Acute and Chronic Effects of Xamoterol in Idiopathic Dilated Cardiomyopathy

Ken-ichi WATANABE, M.D.,* Yoichi HIROKAWA, M.D.,** Kaoru SUZUKI, M.D.,** and Akira SHIBATA, M.D.**

SUMMARY

Xamoterol, a \( \beta \)-1-partial agonist, was given to 10 patients with idiopathic dilated cardiomyopathy in NYHA functional classes II and III. The acute and chronic effects of xamoterol were assessed by changes in effort tolerance measured by multistage bicycle ergometry, echocardiography, radionuclide ventriculography and right heart catheterization. The acute effect was determined after a single intravenous injection of 0.2 mg/kg of xamoterol. Exercise heart rate decreased from 117±10 (mean±1SD) to 97±19 beats/min (p<0.01), but blood pressure and cardiac index were unaffected. When the drug was given orally at 200 mg/day for 3 months, exercise duration increased from 4.2±2.3 to 6.4±2.4 min (p<0.01), echocardiographic ventricular ejection fraction from 29±12 to 33±14% (NS) and radionuclide left ventricular ejection fraction from 37±11 to 45±14% (p<0.01), while pulmonary wedge pressure during exercise decreased from 40±10 to 31±10 mmHg (p<0.01). It may be concluded that xamoterol, by its action as a partial agonist, demonstrated both \( \beta \)-agonist and antagonist effects in patients with idiopathic dilated cardiomyopathy. It thereby had beneficial effects on left ventricular function with resultant improvements in effort tolerance and subjective symptoms during long term treatment.

Additional Indexing Words: Xamoterol Dilated cardiomyopathy Heart failure \( \beta \)-1-partial agonist Norepinephrine

IDIOPATHIC dilated cardiomyopathy is characterised by ventricular dilatation. Reduced left ventricular contractility results in dyspnea due to pulmonary congestion and fatigue due to reduced cardiac output, while the reduction in right ventricular contractility results in signs of peripheral venous congestion (e.g. hepatomegaly, and dependent edema). The prognosis is variable but is generally poor. \(^{31-33}\) Present therapy is unsatisfactory as it is
palliative and not curative.\textsuperscript{4,5} Drugs, such as diuretics, vasodilators and angiotensin converting enzyme inhibitors, only relieve the deranged hemodynamic consequences of the failing myocardium. It has been postulated that increased levels of catecholamines found in patients with dilated cardiomyopathy may damage the myocardium and cause a progressive decrease in cardiac contractility.\textsuperscript{6} Studies of failing human hearts demonstrated a decrease in $\beta$-receptor density, i.e., down-regulation,\textsuperscript{7} possibly as a result of increased circulating catecholamine levels. Another study reported that increased plasma norepinephrine levels were related to increased mortality.\textsuperscript{8} Therapy with $\beta$-antagonists has been attempted and, in some uncontrolled studies, both objective and subjective improvements have been reported in a proportion of patients.\textsuperscript{9,10}

Xamoterol (ICI 118,587, Corwin) is a $\beta_1$-partial agonist whose maximum activity is 43\% of the maximum activity of a full agonist such as isoprenaline.\textsuperscript{11} As a partial agonist, xamoterol demonstrates both agonist and antagonist properties which depend on the prevailing sympathetic tone. When the sympathetic tone is low, for example at rest or during light exercise, xamoterol acts as an agonist and exerts a positive inotropic action.\textsuperscript{12,13} During heavy exercise when the sympathetic tone is high, xamoterol competes with the raised levels of norepinephrine for the $\beta$-adrenoceptor and hence acts as an antagonist.\textsuperscript{14} In animal studies, xamoterol, unlike isoprenaline, did not produce $\beta$-adrenoceptor down-regulation and uncoupling from cyclase.\textsuperscript{15}

An acute study of xamoterol showed that intravenous doses had a positive inotropic action in patients with dilated cardiomyopathy and moderate cardiac failure.\textsuperscript{16} It was therefore decided to evaluate the acute and chronic effects of xamoterol in patients with dilated cardiomyopathy based on changes in hemodynamics (right heart catheterization, echocardiography, radionuclide angiography), effort tolerance (supine bicycle ergometer), arrhythmias (24 hour Holter monitoring), functional capacity (NYHA classification) and catecholamines (plasma norepinephrine) using an open design study.

