOBUTAMINE AND CAPTOPRIL ADMINISTRATION

<table>
<thead>
<tr>
<th></th>
<th>DBcAMP n = 9</th>
<th>Dobutamine n = 9</th>
<th>Captopril n = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Max</td>
<td>Base</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>116 ± 18</td>
<td>109 ± 16*</td>
<td>119 ± 19</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>67 ± 13</td>
<td>58 ± 10*</td>
<td>71 ± 13</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>84 ± 14</td>
<td>75 ± 11*</td>
<td>87 ± 13</td>
</tr>
<tr>
<td>HR (beat/min)</td>
<td>70 ± 12</td>
<td>81 ± 10***</td>
<td>68 ± 8</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.29 ± 2.15</td>
<td>6.61 ± 2.45***</td>
<td>4.19 ± 1.74</td>
</tr>
<tr>
<td>PAMP (mmHg)</td>
<td>23 ± 11</td>
<td>23 ± 11</td>
<td>22 ± 11</td>
</tr>
<tr>
<td>PADP (mmHg)</td>
<td>16 ± 8</td>
<td>15 ± 8</td>
<td>17 ± 10</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>5 ± 3</td>
<td>7 ± 4</td>
<td>5 ± 3</td>
</tr>
<tr>
<td>SVR (dyn-sec-cm⁻¹)</td>
<td>1701 ± 550</td>
<td>961 ± 311***</td>
<td>1812 ± 724</td>
</tr>
<tr>
<td>PRP</td>
<td>8028 ± 1369</td>
<td>8559 ± 1613</td>
<td>8075 ± 1477</td>
</tr>
<tr>
<td>Dd (mm)</td>
<td>69 ± 9</td>
<td>69 ± 9</td>
<td>69 ± 10</td>
</tr>
<tr>
<td>Ds (mm)</td>
<td>56 ± 8</td>
<td>50 ± 9***</td>
<td>56 ± 9</td>
</tr>
<tr>
<td>%FS (%)</td>
<td>19 ± 5</td>
<td>28 ± 7***</td>
<td>19 ± 5</td>
</tr>
<tr>
<td>mVcf</td>
<td>0.80 ± 0.25</td>
<td>1.17 ± 0.41***</td>
<td>0.84 ± 0.25</td>
</tr>
</tbody>
</table>

Values are means ± SD. *:p < 0.05; **:p < 0.01; ***:p < 0.001
SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; PAMP = mean pulmonary artery pressure; PADP = diastolic pulmonary artery pressure; RAP = right atrial pressure; SVR = systemic vascular resistance; PRP = pressure rate product; Dd = end-diastolic dimension; Ds = end-systolic dimension; %FS = percent fractional shortening.
Fig.1. Effects of DBCAMP, dobutamine (DOB) and captopril (CAP) on the relation between cardiac output (CO) and systolic arterial pressure (SAP).

Fig.2. Effect of DBCAMP, dobutamine (DOB) and captopril (CAP) on the relation between cardiac output (CO) and systemic vascular resistance (SVR).

Echocardiographic data were analyzed at the control and at the point of maximum increase of CO for each drug. Analysis was performed by the t-test for paired and unpaired data. Data points with P values < 0.05 were considered to be significant.

RESULTS

Effect on hemodynamics (Table I): Compared with the baseline value, systolic arterial pressure fell with administration of DBCAMP (116 ± 18 to 109 ± 16 mmHg, p < 0.05) and captopril (113 ± 12 to 102 ± 19 mmHg, p < 0.05), but rose during infusion of dobutamine (119 ± 19 to 127 ± 22 mmHg, p < 0.01) (Fig.1). Diastolic arterial pressure decreased with each agent and mean arterial pressure was unchanged during infusion of dobutamine, but it significantly fell with DBCAMP and tended to fall with captopril. Heart rate rose after DBCAMP and dobutamine (70 ± 12 to 81 ± 10/min, p < 0.001, and 68 ± 8 to 82 ± 16 min, p < 0.05, respectively), but did not significantly change (70 ± 12 to 68 ± 13/min) after captopril. The pressure rate product did not significantly change after DBCAMP, but it rose significantly (8075 ± 1477 to 10395 ± 2433, p < 0.001) during dobutamine and fell significantly (7835 ± 1217 to 6859 ± 1442, p < 0.01) after captopril. Compared with the baseline value, cardiac output increased significantly with all agents tested. The degree of increase with DBCAMP (4.29 ± 2.15 to 6.61 ± 2.45 l/min, p < 0.001), was significantly (p < 0.05) greater than that with captopril (3.70 ± 0.98 to 4.13 ± 0.79 l/min, p < 0.05) (Fig. 1). All of these agents produced a significant decrease in systemic vascular resistance (Fig. 2). The mean

