Aprotinin, Blood Loss, and Renal Dysfunction in Deep Hypothermic Circulatory Arrest

Christina T. Mora Mangano, MD; Michael J. Neville, MD; Ping H. Hsu, PhD; Iulia Mignea, BS; Jennifer King, MD; D. Craig Miller, MD

Background—The technique of deep hypothermic circulatory arrest (DHCA) for cardiothoracic surgery is associated with increased risk for perioperative blood loss and renal dysfunction. Although aprotinin, a serine protease inhibitor, reduces blood loss in patients undergoing cardiopulmonary bypass, its use has been limited in the setting of DHCA because of concerns regarding aprotinin-induced renal dysfunction. Therefore, we assessed the affect of aprotinin on both blood transfusion requirements and renal function in patients undergoing cardiovascular surgery and DHCA.

Methods and Results—We reviewed the records of 853 patients who underwent aortic or thoracoabdominal surgery at Stanford University Medical Center between January 1992 and March 2000. Two hundred three of these patients were treated with DHCA, and 90% (183) survived for more than 24 hours. Preoperative patient characteristics and intraoperative and postoperative clinical and surgical variables were recorded, and creatinine clearance (CRCl) was calculated for the preoperative and postoperative periods; renal dysfunction was prospectively defined as a 25% reduction in CRCl. The association between perioperative variables, including aprotinin use, and renal dysfunction was assessed by ANOVA techniques. Total urine output was 1294 ± 1024 mL and 3492 ± 1613 mL during and after surgery, respectively. CRCl decreased significantly after DHCA from 86 ± 8 mL/min (before surgery) to 67 ± 4 mL/min (in the intensive care unit) (P < 0.01). Thirty-eight percent of patients (70 of 183) had postoperative renal dysfunction. Multivariate regression analyses identified 5 factors independently associated with a >25% reduction in CRCl: requirement for ≥5 U of packed red blood cells (P = 0.0002; OR = 2.1), ≥800 mL of urine collected in the operating room (P = 0.0011; OR = 1.9), nonuse of dopamine (P = 0.0430; OR = 1.6), hematocrit ≥21 mg% (P = 0.0343; OR = 1.5), and ≥2100 mL of urine during the first 24 hours in the intensive care unit (P = 0.0039; OR = 2.0). Aprotinin did not increase the likelihood of postoperative renal dysfunction (P = 0.951), nor did it significantly reduce packed red blood cell transfusion requirements in either primary (n = 107) (P = 0.456) or reoperative cardiovascular (n = 76) (P = 0.176) procedures. During the operative period, the aprotinin group received a greater number of units of platelets (10.0 versus 6.6 U, P < 0.012), fresh frozen plasma (4.8 versus 3.1 U, P < 0.03), and cryoprecipitate (9.9 versus 5.4 U, P < 0.002) than patients not prescribed aprotinin. Similarly, patients given aprotinin received more cryoprecipitate in the intensive care unit (7.3 versus 3.0 U, P < 0.024).

Conclusions—These data suggest that the administration of aprotinin to patients treated with DHCA does not increase the risk of renal dysfunction. However, aprotinin may not ameliorate the problem of perioperative blood loss in DHCA. Patients with greater requirements for packed red blood cell transfusions or reduced urine production are more likely to have postoperative renal dysfunction. Dopamine may provide renal protection in the setting of DHCA. (Circulation. 2001;104[suppl I]:I-276-I-281.)

Key Words: circulation • cardiopulmonary bypass • hemorrhage • kidney • complications

In 1950, Bigelow identified the relation between temperature and metabolism and initiated the advent of modern cardiovascular surgery. Although deep hypothermic circulatory arrest (DHCA) had proven to be life-saving for thousands of children and adults, control of the adverse sequelae associated with this technique has remained a challenge over the last 50 years.

