Hemodynamic Effects of Bosentan, an Endothelin Receptor Antagonist, in Patients With Pulmonary Hypertension

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Background—Few treatments are available for isolated pulmonary hypertension (PHT), which has a high morbidity and mortality. This trial was designed to assess the hemodynamic effects of bosentan, an endothelin receptor antagonist, in patients with PHT, in which local overproduction of endothelin-1 (ET-1) is thought to play a pathogenic role.

Methods and Results—An open-label, dose-ranging study was performed in 7 female patients with primary PHT (n=5) or isolated PHT associated with limited scleroderma (n=2). Infusions of 50, 150, and 300 mg were administered at 2-hour intervals, and the hemodynamic responses were measured. Bosentan caused a dose-dependent fall in total pulmonary resistance (−20.0±11.0%, P=0.01) and mean pulmonary artery pressure (−10.6±11.0%, P>0.05). However, there was also a fall in the systemic vascular resistance (−26.2±12.8%, P<0.005) and mean arterial pressure (−19.8±14.4%, P<0.001). There was a slight increase in cardiac index (15±12%, P>0.05) and a dose-dependent rise in ET-1 but no significant change in other hemodynamic variables, gas exchange, or other vasoactive mediators.

Conclusions—Intravenous bosentan is a potent but nonselective pulmonary vasodilator at the doses tested, even in patients resistant to inhaled nitric oxide. Transient increases in plasma ET-1 were observed, consistent with a blockade of endothelial ET\textsubscript{A} receptors. Systemic hypotension and other significant events during the study indicate that its intravenous use in patients with severe PHT may be limited. Implications for future trial design and studies of chronic oral treatment are discussed. (Circulation. 2000;102:411-418.)

Key Words: hypertension, pulmonary ■ scleroderma ■ endothelin ■ trials

Primary pulmonary hypertension (PHT) is a rare but debilitating disease with a median survival of 2.8 years.\textsuperscript{1,2} A proportion (≈10%) of patients with long-standing limited cutaneous systemic sclerosis (lcSSc, scleroderma) may also develop PHT without interstitial lung disease (isolated PHT) with a similar outcome.\textsuperscript{3} Few drug treatments other than anticoagulants\textsuperscript{4,5} and prostacyclin\textsuperscript{6,7} are thought to influence the prognosis. The latter is inconvenient and associated with significant morbidity when administered by continuous infusion,\textsuperscript{7} but its analogue iloprost has shown promise when administered by inhalation.\textsuperscript{9} The use of high-dose calcium antagonists is controversial, but the small proportion of patients who respond immediately (<25%) may have a better prognosis.\textsuperscript{5,10} The major limitation of vasodilators is their nonselectivity for the pulmonary vasculature and dose-limiting systemic hypotension, particularly when they are administered intravenously. Pending the development of new therapeutic approaches, transplantation\textsuperscript{11} may be offered to suitable recipients, who are then at risk of rejection and the complications of long-term immunosuppression.\textsuperscript{12}

The pathogenesis of isolated PHT, with or without lcSSc, is poorly understood. Plexogenic lesions are typical of primary PHT, and vascular remodeling in the resistance vessels with progressive luminal obliteration is characteristic of both.\textsuperscript{3,13,14} Despite the development of fixed obstruction, there is often a significant reversible component, as demonstrated by a selective vasodilator response to inhaled nitric oxide (NO).\textsuperscript{15–17} Endothelin-1 (ET-1) is a constrictor of human pulmonary arteries through its action on smooth muscle ET\textsubscript{A} receptors,\textsuperscript{18} but it can also induce vasodilatation through endothelial ET\textsubscript{B} receptors. In addition to its potent vasomotor actions, it has been implicated in vascular remodeling in a number of animal models of restenosis. Endothelin is overexpressed in rats developing hypoxic PHT, and an ET receptor antagonist, bosentan, could prevent or reverse the associated histological changes.\textsuperscript{19,20} A central role for ET-1 in...
the pathogenesis of primary PHT has also been proposed, because plasma levels are increased and there is evidence of local production in the lung.21,22