Patients and Methods

\textit{Patients:}

Ten patients (8 males and 2 females), aged 31 to 65 years with a mean age of 51 years, were admitted to the study (Table I). All patients had symptoms of dyspnea and fatigue on effort, despite treatment with digitalis, diuretics and/or vasodilators. Five patients were in NYHA class II and 5 in class III. Of the 10 patients, 5 were in sinus rhythm and 5 in atrial fibrillation. Dilated cardiomyopathy was diagnosed by left ventriculography, coro-
nary catheterization, echocardiography, and myocardial biopsy according to the criteria of WHO/ISFC. Patients entered the study only when their condition had been stable for more than 1 month. Digitalis, diuretics, antiarrhythmics, anticoagulants and vasodilators were also used and doses were kept constant throughout the study. Patients who had received β-agonists or antagonists were excluded from the study.

Study design:
Baseline data

Pretreatment baseline data were obtained as follows: The NYHA functional class was determined by one physician who interviewed all the patients to evaluate in detail the functional capacity and symptoms during daily activities. Plasma norepinephrine levels were measured in blood samples drawn early in the morning with the patients at rest. Plasma concentrations of norepinephrine were determined by high performance liquid chromatography with fluorescence detection (RF-530, Shimadzu) and electrochemical detection (VMD-101 A, Yanaco).

The cardiothoracic ratio was calculated from the X-ray. Ventricular premature contractions and ventricular tachycardia were evaluated from 24 hour Holter electrocardiogram recordings. The effort tolerance of all patients was determined by multistage bicycle ergometer exercise testing in the supine position the day before the hemodynamic measurements. The initial load was 25 watts, followed by an increase of 25 watts every 3 min. The

Table I. Patient Characteristics

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr) &amp; Sex</th>
<th>NYHA class</th>
<th>EF (%)</th>
<th>ECG</th>
<th>NE (ng/ml)</th>
<th>Medical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 M</td>
<td>II</td>
<td>49</td>
<td>SR</td>
<td>0.31</td>
<td>Digoxin, furosemide, warfarin</td>
</tr>
<tr>
<td>2</td>
<td>55 M</td>
<td>III</td>
<td>23</td>
<td>Af/VT</td>
<td>1.26</td>
<td>Digoxin, furosemide, prazosin, procaineamide, warfarin</td>
</tr>
<tr>
<td>3</td>
<td>60 F</td>
<td>III</td>
<td>19</td>
<td>Af/VT</td>
<td>0.93</td>
<td>Digoxin, furosemide, prazosin, captopril, isosorbide dinitrate, procaineamide, mexiletine</td>
</tr>
<tr>
<td>4</td>
<td>62 M</td>
<td>III</td>
<td>34</td>
<td>Af</td>
<td>0.74</td>
<td>Digoxin, furosemide, warfarin</td>
</tr>
<tr>
<td>5</td>
<td>65 M</td>
<td>II</td>
<td>45</td>
<td>SR</td>
<td>0.12</td>
<td>Digoxin, furosemide</td>
</tr>
<tr>
<td>6</td>
<td>51 M</td>
<td>II</td>
<td>48</td>
<td>SR/VT</td>
<td>0.44</td>
<td>Digoxin, furosemide, procaineamide</td>
</tr>
<tr>
<td>7</td>
<td>43 M</td>
<td>III</td>
<td>38</td>
<td>Af</td>
<td>0.58</td>
<td>Digoxin, furosemide, warfarin</td>
</tr>
<tr>
<td>8</td>
<td>63 M</td>
<td>II</td>
<td>31</td>
<td>SR</td>
<td>0.25</td>
<td>Digoxin, furosemide, warfarin</td>
</tr>
<tr>
<td>9</td>
<td>53 F</td>
<td>II</td>
<td>47</td>
<td>SR</td>
<td>0.21</td>
<td>Digoxin, furosemide, captopril</td>
</tr>
<tr>
<td>10</td>
<td>51 M</td>
<td>III</td>
<td>37</td>
<td>Af/VT</td>
<td>0.44</td>
<td>Digoxin, furosemide, captopril, prazosin, procaineamide, mexiletine</td>
</tr>
</tbody>
</table>

