Elevation of Prostate-Specific Markers After Cardiopulmonary Resuscitation

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Background—Prostate-specific antigen (PSA), acid phosphatase (AP), and prostatic acid phosphatase (PAP) are serum markers for adenocarcinoma of the prostate gland. Previous studies indicated that prostatic ischemia may also produce elevations of PSA. Cardiopulmonary resuscitation (CPR) is frequently associated with profound tissue hypoperfusion. The present study investigated whether PSA, AP, and PAP are influenced by prolonged CPR.

Methods and Results—PSA, AP, and PAP were assessed immediately, 12 hours, 24 hours, 2 days, 3 days, 5 days, and 7 days after prolonged CPR (>5 minutes) in 14 male and 5 female patients. No changes were noted in women. In men, serum levels increased significantly after CPR and gradually decreased to near baseline values after 7 days. PSA, AP, and PAP values above the normal range were observed in 63%, 71%, and 64% of all patients, respectively. Compared with survivors, nonsurvivors exhibited higher peak serum levels of PSA (98.6 ± 14.3 versus 1.1 ± 2.2 µg/L; P < 0.03), AP (57.0 ± 71 versus 8.6 ± 8.8 U/L; P < 0.05), and PAP (47.0 ± 62 versus 5.7 ± 8.0 U/L; P = NS). Patients with poor neurological outcome exhibited higher peak serum levels of PSA (86.4 ± 135.5 versus 12.0 ± 23.8 µg/L; P < 0.05), AP (50.9 ± 68.1 versus 8.7 ± 9.6 U/L; P = NS), and PAP (41.6 ± 59.5 versus 5.8 ± 8.8 U/L; P = NS) than patients with good neurological outcome.

Conclusions—Prolonged CPR is frequently associated with increases of PSA, AP, and PAP serum levels. Therefore, PSA cannot be used for diagnosis of adenocarcinoma of the prostate during the first weeks after CPR. Further evaluation of these parameters as additional prognostic markers after CPR is warranted. (Circulation. 2000;102:290-293.)

Key Words: antigens ■ cardiopulmonary resuscitation

Prostate-specific antigen (PSA), a serine protease, is specific for prostatic tissue and is produced by the epithelial cells of the ductal or acinar elements of the prostate gland. It is considered specific for prostatic tissue, and any condition that disrupts the cellular basement membrane within these acini and ducts leads to leakage of PSA into the prostatic parenchyma and to an increase in PSA serum concentrations.1–3 Increased serum levels of PSA were found to be closely associated with adenocarcinoma of the prostate1,4 and show a good correlation to the clinical stage of prostatic cancer.5 Thus, PSA has replaced prostatic acid phosphatase (PAP) and acid phosphatase (AP) as a more sensitive and specific serum marker for malignancy of the prostate.

Such nonmalignant diseases as benign prostatic hyperplasia, acute or chronic prostatitis, prostatic trauma, and prostatic infarction, however, are also known to be associated with increased PSA serum levels.1,5,6 Prostatic infarction has been described after presumed pelvic ischemia after cross-clamping of the aorta for coronary or aortic surgery, hypertensive myocardial infarction, and septic shock.6,7 Because CPR is frequently associated with profound tissue hypoperfusion, we hypothesized that increases in serum PSA, AP, and PAP levels due to ischemic prostatic damage might also occur after prolonged CPR.

The aim of the present study was to investigate the effect of prolonged CPR on PSA, AP, and PAP serum levels and whether PSA might serve as a prognostic marker after CPR.

Methods

Patients

The study protocol was approved by the Ethics Committee of Vienna University. Nineteen patients (14 male, 5 female) with a mean age of 59.1 ± 14.8 years who had undergone prolonged, successful CPR (>5 minutes) were prospectively enrolled into the study. Patients with a history of cancer, adenocarcinoma of the prostate gland, pathological findings on rectal examination, or elevated PSA levels before CPR were excluded from the study.

The first documented arrhythmia on the ECG was ventricular fibrillation in 10 patients and bradycardia or asystole in 9 patients. Underlying disease was acute myocardial infarction in 9 patients and ischemic or dilated cardiomyopathy in 8 patients; 1
TABLE 1. Mean Serum Levels of PSA, AP, PAP, and Lactate After Prolonged CPR in 12 Male Patients Surviving the Study Period