Bosentan is a nonpeptide, orally active antagonist of both ET<sub>A</sub> and ET<sub>B</sub> receptors whose pharmacological properties have been well characterized in animals<sup>23,24</sup> and healthy volunteers.25 A study of its use in patients with chronic heart failure suggested that it may demonstrate some selectivity for the pulmonary vasculature.26 Baseline ET-1 and big ET-1 concentrations were elevated and correlated with atrial filling pressures and pulmonary artery pressure.27 Bosentan significantly reduced mean pulmonary artery pressure (MPAP), pulmonary vascular resistance (PVR), and mean arterial pressure (MAP). This exploratory trial was designed to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of bosentan in patients with PHT. Because of concerns about the administration of potent vasoactive drugs to patients with PHT, who are often hemodynamically unstable, an open-label, dose-ranging study of intravenous bosentan was performed initially (part 1). The intention then was to randomize patients who tolerated the drug to a double-blind, placebo-controlled trial of oral bosentan (1000 mg BID) over 8 weeks with hemodynamic and functional end points (part 2). However, serious adverse events resulted in early termination of part 2. The part 1 data are presented here, and the adverse events and the implications for future trials are discussed.

**Methods**

The protocol was approved by the St Vincent’s Hospital Research Ethics Committee and conducted in accordance with the Declaration of Helsinki (1975) as revised in 1983. Written, informed consent was obtained from all participants before screening procedures were initiated within 2 weeks of the study. The patients had isolated PHT with or without lcSSc<sup>28</sup> and were 18 to 70 years old. Isolated PHT was initiated within 2 weeks of the study. The patients had isolated PHT (NYHA grade II to IV) with severely impaired pulmonary vascular resistance (PVR), and mean arterial pressure (MAP). This exploratory trial was designed to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of bosentan in patients with PHT. Because of concerns about the administration of potent vasoactive drugs to patients with PHT, who are often hemodynamically unstable, an open-label, dose-ranging study of intravenous bosentan was performed initially (part 1). The intention then was to randomize patients who tolerated the drug to a double-blind, placebo-controlled trial of oral bosentan (1000 mg BID) over 8 weeks with hemodynamic and functional end points (part 2). However, serious adverse events resulted in early termination of part 2. The part 1 data are presented here, and the adverse events and the implications for future trials are discussed.

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After a further equilibration period of ≥30 minutes, over which baseline hemodynamic measurements were shown to be stable, intravenous bosentan administration was commenced with invasive monitoring as previously described.17 Hemodynamic measurements were taken before, on completion, and at 15, 30, 45, and 60 minutes after the commencement of each infusion. Blood was also taken periodically for blood gas analysis, pharmacokinetic studies, and measurements of atrial natriuretic peptide (ANP), norepinephrine, and ET-1<sup>10</sup> (Medilab).

Cardiac output (CO) was estimated by the thermodilution method using the mean of triplicate measurements. The cardiac index (CI=CO/BSA) was derived using the body surface area (BSA: [height in meters]<sup>2</sup>×weight in kilograms)<sup>0.425</sup>×71.84×10<sup>-3</sup>. Heart rate, MAP, and mean RAP (MRAP) were monitored continuously. PVR was calculated from the transpulmonary gradient (TPG=MPAP−PAOP) and CO (PVR=TPG/CO). Because complete PAOP data were not available, the total pulmonary resistance was calculated for all subjects (TPR=MPAP/CO). Systemic vascular resistance (SVR) was also derived (SVR=(MBP−RAP)/CO), and changes from baseline were expressed as a percentage of the initial value.