The coagulopathy induced by DHCA is among the most formidable problems accompanying hypothermia and circulatory stasis. The introduction of aprotinin (a serine protease inhibitor) in the early 1990s was heralded as an important addition to the armamentarium available to attenuate the bleeding observed in patients with circulatory arrest. However, the publication of reports describing excessive thromboembolic events and end-organ damage in DHCA patients receiving aprotinin has prevented the routine adoption of this drug.

The affect of aprotinin on renal function is arguably one of the least well-defined or understood of the phenomena.

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observed in patients undergoing DHCA. The majority of publications assessing the impact of aprotinin in hypothermic circulatory arrest include a retrospective study design; this lack of prospective trials has contributed to the confusion regarding the safety and efficacy of aprotinin in DHCA.4–16

The purpose of the present study was to assess the affect of aprotinin on perioperative renal function and blood product transfusion requirements in patients undergoing cardiovascular surgery and DHCA.

**Methods**

With institutional review board approval, the records of 853 patients who underwent thoracic or thoracoabdominal aortic surgery during the period between January 1992 and March 2000 at Stanford University were reviewed. Patients treated with DHCA (203 of 853) during their operative procedures were identified and their hospital records were reviewed for demographic, preoperative, intraoperative (duration of cardiopulmonary bypass [CPB], heparin dose, duration of DHCA, minimal bladder temperature, minimal hematocrit, use of inotropic/vasoconstrictive drug infusions, use of dopamine, use of aprotinin, protamine dose, number of packed red blood cells [RBC], platelets, fresh frozen plasma [FFP], and cryoprecipitate units transfused, urine output, cell saver volume reinfused), and postoperative (urine output and the number of packed RBC, platelets, FFP, and cryoprecipitate units transfused over 36 hours, maximum postoperative creatinine value within 7 days of operation, chest tube drainage in the first 36 hours, and the need for hemodialysis during the hospital stay) variables. Patients admitted to the intensive care unit (ICU) and surviving at least 24 hours (183 of 203) were included in the statistical analyses to assess perioperative blood loss and blood product requirements. Except for 2 patients requiring hemodialysis before DHCA, the same patients (n=181) were included in the analyses of renal dysfunction. Postoperative changes in creatinine clearance (CRCl) were calculated according to the formula of Cockcroft and Gault, and patients with a >25% decrement in CRCl were considered to have renal dysfunction.17

All patients administered aprotinin (44 of 183) received the drug according to the following prescription: loading dose aprotinin, $2 \times 10^6$ KIU; pump priming aprotinin, $2 \times 10^6$ KIU; and maintenance aprotinin, 500 KIU/per hour. Aprotinin was discontinued within 5 hours of arrival in the ICU. Heparin dosage was titrated to maintain blood levels between 3.5 and 4.0 U/kg in all patients (Hepcon HMS, 