Japanese Circulation Journal Vol. 52, June 1988
Effects of DBcAMP on Congestive Heart Failure

![Graph](image)

Fig. 5. Relation between the change in systolic arterial pressure ($\Delta$SAP) and the change in cardiac output ($\Delta$CO) after DBcAMP (open circles) and dobutamine (closed circles) administration.

![Graph](image)

Fig. 6. Effect of dobutamine on the relation between cardiac output (CO) and pulmonary arterial diastolic pressure (PADP).

![Graph](image)

Fig. 7. Effect of DBcAMP on the relation between cardiac output (CO) and pulmonary arterial diastolic pressure (PADP).

![Graph](image)

Fig. 8. Relation between the change in systemic vascular resistance ($\Delta$SVR) and the change in cardiac output ($\Delta$CO) after DBcAMP (open circles) and captopril (triangles) administration. + patient who died during follow-up period.

Pulmonary artery pressure and right atrial pressure were both unchanged with each agent. Although the pulmonary arterial diastolic pressure tended to fall with each agent, the change was not statistically significant.

Echocardiographic data (Table I): Left ventricular end-diastolic dimension was unchanged by each agent. Left ventricular end-systolic dimension decreased significantly with each agent (DBcAMP $56 \pm 8$ to $50 \pm 9$ mm, $p < 0.001$, dobutamine $56 \pm 9$ to $50 \pm 10$ mm, $p < 0.01$, captopril $58 \pm 9$ to $57 \pm 9$ mm, $p < 0.001$), and then the % fractional shortening significantly increased with each agent (DBcAMP $19 \pm 5$ to $28 \pm 7\%$, $p < 0.001$, dobutamine $19 \pm 5$ to $26 \pm 8\%$, $p < 0.001$, captopril $19 \pm 7$ to $20 \pm 7\%$, $p < 0.001$). The mean Vcf also increased significantly with all these agents (DBcAMP $0.80 \pm 0.25$ to $1.17 \pm 0.41$, $p < 0.001$, dobutamine $0.84 \pm 0.25$ to $1.18 \pm 0.43$, $p < 0.01$, captopril $0.83 \pm 0.32$ to $0.88 \pm 0.32$, $p < 0.05$).

Comparison of effects between DBcAMP and dobutamine: Although administration of DBcAMP tended to result in a slightly higher cardiac output and % fractional shortening and in a lower systemic vascular resistance than those achieved with dobutamine ($6.61 \pm 2.45$ versus $5.85 \pm 2.37 l/min$, $28 \pm 7$ versus $26 \pm 8\%$ and $961 \pm 311$ versus $1311 \pm 602$ dynes-s-cm$^{-5}$, respectively), these differences were not statistically significant. Cardiac output, % fractional shortening and men Vcf increased in all subjects with both drugs (Fig. 3, 4). And systolic arterial pressure increased in 8 of 9 patients during dobutamine, whereas it decreased in 7 of 9 subjects after DBcAMP (Fig. 5). Peak systolic wall stress also increased in 7 of 9 patients during dobutamine but was decreased in 8 of 9 patients.
by DBcAMP. The pressure rate product rose significantly during dobutamine, but did not change significantly after DBcAMP. Although pulmonary arterial diastolic pressure (PADP) did not significantly change with either drug, the degree of decrease in PADP was more in patients with a baseline PADP of more than 15 mmHg than in patients with a baseline of less than 15 mmHg (Fig. 6, 7).