Bosentan doses of 50, 150, and 300 mg (concentrations <0.2%) were infused through a peripheral line in ascending order at 2-hour intervals over 5, 10, and 15 minutes, respectively. The dose range was based on a previous placebo-controlled study in patients with chronic heart failure in which the hemodynamic variables were relatively stable in the placebo group over time, and there was little hemodynamic or pharmacodynamic difference between those treated with 100 or 200 mg.26 Furthermore, because some relative selectivity for the pulmonary circulation had been demonstrated in this study, we thought this effect might be emphasized at lower doses, particularly if local ET-1 production was contributing to PHT.

Bosentan plasma levels were measured as previously reported.25 Data are expressed and illustrated as the mean±SEM unless stated otherwise. Statistical comparisons with raw baseline data were performed with repeated-measures ANOVA. The pharmacokinetic data were estimated with model-independent methods. The concentration-effect relationship was analyzed by applying a 2-compartment pharmacokinetic model (with elimination from the central compartment) to the plasma concentration data and linking the pharmacodynamic data (TPR, SVR) to the plasma concentrations of bosentan by use of the inhibitory E<sub>max</sub> model. The available data for SVR and TPR versus [bosentan]<sub>intra</sub> fitted well (in 6 of 7 and 5 of 7 patients, respectively).

**Results**

Seven female patients were enrolled (baseline characteristics shown in Table 1), 2 with lcSSc and 5 with primary PHT, including 1 familial case (patient 3). All had functionally limiting PHT (NYHA grade II to IV) with severely impaired exercise tolerance. Their mean age was 51 ± 5 years (range 28 to 68 years), and all but 1 were Caucasian. The exception (patient 5) was a Fijian Indian who also had a small patent foramen ovale. As shown in Table 2, the mean PVR was 1859 dyne · s · cm<sup>-5</sup> (range 645 to 4923 dyne · s · cm<sup>-5</sup>), and 2 patients had right ventricular failure with elevated MRAP (patients 3 and 6). No patient had a clinically significant fall in MPAP. Only 1 of the patients responded to inhaled NO, as defined by a fall in TPR >20% (patient 2). She had previously been shown to respond in an earlier trial of inhaled NO (patient 3 in Reference 17). In 4 of the nonresponders, the relative falls in TPR and SVR were comparable but generally <10%. The remaining 2 nonresponders showed a disproportionate response in the pulmonary (patient 7, −12% versus +5%) or systemic (patient 4, −1% versus −17%) circulation. No distinction was made between NO responders and
nonresponders in the analysis because of the small sample size.

The individual and combined hemodynamic data are shown in Figures 1 (A and B) and 2, respectively. There was substantial interindividual variation, but in general the maximal effects of bosentan were seen with the highest dose (300 mg). After this, there was a 20.0±11.0% fall in TPR (range 27.3% to 242.2%, \( P < 0.01 \)) accompanied by a 10.6±11.0% fall in MPAP (range 14% to 229%; Figure 2, A and B). However, there was no selectivity for the pulmonary circulation; in fact, the systemic effects were, if anything, more pronounced (26.2±12.8% fall in SVR, \( P < 0.005 \); 19.8±14.4% fall in MAP, \( P < 0.005 \), even at the lower doses. Systemic hypotension was prolonged, often clinically significant, and in 1 case prevented administration of the last dose (patient 5). From the 5 patients in whom complete paired data were available (ie, excluding patient 5), the calculated EC$_{50}$ for D$_{SVR}$ and D$_{TPR}$ was 310±97 and 747±113 ng/mL (\( P < 0.001 \); paired 2-tailed \( t \) test with unequal variance). The corresponding E$_{max}$ values were 2787 and 2588 dyne $\cdot$ s $\cdot$ cm$^{-5}$ (Figure 3A). The pharmacokinetic parameters estimated by model-independent methods were