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**TABLE 1. Preoperative, Intraoperative, and Postoperative Variables in 183 Patients Undergoing Cardiovascular Surgery With DHCA**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Receiving Aprotinin (n=44)</th>
<th>Patients Not Receiving Aprotinin (n=139)</th>
<th>All Patients (n=183)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative factor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>$57 \pm 16$</td>
<td>$61 \pm 14$</td>
<td>$60 \pm 14$</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>$13 (30)$</td>
<td>$55 (39)$</td>
<td>$68 (37)$</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>$82 \pm 17$</td>
<td>$73 \pm 16$</td>
<td>$75 \pm 17$</td>
</tr>
<tr>
<td>Previous heart surgery, n (%)</td>
<td>$31 (41)$</td>
<td>$45 (12)$</td>
<td>$76 (42)$</td>
</tr>
<tr>
<td><strong>Intraoperative factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of CPB, min</td>
<td>$217 \pm 73$</td>
<td>$183 \pm 58$</td>
<td>$192 \pm 64$</td>
</tr>
<tr>
<td>Duration of DHCA, min</td>
<td>$32 \pm 15$</td>
<td>$34 \pm 15$</td>
<td>$33 \pm 15$</td>
</tr>
<tr>
<td>Minimal temperature, °C</td>
<td>$19 \pm 2$</td>
<td>$19 \pm 3$</td>
<td>$19 \pm 3$</td>
</tr>
<tr>
<td>Highest hematocrit, mg%</td>
<td>$25 \pm 5$</td>
<td>$26 \pm 5$</td>
<td>$25 \pm 5$</td>
</tr>
<tr>
<td>Minimal hematocrit, mg%</td>
<td>$18 \pm 4$</td>
<td>$19 \pm 4$</td>
<td>$19 \pm 4$</td>
</tr>
<tr>
<td>RBC transfusion, units</td>
<td>$4.6 \pm 4.8$</td>
<td>$3.7 \pm 3.6$</td>
<td>$3.9 \pm 3.9$</td>
</tr>
<tr>
<td>$\geq 5$ units of RBC, * n (%)</td>
<td>$15 (44)$</td>
<td>$43 (30)$</td>
<td>$58 (32)$</td>
</tr>
<tr>
<td>Cell-saver reinfusion, mL</td>
<td>$607 \pm 486$</td>
<td>$601 \pm 411$</td>
<td>$602 \pm 429$</td>
</tr>
<tr>
<td>Use of dopamine, n (%)</td>
<td>$34 (77)$</td>
<td>$113 (81)$</td>
<td>$147 (80)$</td>
</tr>
<tr>
<td>Urine output, mL</td>
<td>$1328 \pm 1319$</td>
<td>$1284 \pm 914$</td>
<td>$1294 \pm 1024$</td>
</tr>
<tr>
<td><strong>Postoperative factor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC transfusion, units†</td>
<td>$8.7 \pm 9.1$</td>
<td>$2.2 \pm 4.1$</td>
<td>$2.6 \pm 5.0$</td>
</tr>
<tr>
<td>Urine output, mL†</td>
<td>$3483 \pm 1809$</td>
<td>$3494 \pm 1552$</td>
<td>$3492 \pm 1613$</td>
</tr>
<tr>
<td>Chest tube drainage, 12 h, mL§</td>
<td>$947$</td>
<td>$767$</td>
<td>$858$</td>
</tr>
<tr>
<td>Chest tube drainage, 36 h, mL∥</td>
<td>$887$</td>
<td>$581$</td>
<td>$647$</td>
</tr>
<tr>
<td><strong>Outcome factor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction, n (%)</td>
<td>$17 (39)$</td>
<td>$53 (38)$</td>
<td>$70 (38)$</td>
</tr>
</tbody>
</table>

All values expressed as mean±SD or number (percent) of patients.

*Number and (percent) of patients administered 5 or more units of packed RBCs in the operating room.

†Packed RBCs transfused in the initial 24 hours in the ICU.

‡Total urine output during the initial 24 hours in the ICU.

§Output in first 12 hours after surgery.

∥Output in the second and third 12-hour periods after surgery.

¶Renal dysfunction defined as >25% decrease in CRCl from preoperative value to postoperative value.
Medtronic Hemotec, Inc). Those who received dopamine alone (119 of 183) or in combination with other inotropic/vasoconstrictor drugs (25 of 183) were included in the dopamine-treated group.

The initial step in the statistical analysis assessed potential associations between postoperative renal dysfunction and preoperative, intraoperative, and immediate (36 hours) postoperative variables, with the use of univariate procedures (Student's t test and Fisher's exact test). The variables identified by the univariate analysis (\(P \leq 0.10\)) (Table 2) were then analyzed by multivariate logistic regression. Several continuous variables were transposed into dichotomous measures: number of packed RBC transfusions >5 versus <5; minutes of circulatory arrest ≥30 versus <30 minutes; minimal hematocrit ≤21 versus >21 mg%; urine output in the operating room ≤800 mL versus >800 mL; and urine output in the ICU for the initial 24 hours ≤2100 mL versus >2100 mL. Statistical analyses were performed with JMP Version 4 (SAS Institute) software. Variables with a value of \(P < 0.05\) were considered significant, and odds ratios were calculated for these variables. A final model with significant and independent factors was selected.