Comparison of effects of DBcAMP and captopril: Cardiac output rose and systemic vascular resistance fell with each drug. The absolute change in CO correlated closely with the change of SVR in response to captopril (r = −0.81, p < 0.05) but not in response to DBcAMP, and CO/SVR is greater with DBcAMP than with captopril (Fig. 8). %FS and mVcf were also increased significantly by both drugs but the degree of increase was larger with DBcAMP than with captopril.

Adverse effects: In one patient nausea occurred during infusion of DBcAMP. One other patient complained of thirst after DBcAMP. No other complaint was reported by any of them, and arrhythmia did not increase with DBcAMP. On the other hand, ventricular ectopic beats increased markedly in some patients during dobutamine. No adverse effects appeared after captopril administration.

DISCUSSION

Though cyclic AMP, discovered by Sutherland et al. in 1958, acts as an intracellular mediator of various metabolic effects of drugs and hormones, exogenous cyclic AMP does not produce this action because it penetrates the cell membrane with difficulty except in the liver. On the other hand, DBcAMP, synthesized by Posternak et al. in 1962, penetrates the cell membrane more easily than cyclic AMP and acts similarly to intracellular cyclic AMP1−3. In addition, DBcAMP acts also as an inhibitor of phosphodiesterase and increases the concentration of intracellular cyclic AMP. Its cardiac effect was first reported by Robison et al. in 1965. Since then, many reports have been published about the cardiovascular effect of DBcAMP1−4,11,14,25−27; it is believed to have a positive inotropic effect independent of the function of the receptor and to have vasodilator action according to the relaxation of vascular smooth muscle. In our study, the degrees of increase in cardiac output and decrease in peripheral vascular resistance caused by DBcAMP were equal to or more than those caused by dobutamine and captopril. As the order of the drug administration was fixed in this study, it might have influenced the results. But the elimination half-life of dobutamine is only a few minutes28 while the duration of the effect of DBcAMP is reported to be about 120 min.29 We gave the latter agent at intervals enough to make the effects of the former agent disappear. Moreover, in this study, latter agent (DBcAMP) was administered and its effects studied after all the hemodynamic measurements returned to baseline level in all cases.

The absolute change in SVR was closely correlated with that in CO caused by captopril, because the increase in CO by vasodilator drugs is thought to result from reduction in afterload. While there is no significant correlation between the change in CO and the change in SVR after DBcAMP, the increase in CO caused by DBcAMP was larger than that expected from the degree of the decrease in SVR. Therefore, the increase in CO caused by DBcAMP is thought to be the result not only of a decrease in SVR but also of its positive inotropic effect.

Follow-up period. In these two patients the increase in CO with DBcAMP was smaller than that expected from both its positive inotropic and vasodilator actions. In fact, the response was similar to that of captopril. So it appeared that in these cases, DBcAMP was mostly vasodilative in effect, and had little inotropic effect. So it was thought that in these 2 cases there was no positive inotropic effect of DBcAMP despite the increase in the tissue cyclic AMP. Satoh et al.5 reported that in the patient with extracorporeal circulation DBcAMP does not increase contractility but produces only the vasodilative effect. Amrinone and milrinone, the inhibitors of phosphodiesterase, were thought to increase the concentration of intracellular cyclic AMP30,31. Wilmshurst et al.30 reported that amrinone produced no positive inotropic effect in a patient with severe heart failure in 1984. These findings may indicate that the inotropic effect of these drugs depends on the severity of the damage in the cardiac muscle.

Compared with DBcAMP and dobutamine, although CO, %FS and mVcf were markedly increased by both drugs, SAP rose with dobutamine and fell significantly with DBcAMP. These results indicate that DBcAMP had not only a positive inotropic effect like dobutamine but also a strongly reduced afterload. And this drug did
not change the pressure rate product, which increased during dobutamine administration. Though ventricular arrhythmia was increased significantly by dobutamine, DBcAMP does not increase it. It might be a result of the decrease in the plasma free fatty acid concentration caused by DBcAMP. Recently, it is known that in chronic heart failure a high concentration of plasma norepinephrine decreases in the down regulation of β adrenergic receptor and reduces the response to exogenous catecholamine. DBcAMP was thought to be useful even in those patients whose response to the catecholamine was reduced. Thus, it is thought that DBcAMP is useful for treatment in patients with congestive heart failure.

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