NYHA=New York Heart Association; EF=radionuclide left ventricular ejection fraction; ECG=electrocardiogram; NE=plasma norepinephrine; SR=sinus rhythm; Af=atrial fibrillation; VT=nonsustained ventricular tachycardia.
exercise test was stopped when dyspnea or fatigue occurred or if chest pain, hypotension, or dangerous arrhythmias appeared. Echocardiograms were recorded using a phased array electronic sector scanner (at a frequency of 2.4 MHz, Model SSH-11 A, Toshiba Co). Left ventricular ejection fraction was calculated from left ventricular end-systolic and end-diastolic dimensions using Teichholz's formula.\(^{19}\)

Radionuclide left ventricular ejection fraction was measured simultaneously with intracardiac pressures and cardiac output by right heart catheterization. Erythrocytes were labelled with 30 mCi of technetium-99 m \textit{in vivo}, then photographed with a gamma camera (PHO/Gamma LFOV, Searle Inc). The records were processed in a digital computer (Scintipac 1200, Shimadzu). The radionuclide ejection fraction was determined by equilibrium radionuclide angiography.

Hemodynamic changes in pulmonary artery pressures, pulmonary wedge pressure and cardiac output were measured by means of a 7F Swan-Ganz catheter introduced percutaneously from the femoral vein into the pulmonary artery. Measurement of cardiac output was made in triplicate by the thermodilution method. These variables were used to calculate cardiac index, stroke volume index and mean pulmonary wedge pressure. The heart rate was calculated from the electrocardiogram. Systemic blood pressures were measured by sphygmomanometer and cuff. Hemodynamic measurements during exercise were made at the same exercise load which had been recorded the day before the study.

Acute effects of xamoterol

The patients rested for 30 min after an initial exercise test and then predose measurements at rest were made. A single intravenous dose of xamoterol (0.2 mg/kg) was given over a 10 min period. Hemodynamic measurements at rest were made 15 min later and repeated during a second exercise test.

Chronic effects of xamoterol

Xamoterol (100 mg twice daily) was administered orally to all 10 patients. After 3 months therapy, NYHA functional class, plasma norepinephrine concentrations, cardiothoracic ratio, 24 hour electrocardiogram records, echocardiograms, exercise tolerance and radionuclide ejection fraction were evaluated. Hemodynamic variables were measured by Swan-Ganz catheterization at rest and during exercise. Hemodynamic variables during exercise were measured at the same work load that had stopped exercise before treatment. To measure effort tolerance, exercise was allowed to continue until the patient stopped because of symptoms.
Statistical methods:

All data are expressed as the mean ± standard deviation and differences in means were assessed by the Student’s t-test. Values of p < 0.05 were considered to be significant.

RESULTS

All 10 patients completed both the acute and chronic studies. In the chronic study, all received xamoterol for 3 months. No adverse effects were observed.

Hemodynamic responses and exercise testing

The pattern of hemodynamic changes varied in the acute and chronic studies (Table II). The mean baseline cardiac index at rest was 2.4 ± 0.5 L/min/m² and increased to 4.7 ± 1.2 L/min/m² during exercise. After intravenous xamoterol the resting cardiac index was unaffected, but the exercise value was reduced to 4.4 ± 1.4 L/min/m² (p < 0.05). After 3 months of xamoterol therapy, cardiac index at rest and during exercise was unchanged (2.4 ± 0.4 and 4.5 ± 1.0 L/min/m²). The stroke index was unaffected at rest or during exercise by xamoterol, either acutely or after chronic treatment. Mean pulmonary artery and pulmonary wedge pressures at rest were not affected