## Results

Of the 853 patients studied, 203 were treated with DHCA and 183 survived the first 24 hours in the ICU. Seventy percent of all patients had a history of hypertension, and 7.4% had insulin-dependent diabetes mellitus (IDDM). Two patients required hemodialysis before their operation; an additional 12 (4 patients given aprotinin and 8 patients not prescribed aprotinin) were treated with hemodialysis in the postoperative period. Preoperative and postoperative creatinine values were 1.22±0.79 mg/dL (range, 0.5 to 6.3) and 1.89±1.47 mg/dL (range, 0.5 to 9.4), respectively. Other patient characteristics are listed in Table 1.

Twenty-four percent of 183 (44) patients received aprotinin; a greater percentage of patients (31 of 76) with a history of a previous cardiovascular procedure received aprotinin compared with patients undergoing a primary procedure (13 of 107). Aprotinin-treated patients received mean (SE) doses of heparin [66 425 (2993) units] and protamine [364 (14) mg]. Patients not treated with aprotinin received significantly less heparin (mean [SE] 45 298 [1699] units, \(P < 0.0001\)) and protamine (mean [SE] 286[80] mg, \(P < 0.0001\)). Dopamine was administered as the sole vasoactive/inotropic drug in 125 of 183 patients and in combination with other infusions (epinephrine, norepinephrine, dobutamine, amrinone, milrinone, and/or isoproterenol) in 22 of 183 subjects (the most common combination, 19 of 22, was dopamine and epinephrine). Twenty-seven patients did not receive any vasoactive/inotropic drugs by infusion. A variety of surgical procedures were completed with a mean (SD) duration of circulatory arrest: 33 (15) minutes, (range, 2 to 71 minutes). Preoperative and postoperative mean (SD) CRCl values were 19 (6) mL/min and 67 (4) mL/min, respectively. The mean (SD) decrement in CRCl was 19 (6) mL/min.

The univariate analysis showed 2 patient characteristics (age and a history of hypertension) and 8 intraoperative and postoperative variables to be associated with postoperative renal dysfunction (Table 2). Variables not associated with a decrement in renal function included sex, a history of IDDM, duration of CPB, or volume of scavenged and washed blood (cell saver) returned to the patient during the operative period. Patients given aprotinin did not have an increased risk of postoperative renal dysfunction (\(P = 0.951\)).

Multivariate analyses identified 5 variables to be significantly and independently associated with an increased risk of a >25% decrement in postoperative CRCl. Patients not administered dopamine (as the sole drug or in combination with other inotropic/vasoactive drugs) were at increased risk for renal dysfunction (\(P = 0.0430\); OR=1.6). Patients receiving ≥5 U of packed RBC in the operating room (\(P = 0.0002\); OR=2.1), with an intraoperative hematocrit ≤21 mg% (\(P = 0.0343\); OR=1.5), producing ≤800 mL of urine during the operative period (\(P = 0.0011\); OR=1.9) or ≤2100 mL of urine during the first 24 hours in the ICU (\(P = 0.0039\); OR=2.0), had an increased likelihood of postoperative renal dysfunction (Table 3).

Of the 6 factors considered as possible variables associated with an increase in packed RBC requirements (history of hypertension, history of a previous cardiovascular procedure, duration of CPB, duration of DHCA, minimal hematocrit, and...
cell saver volume), only a reoperative procedure ($P=0.0121$) was significantly associated with a need for an increased number of units of packed RBC. Although aprotinin had no effect on packed RBC transfusion requirements ($P=0.7384$), aprotinin-treated patients required a greater number of units of (mean [SE]) platelets (10.0 [1.1] versus 6.5 [0.7] units, $P<0.012$), FFP (4.8 [0.7] versus 3.1 [0.4] units, $P<0.03$), and cryoprecipitate (9.9 [1.3] versus 5.4 [0.7] units, $P<0.024$) than patients not administered aprotinin. In the ICU, the aprotinin group received a greater number of units of cryoprecipitate (mean [SE] 7.3 [1.6] versus 3.0 [0.9] units, $P<0.024$) (aprotinin versus nonaprotinin groups, respectively) (Table 4).