### TABLE 1. Demographic and Clinical Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Diagnosis</th>
<th>Time Since Diagnosis of PHT, mo</th>
<th>NYHA Grade</th>
<th>MV$\dot{O}_{2}$, mL $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$</th>
<th>6-Minute Walking Distance, m</th>
<th>Plasma Creatinine, mmol/L</th>
<th>KCO, % of Predicted</th>
<th>Pulmonary Hypertension Therapy</th>
<th>Other Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>51</td>
<td>PPH</td>
<td>21</td>
<td>II</td>
<td>14.0</td>
<td>570</td>
<td>0.10</td>
<td>76</td>
<td>Warfarin</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>68</td>
<td>IcSSc/PHT</td>
<td>17</td>
<td>III</td>
<td>6.4</td>
<td>226</td>
<td>0.14</td>
<td>44</td>
<td>Warfarin</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>50</td>
<td>fPPH</td>
<td>15</td>
<td>IV</td>
<td>4.5</td>
<td>204</td>
<td>0.19</td>
<td>71</td>
<td>Aspirin</td>
<td>Gout</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>49</td>
<td>PPH</td>
<td>40</td>
<td>II</td>
<td>13.3</td>
<td>431</td>
<td>0.08</td>
<td>94</td>
<td>Warfarin</td>
<td>Hypertension</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>28</td>
<td>PPH</td>
<td>21</td>
<td>III</td>
<td>6.8</td>
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<td>0.08</td>
<td>90</td>
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<tr>
<td>6</td>
<td>F</td>
<td>48</td>
<td>PPH</td>
<td>40</td>
<td>III</td>
<td>12.5</td>
<td>338</td>
<td>0.10</td>
<td>69</td>
<td>Warfarin</td>
<td>Minimal airflow limitation</td>
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<tr>
<td>7</td>
<td>F</td>
<td>66</td>
<td>IcSSc/PHT</td>
<td>69</td>
<td>IV</td>
<td>13.0</td>
<td>203</td>
<td>0.11</td>
<td>66</td>
<td>Diltiazem</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Mean 51.4 31.8 10.1 334 0.11
SEM 5.0 7.3 1.5 52 0.01

PPH indicates primary pulmonary hypertension; PHT, pulmonary hypertension; fPPH, familial PPH; and KCO, transfer factor corrected for alveolar volume.

### TABLE 2. Baseline Hemodynamic Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Heart Rate, bpm</th>
<th>CI, L $\cdot$ min$^{-1} $ $\cdot$ m$^{-2}$</th>
<th>MRAP, mm Hg</th>
<th>MAP, mm Hg</th>
<th>SVR, dynes $\cdot$ s $\cdot$ cm$^{-5}$</th>
<th>PAOP, mm Hg</th>
<th>MPAP, mm Hg</th>
<th>PVR, dynes $\cdot$ s $\cdot$ cm$^{-5}$</th>
<th>NO response, max % $\Delta$TPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>2.0</td>
<td>4</td>
<td>100</td>
<td>3804</td>
<td>5</td>
<td>69</td>
<td>1463</td>
<td>−10</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>1.8</td>
<td>5</td>
<td>71</td>
<td>2872</td>
<td>9</td>
<td>54</td>
<td>1029</td>
<td>−29</td>
</tr>
<tr>
<td>3</td>
<td>84</td>
<td>0.8</td>
<td>21</td>
<td>91</td>
<td>6843</td>
<td>8</td>
<td>88</td>
<td>4923</td>
<td>−5</td>
</tr>
<tr>
<td>4</td>
<td>87</td>
<td>2.5</td>
<td>2</td>
<td>91</td>
<td>2845</td>
<td>4</td>
<td>61</td>
<td>1146</td>
<td>−17</td>
</tr>
<tr>
<td>5</td>
<td>108</td>
<td>1.7</td>
<td>6</td>
<td>98</td>
<td>4288</td>
<td>5</td>
<td>58</td>
<td>1643</td>
<td>+11</td>
</tr>
<tr>
<td>6</td>
<td>94</td>
<td>1.6</td>
<td>14</td>
<td>110</td>
<td>4686</td>
<td>7</td>
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<tr>
<td>7</td>
<td>110</td>
<td>2.6</td>
<td>−1</td>
<td>100</td>
<td>3041</td>
<td>7</td>
<td>46</td>
<td>645</td>
<td>+5</td>
</tr>
</tbody>
</table>

Mean±SEM 91±5 1.9±0.2 7.1±2.9 94±4.6 4054±538 6.4±0.7 66.4±6.4 1859±542 −8±5.0
(mean ± SD) half-life 3.8 ± 1.0 hours, systemic plasma clearance 3.8 ± 1.8 L/h, and volume of distribution at steady state 21.0 ± 8.8 L. The plasma concentration-time data were well approximated by the 2-compartment open model (Figure 3B).