Table II. Acute and Chronic Effects of Xamoterol on Hemodynamic Parameters (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Acute effect</th>
<th>Chronic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>64 ± 15</td>
<td>117 ± 10</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>132 ± 23</td>
<td>157 ± 28</td>
<td>131 ± 25</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72 ± 10</td>
<td>86 ± 13</td>
<td>76 ± 9</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.4 ± 0.5</td>
<td>4.7 ± 1.2</td>
<td>2.6 ± 0.5</td>
</tr>
<tr>
<td>SI (ml/min/m²)</td>
<td>39 ± 9</td>
<td>42 ± 9</td>
<td>36 ± 5</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>23 ± 4</td>
<td>50 ± 14</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>PWP (mmHg)</td>
<td>17 ± 4</td>
<td>40 ± 10</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>LVDd (cm)</td>
<td>6.1 ± 0.6</td>
<td></td>
<td>5.9 ± 0.7</td>
</tr>
<tr>
<td>LVDs (cm)</td>
<td>5.3 ± 0.7</td>
<td></td>
<td>4.7 ± 0.9*</td>
</tr>
<tr>
<td>Echo-EF (%)</td>
<td>29 ± 12</td>
<td></td>
<td>33 ± 14</td>
</tr>
<tr>
<td>RN-EF (%)</td>
<td>37 ± 11</td>
<td></td>
<td>45 ± 14**</td>
</tr>
</tbody>
</table>

HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; CI=cardiac index; SI=stroke index; mPAP=mean pulmonary artery pressure; PWP=pulmonary wedge pressure; LVDd=left ventricular end-diastolic dimension; LVDs=left ventricular end-systolic dimension; Echo-EF=echocardiographic left ventricular ejection fraction; RN-EF=radionuclide left ventricular ejection fraction.

* p < 0.05, ** p < 0.01 compared with basal value.
by the acute or chronic administration of xamoterol. The mean resting
values at baseline, after acute and after chronic dosing were 23±4, 24±4
and 22±5 mmHg for mean pulmonary artery pressure and 17±4, 17±4 and
16±3 mmHg for pulmonary wedge pressure, respectively.

Differences between the acute and chronic effects of xamoterol, however,
became apparent in the values for pulmonary wedge pressure during exercise.
The values for pulmonary wedge pressure were 40±10, 38±12 (NS) and
31±10 mmHg (p<0.01) for baseline, acute and chronic treatments, respec-
tively (Fig. 1).

Echocardiographic measurements showed significant changes in some
variables when the results at baseline and after 3 months of xamoterol therapy
were compared. The left ventricular end-diastolic dimension decreased from
a baseline value of 6.1±0.6 to 5.9±0.7 cm (NS) after 3 months, while the
end-systolic dimension decreased from 5.3±0.7 to 4.7±0.9 cm (p<0.05). The
ejection fraction calculated from these variables increased from 29±12 to 33±
14% after 3 months on xamoterol (NS). There was a corresponding increase
in radionuclide ejection fraction from 37±11 to 45±14% (p<0.01) (Fig. 2).
The cardiothoracic ratio was similar at baseline and after 3 months on xamo-

Fig. 1 (left). Changes in individual exercise pulmonary wedge pressure
during a single intravenous and 3 months oral administration of xamoterol.
Numbers are case numbers. Mean±1SD is indicated.

Fig. 2 (right). Individual resting radionuclide left ventricular ejection
fraction values before and after 3 months administration of xamoterol. Num-
bers are case numbers. Mean±1SD is indicated.
terol (56±6 and 54±5%, respectively).

Resting blood pressures (systolic/diastolic) at baseline, and after acute and chronic xamoterol were similar (132±23/72±10, 131±25/76±9 and 132±18/77±16 mmHg, respectively). Similar findings applied to exercise blood pressures where the respective values were 157±28/86±13, 156±32/87±16 and 158±21/88±15 mmHg.

Resting heart rates at baseline, and after acute and chronic xamoterol therapy were similar (64±15, 65±11 and 64±14 beats/min, respectively). Exercise heart rate was, however, significantly decreased during acute and chronic xamoterol treatment. The baseline value was 117±10 beats/min and decreased to 97±19 and 99±16 beats/min (p<0.01) after the intravenous dose and oral treatment, respectively (Fig. 3).