There was no significant difference between the groups in chest tube drainage in the first 12 hours after surgery (mean [SE], 947 [168] versus 761 [91] mL, $P=0.33$, aprotinin versus no aprotinin) nor on the first postoperative day (mean [SE], 779 [119] versus 572 [65] mL, $P=0.13$) (Table 1).

**Discussion**

The present study suggests that the use of aprotinin is not associated with renal dysfunction in patients requiring DHCA. However, in our study population of 183 patients with circulatory arrest, aprotinin did not attenuate perioperative blood loss, as quantified by a number of measures (blood products transfused during and/or after the operation, intraoperative hematocrit value, postoperative chest tube drainage). Importantly, aprotinin did not reduce excessive blood transfusion requirements in either patients at increased risk (patients with a previous cardiovascular operation) or patients undergoing a primary procedure with DHCA. This investigation is the first to report this finding and is inconsistent with the published results from patients with reoperative cardiac surgery who were treated with CPB but not DHCA.18–20

The primary purpose of this study was to assess specifically the association of renal dysfunction and intraoperative aprotinin administration in patients with DHCA. Although aprotinin was not associated with a compromise in renal function, the multivariate analysis identified 4 factors that were independently associated with a decrement in creatinine clearance and revealed a single variable associated with a decreased risk of postoperative renal impairment. Patients prescribed dopamine, either alone or in combination with one or more inotropic/vasoactive drugs during the operative and early postoperative recovery periods, were less likely to have renal compromise. Despite decades of the ubiquitous prescription of dopamine for the prevention of renal dysfunction, this is the first report of a multivariate analysis suggesting that dopamine provides renal protection in the setting of DHCA. Numerous retrospective studies and case reports argue either the benefit or lack of palliative affect of dopamine on perioperative renal function.21–23 We found two surrogates of blood loss (minimal hematocrit and the number of packed RBC transfusions) that were independently associated with postoperative renal dysfunction. These findings are consistent with other studies of patient groups at risk for hemorrhage and renal dysfunction.11,24 In contrast, we did not find an association between the volume of scavenged and washed blood volume and renal dysfunction in thoracoabdominal surgery as noted by other investigators.11

The coagulopathy induced by hypothermia and circulatory stasis is complex, multifactorial in pathogenesis, and is described in detail elsewhere.25–27 Briefly, a combination of kinetic factors, kinin/kallikrein perturbations, platelet dysfunction, and an imbalance of fibrinolytic and antifibrinolytic systems, all contribute to the coagulopathy induced by hypothermia. The physiological response to circulatory stasis includes a thrombin-induced increase in activated Protein C, a serine protease. Activated Protein C prevents clotting and maintains blood fluidity through proteolysis of procoagulant factors V, and VIII, and induction of fibrinolysis by causing endothelial release of tissue plasminogen activator. Because aprotinin is a serine protease inhibitor, it may attenuate the role of activated Protein C in maintaining blood fluidity in the face of circulatory stasis. This potential untoward effect of aprotinin may be exaggerated in the presence of inadequate anticoagulation with heparin. Importantly, in the present study, blood heparin values were measured and maintained between 3.5 and 4.0 U/mL in all of our patients receiving aprotinin throughout extracorporeal circulation. This may have attenuated the problem of excessive thrombosis and Protein C activation and consumption and thus prevented an increase in the risk of renal dysfunction.