There was a small but statistically insignificant increase in CI (1.89 ± 0.6 to 2.12 ± 0.6 L · min⁻¹ · m⁻², Figure 2C), with no significant changes in heart rate, PAOP (in the 3 patients for whom complete data were available), or MRAP (data not shown). Although there was a transient, insignificant increase in $SvO_2$ immediately after each infusion, there was no overall change in $PaO_2$ or oxygen delivery (Table 3). Baseline venous ET-1 concentrations were elevated (7.54 ± 1.89 ng/L, reference range 2.0 to 4.4 ng/L), but there was no correlation with PAP or TPR (data not shown). The baseline arteriovenous ratios were consistently less than unity, but they increased after bosentan infusion (Figure 4). Baseline ANP levels were elevated (147 ± 32 ng/L, reference range 21 to 63 ng/L), but there were no significant changes in ANP or norepinephrine concentration immediately after bosentan infusions (Table 3).

Discussion

This study was designed to investigate the potential of bosentan to achieve a sustained decrease in PAP and PVR, thus fulfilling the need for an efficacious and cost-effective treatment for PHT. For the results to be broadly applicable, the study population had to be representative of the patients most likely to benefit. Patients with either primary PHT or isolated PHT associated with lcSSc were included. The latter are usually excluded from transplantation programs, and long-term prostacyclin infusions are too costly for many health systems. However, a trial is in progress, and iloprost infusion has shown promise. Although some histological differences suggest that the pathogeneses of these conditions may differ, both groups of patients are comparable in their responses to such vasodilators as NO.

Intravenous bosentan caused a small, sustained fall in PAP and PVR, but there was no selectivity for the pulmonary vasculature at the doses tested. Indeed, the lower EC₅₀ and greater $E_{max}$ for its systemic effects suggest that the pulmonary vasculature of these patients may be relatively resistant to bosentan, in contrast to those with chronic heart failure. It is uncertain whether this may represent a consequence of local ET-1 production, as suggested by others, or structural changes in view of the relatively late stage of disease of these patients. In the absence of a placebo group, the demonstration of a concentration-response relationship strongly supports the con-
clusion that there was a true hemodynamic effect. Systemic hypotension may limit the use of bosentan in this condition, as it does the use of prostacyclin and other vasodilators. On the other hand, it remains possible that chronic low doses may have effects on pulmonary vascular remodeling or other clinical benefits at doses that do not induce systemic hypotension. Further studies to address this would be required.

ANP and norepinephrine have been implicated in the pathogenesis of PHT, in which concentrations of the latter are correlated with MPAP and PVR. In the present study, we noted elevated baseline ANP concentrations in most patients and a weak correlation with PVR, as described previously in patients with secondary PHT (data not shown).

The trial was terminated prematurely when 2 patients (patients 3 and 7) died within 36 hours of entering part 2 after developing hypotension that was unresponsive to inhaled NO or standard inotropic support. Both had received oral placebo after randomization on day 2 after receiving all doses of the acute infusion. An autopsy was not obtained in the first case (patient 3), and the cause of death is uncertain, although sepsis could not be excluded. She had a significantly impaired clearance of bosentan (≈15% of that of normal volunteers; clearance 1.24 L/h; Figure 1C), probably due to hepatic congestion.