Mean exercise duration increased from a mean baseline value of 4.2±2.3 min to 6.4±2.4 min (p<0.01) after 3 months on xamoterol (Fig. 4). An increase in exercise duration was observed in all patients.

Functional capacity
The functional capacity of 5 patients improved (Fig. 5). Before treatment 5 patients were in NYHA class II and 5 in class III. After 3 months
Fig. 4. Individual exercise duration values before and after 3 months administration of xamoterol. Numbers are case numbers. Mean±1SD is indicated.

Fig. 5. New York Heart Association (NYHA) functional class before and after 3 months administration of xamoterol.

on xamoterol, 2 patients were in class I, 6 patients in class II and only 2 remained in class III. No patient became worse on xamoterol.

24 hour Holter electrocardiography

The 24 hour electrocardiogram monitoring revealed that at baseline all patients in the study had ventricular premature contractions and 4 patients
had nonsustained ventricular tachycardia. After xamoterol treatment, the ventricular premature contractions persisted in all the patients and the mean daily number was unaffected. Of the 4 patients with nonsustained ventricular tachycardia, the arrhythmia persisted in 2 while the remaining 2 patients showed only couplet ventricular premature contractions after xamoterol.

Plasma norepinephrine concentrations

The plasma norepinephrine concentration at baseline was 0.53±0.36 ng/ml. Three patients had concentrations above 0.6 ng/ml, viz 0.74, 0.93 and 1.26 ng/ml. After 3 months of xamoterol therapy, the plasma norepinephrine concentration was 0.48±0.23 ng/ml (NS). The patients with elevated pretreatment concentrations showed reductions to 0.41, 0.65 and 0.72 ng/ml, respectively.

DISCUSSION

The major therapeutic aims in the treatment of patients with dilated cardiomyopathy are the reversal of the heart failure and reduction in mortality. Approximately half the patients with dilated cardiomyopathy die suddenly and it is presumed that an arrhythmia is the cause. For this reason, many antiarrhythmic drugs have been used in this disease, although none has been shown to prolong life expectancy. Surgical operations and the use of automatic implantable defibrillators have also been attempted. In the present study, 24 hour electrocardiographic monitoring demonstrated ventricular premature contractions in all 10 patients and ventricular tachycardia in 4 before treatment with xamoterol. Ventricular tachycardia disappeared in 2 of the 4 patients after treatment with xamoterol for 3 months. Digitalis, diuretics and vasodilators are the mainstay of treatment of cardiac failure associated with dilated cardiomyopathy. The use of cardiotonics such as amrinone and milrinone has recently been proposed. These drugs produce acute improvement but there is no definite evidence of long term response or improved prognosis. They may even make the prognosis worse, because the limited energy supply is used up, and arrhythmias may become even more severe.

Interestingly, β-blockers are effective in some patients with dilated cardiomyopathy. The likely mechanisms of this response are improved diastolic performance of the heart, protection of the myocardium from excessively high concentrations to catecholamines and restoration of β-adrenoceptor sensitivity for catecholamines. In general, however, β-blockers are likely to aggravate heart failure due to their negative inotropic action and are used in the treatment of dilated cardiomyopathy in only a few centers.
β-adrenergic full agonists are effective in improving heart failure only in the short term and the effect disappears because of a decrease in the density of myocardial β-adrenoceptors, i.e., down-regulation when dosage is continued over a long period. In this context, attention has recently been directed to β-adrenergic partial agonists as they should retain the beneficial effects of the β-antagonists (reduction of excessive tachycardia, protection of the myocardium from the deleterious effects of catecholamines, and prevention of β-adrenoceptor down-regulation) and yet provide positive inotropic support to the heart due to the moderate agonist activity.

It is now generally accepted that the efficacy of any drug for the treatment of cardiac failure needs to be evaluated over long term use because of the problem of tachyphylaxis. Thus pirbuterol, a full β-agonist, was found to produce beneficial effects acutely but these had disappeared after 4 weeks. Methods of assessment must include effort tolerance and symptomatology, which limit the patient’s activity, as hemodynamic measurements are not necessarily predictive of clinical efficacy. Nevertheless, measurement of hemodynamic changes at rest and, especially, during exercise are important in understanding the mechanism of action of a drug used in the treatment of cardiac failure. This is especially relevant to drugs which act on the β-adrenoceptor as hemodynamic changes during exercise are largely mediated through changes in sympathetic activity.