Few studies include data regarding the use of aprotinin in reoperative procedures conducted with DHCA. However, review of the literature suggests that a substantial proportion (15% to 21%) of all patients requiring operations with DHCA have a history of a previous cardiovascular operation.11,28 The earliest studies of the use of aprotinin in DHCA are more likely to report a greater number of adverse sequelae in

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### TABLE 4. Blood Product Transfusions Administered in the Operating Room and During the First 36 Hours in the ICU in Patients Receiving Aprotinin and Not Prescribed Aprotinin

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Location</th>
<th>Aprotinin</th>
<th>No Aprotinin</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>Operating room</td>
<td>10.0 (1.1)</td>
<td>6.6 (0.6)</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>ICU</td>
<td>4.6 (1.4)</td>
<td>2.9 (0.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>Operating room</td>
<td>4.8 (0.7)</td>
<td>3.1 (0.4)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>ICU</td>
<td>3.8 (0.9)</td>
<td>2.2 (0.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Operating room</td>
<td>9.9 (1.3)</td>
<td>5.4 (0.7)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>ICU</td>
<td>7.3 (1.6)</td>
<td>3.0 (0.9)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Values are units (SE).
patients administered aprotinin.4,5 Importantly, these investigations were conducted before the identification of appropriate heparin treatment strategies for patients receiving aprotinin, and patients in these studies probably received inadequate dosages of heparin.5 Similariy, earlier studies reported an ineffective or putative impact of aprotinin on blood loss or transfusion requirements in patients with circulatory arrest.4,5 In a study by Westaby and colleagues,4 the mean blood loss in 27 patients not administered aprotinin was 837 mL over a period of 24 hours. In contrast, the 53 aprotinin-treated patients had an average 24-hour blood loss of 1929 mL. Although more recent studies report a palliative affect of aprotinin on measures of blood conservation,7,10,13 this is not a uniform finding.9 In the late 1990s, both Okita and colleagues11 and Ehrlich et al10 assessed the effectiveness of aprotinin on reducing measures of blood loss in DHCA and found that a low-dose aprotinin protocol decreased the need for blood transfusions. The latter study included 50 patients randomly assigned to receive aprotinin or placebo and reported that aprotinin did not increase the incidence of renal dysfunction in DHCA as defined by several measures (β₂-microglobulin values, the incidence of postoperative creatinine values >1.5 the preoperative creatinine level).10 However, in this study, only 1 in 4 patients was older than 65 years of age, and patients with a preoperative creatinine >2.0 mg/dL were excluded from participating in the investigation.

Several phenomena, including the retrospective design of this study, limited our assessment of potentially important demographic characteristics and perioperative variables on renal function in patients requiring DHCA. The study population was aged, preventing an analysis of advanced age on risk; few patients (7.4%) had IDDM, and only 24% of the subjects received aprotinin. As expected, the majority of patients in this study had a history of hypertension, and we observed a trend toward an association between hypertension and a reduced postoperative CrCl (P=0.0793). However, the small subset of patients without hypertension prevented a robust analysis of the association of systemic hypertensive disease and postoperative renal function. Additionally, the blood product data reported here represent transfusion practice that evolved over nearly a decade of clinical practice. Although one attending surgeon cared for the majority of patients, different teams of cardiac surgery residents made transfusion decisions (often urgently), based on different clinical variables and/or coagulation laboratory assessments. Nonetheless, the majority of measures used in this study to quantify blood loss suggest that aprotinin does not attenuate perioperative blood product requirements in patients undergoing DHCA. Finally, because the majority of the aprotinin-treated patients were at greater risk for blood loss, these data do not permit an assessment of aprotinin on renal function in patients undergoing primary cardiovascular procedures.

In conclusion, these data suggest that aprotinin does not increase the likelihood of postoperative renal dysfunction in patients treated with DHCA. However, we found that aprotinin was not effective in limiting the requirement for blood transfusions in either “high-risk” or “low-risk” patients. Because of the findings of the present study and those of other investigators that an increased need for blood transfusions is associated with postoperative renal dysfunction, the role of aprotinin and other blood-sparing strategies for circulatory arrest patients must be more clearly understood. The need for DHCA is likely to increase as our population survives into advanced age and has life-threatening cardiovascular disease. Similarly, children with surgically corrected congenital heart disease are achieving adulthood and undergoing complicated reoperative procedures that require the use DHCA. It is therefore imperative that we continue to improve our ability to decrease the adverse sequelae associated with DHCA, a frequently life-saving but profound physiological perturbation.

Acknowledgments

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References


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