An autopsy was performed on patient 7, but no specific cause of death other than PHT could be ascertained. Pharmacokinetic analyses did not reveal any abnormal parameters specific to this patient (clearance 3.7 L/h). The possibility of rebound PHT after withdrawal of her standard vasodilators seemed unlikely, because her PVR and PAP immediately before randomization to phase 2 were only slightly higher than at baseline, and she had relatively unresponsive pulmonary vascular disease. Although rebound increases in PAP have been observed in patients with PHT after withdrawal of calcium antagonists, prostacyclin, and NO, such phenomena have not been observed after the use of bosentan in heart failure or hypertension. Both patients had a very poor exercise tolerance, now recognized as an independent prognostic factor, and this should be considered in the design of future trials.

A third patient (patient 1) was also randomized to receive placebo in part 2 and completed the 8-week protocol without
any deterioration in her cardiorespiratory status. Only 1 patient (patient 2) randomized to active drug therapy completed part 2 before termination of the trial. She deteriorated clinically, with increasing dyspnea and peripheral edema during and immediately after the study. Other serious adverse events included respiratory tract infection with marked cardiac decompensation (patient 5) and *Clostridium difficile* diarrhea with metabolic acidosis and severe hypoxemia in the context of a urinary tract infection and its treatment (patient 4). Most adverse events were mild or moderate in severity and included hypotension (n=2), peripheral edema (n=2), headache (n=4), and urinary tract infections unrelated to urinary catheterization (n=2). All patients had ≥1 adverse event.

The long-term clinical benefits of prostacyclin are independent of its short-term vasodilator action. Bosentan may

**TABLE 3. Vasoactive Hormones and Oxygen Parameters After Each Bosentan Infusion**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Infusion 1*</th>
<th>Infusion 2*</th>
<th>Infusion 3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine, nmol/L†</td>
<td>2.94±0.59</td>
<td>2.91±0.62</td>
<td>3.28±0.56</td>
<td>2.71±0.55</td>
</tr>
<tr>
<td>ANP, ng/L†</td>
<td>147±31</td>
<td>107±28</td>
<td>163±46</td>
<td>103±28</td>
</tr>
<tr>
<td>ET-1arterial:ET-1mixed venous ratio</td>
<td>0.82±0.08</td>
<td>0.76±0.09</td>
<td>0.90±0.13</td>
<td>0.81±0.15</td>
</tr>
<tr>
<td>PaO₂ mm Hg</td>
<td>27±1.8</td>
<td>28±1.9</td>
<td>29±1.3</td>
<td>27±1.7</td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>54±4.9</td>
<td>56±5.1</td>
<td>59±3.8</td>
<td>57±5.8</td>
</tr>
<tr>
<td>Mean O₂ delivery, U</td>
<td>1266±55</td>
<td>1280±100</td>
<td>1279±86</td>
<td>1435±91</td>
</tr>
</tbody>
</table>

*Samples taken immediately after infusions of 50, 150, and 300 mg of bosentan.
†Reference ranges: noradrenaline, 1.09 to 1.63 nmol/L; ANP, 21 to 63 ng/L.
have similar properties, because in animal models of hypoxic PHT its administration results in pulmonary vascular remodeling and prevention and reversal of PHT. Chronic low doses of bosentan may have effects on pulmonary vascular remodeling, which would potentiate the pulmonary vasodilator response over time. A chronic reduction in PVR of 10% to 15%, as has been shown in the acute phase with bosentan, would be expected to have clinical benefits in the longer term. The greater effect of bosentan than seen with NO inhalation (mean maximal reduction 23% versus 8%; \( P < 0.01 \)) is also noteworthy.

These observations should suggest caution in further studies of long-term oral administration, given the difficulties encountered. Nor can these problems necessarily be attributed to the nonselectivity of bosentan, because it is relatively selective for the ET\(_{\alpha}\) receptor. The high doses used may have been a factor, and subsequent studies would support the use of lower doses in future. On the basis of our experience, we would recommend that future trials exclude patients with significantly elevated RAPs or severely impaired exercise tolerance. The use of acute dose-escalation protocols and prolonged periods of catheterization should also be avoided.

Acknowledgments
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References


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