In this study, no hemodynamic changes at rest were observed in the 3 patients with elevated plasma norepinephrine levels, and the only effect seen during exercise was a reduction in heart rate, i.e., a negative chronotropic effect. We did not observe an acute positive inotropic effect at rest even in the 7 patients with plasma norepinephrine levels <0.6 ng/ml, as blood pressure, cardiac index and pulmonary wedge pressure were unaffected. It is not possible to explain this discrepancy between our results and those previously reported, although our results are in agreement with those reported in another study.

An important finding was that after 3 months of xamoterol therapy, the pulmonary wedge pressure during exercise was significantly lowered compared with baseline, while the cardiac index was unaffected. Since the same cardiac output was achieved at a lower filling pressure, this finding implies that xamoterol was exerting a positive inotropic action at maximum exercise although it was exerting a negative chronotropic action. The fact that the antagonist effect of xamoterol in the failing heart during exercise appears to be confined to a negative chronotropic action and does not include a negative inotropic action cannot be explained. This pattern of responses is different to that observed with β-blockers in normal healthy men where heart rate,
blood pressure and cardiac index were decreased and left ventricular end-
diastolic pressure increased during exercise, i.e., both negative chronotrope and negative inotropic actions are produced by \( \beta \)-blockers. It is uncertain whether this difference between xamoterol and the \( \beta \)-blockers reflects the fact that \( \beta \)-blockers lack intrinsic sympathomimetic activity or that the \( \beta \)-blocker study was performed in normal, not failing, hearts. Myocarditis had been excluded by biopsy and the patients were entered into the study only when their condition had been stable for more than 1 month. Four of them (patients 1, 5, 6 and 9) had a virtually normal baseline ejection fraction, and a completely normal ejection fraction after therapy. There was a significant improvement in mean effort tolerance and all patients increased their exercise capacity. There was also a significant reduction in mean pulmonary wedge pressure during exercise. These beneficial effects were accompanied by symptomatic improvement in the 10 patients who have all continued on xamoterol therapy long term. The observation that xamoterol prevented ventricular tachycardia is noteworthy in view of the high mortality risk in dilated cardiomyopathy. As xamoterol is not known to have any direct antiarrhythmic action, it is presumed that this effect was due to the \( \beta \)-antagonist action preventing the known arrhythmogenic effects of catecholamines. The decrease in plasma norepinephrine in those patients in whom it was elevated may reflect an improvement in the cardiac status and may also provide indirect evidence of a restoration of sensitivity in the down-regulated \( \beta \)-adrenergic pathway. Overall, these observations permit the conclusion that xamoterol improves cardiac performance, prevents the cardiotoxic effects of high levels of norepinephrine, may restore \( \beta \)-adrenoceptor sensitivity and suppresses exercise-induced tachycardia in dilated cardiomyopathy patients with moderate heart failure.

This study has a number of limitations. The study was open in design and this introduced the known observer and patient biases. Nevertheless, it should be noted that all patients showed improvement in one or more of the variables and objective evidence of improvement was obtained in terms of hemodynamics and/or plasma norepinephrine. The number of patients entered into the study was relatively small. The study did not include measurements of the number and affinity of \( \beta \)-adrenoceptors. Patients in severe heart failure (NYHA class IV) were not included in the study. In spite of these limitations, we felt that the positive findings were sufficiently important to be reported.

In summary, xamoterol improved the symptoms, effort tolerance and hemodynamics of patients with dilated cardiomyopathy in moderate heart failure. Some patients who had high plasma norepinephrine concentrations
or who failed to respond to a single intravenous dose showed improved left ventricular function following dosing over a prolonged period. No adverse effects of xamoterol were observed in the study. It is now essential to confirm these findings in a double-blind, randomized placebo-controlled study using a larger number of patients.

ACKNOWLEDGMENT

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REFERENCES