<table>
<thead>
<tr>
<th></th>
<th>Normal Range</th>
<th>0 Hours</th>
<th>12 Hours</th>
<th>24 Hours</th>
<th>2 Days</th>
<th>3 Days</th>
<th>5 Days</th>
<th>7 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA, µg/L</td>
<td>0–4</td>
<td>1.9±1.5</td>
<td>20.0±5.7</td>
<td>35.6±97</td>
<td>18.1±31.5</td>
<td>13.9±22</td>
<td>8.0±11.5</td>
<td>5.0±6.5</td>
</tr>
<tr>
<td>PAP, U/L</td>
<td>0–2.6</td>
<td>0.7±0.5</td>
<td>13.7±38</td>
<td>5.6±10.1</td>
<td>1.5±1.7</td>
<td>1.0±1.5</td>
<td>0.8±0.7</td>
<td>0.9±0.9</td>
</tr>
<tr>
<td>AP, U/L</td>
<td>0–6.5</td>
<td>3.7±17.9</td>
<td>17.9±45</td>
<td>8.6±11.4</td>
<td>4.2±2.4</td>
<td>3.5±1.4</td>
<td>3.8±1.3</td>
<td>4.8±3.2</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>0–2.2</td>
<td>4.4±3.3</td>
<td>5.2±3.9</td>
<td>3.4±2.4</td>
<td>2.0±1.4</td>
<td>1.6±1.5</td>
<td>1.2±0.6</td>
<td>1.2±0.1</td>
</tr>
</tbody>
</table>

Data are mean±SD.

Further data analysis was limited to the male study population. Of 14 male patients, 12 survived the total study period and 2 died 30 and 36 hours, respectively, after study enrollment. Five patients died after completion of the study; the remaining 7 survived the hospital stay. Functional neurological recovery in survivors (n=7) was classified as good in 6 patients and as poor in 1, and in nonsurvivors (n=7), as poor in all 7 patients.

Mean serum levels of PSA, AP, PAP, and lactate of the 12 patients who survived the study period are presented in Table 1. Immediately after CPR, mean PSA values were in the normal range in all patients, increased rapidly after 12 to 24 hours, and gradually decreased to near baseline values 7 days after CPR. Similar serum kinetics were obtained for AP, PAP, and lactate serum levels (Table 1). Two patients, who died 30 and 36 hours after study enrollment, exhibited markedly elevated levels of PSA (269 and 39 µg/L), AP (33.6 and 47.5 U/L), and PAP (138 and 37.1 U/L) at 24 hours. Increases to the individual peak values were highly significant for PSA (1.9±1.5 to 55.0±108.2 µg/L; P<0.0005), AP (3.7±17.9 to 33.1±54.7 U/L; P<0.0011), PAP (0.7±0.5 to 26.6±47.5 U/L; P<0.0011), and serum lactate (4.4±3.3 to 8.0±7.0 mmol/L; P<0.0139).

Peak values for PSA, AP, PAP, and lactate were observed 43.6±25.7, 31.7±31.8, 29.6±31.4, and 8.0±7.0 hours after CPR, respectively (PSA versus lactate: P<0.00004; AP versus lactate: P<0.011; PAP versus lactate: P<0.018; differences between PSA, AP, and PAP were statistically nonsignificant). Seven days after CPR, elevated serum levels were still observed for PSA in 3 patients (20.0, 6.8, and 16.7 µg/L), for AP in 1 patient (11.1 U/L), and for PAP in 1 patient (3.3 U/L).

Significant linear correlations between individual values of PSA and AP (r=0.59, P<0.0001), PSA and PAP (r=0.59, P<0.0001), and AP and PAP (r=0.99, P<0.0001) were observed. Serum lactate levels also correlated significantly with PSA (r=0.24, P<0.02), AP (r=0.37, P<0.0004), and PAP (r=0.37, P<0.0003) values. The presence and extent of increase in serum levels of all parameters evaluated was highly variable. PSA, AP, PAP, and lactate values above the upper limit of the normal range at any time during the study period were observed in 63.3%, 71.4%, 64.3%, and 85.7% of all patients, respectively. The Figure shows the incidence of pathological findings for PSA, AP, PAP, and lactate levels at consecutive time points after CPR.

Peak serum levels of survivors and nonsurvivors are compared in Table 2, showing significantly lower peak values for PSA, AP, and lactate for surviving patients. Similarly, patients who survived with a good functional neurological recovery exhibited significantly lower peak serum levels of
PSA and lactate than patients who survived with a poor neurological outcome (Table 3). There were no significant correlations between time until ROSC and individual peak serum levels of PSA, AP, PAP, and lactate.

Autopsy was performed in 3 patients with elevated PSA levels. It demonstrated mild prostatic hyperplasia in 1 patient and no pathological finding in the other 2.

**Discussion**

PSA, AP, and PSP are well-known markers for adenocarcinoma of the prostate gland. Compared with AP and PSP, PSA serum levels are considered more specific for prostatic malignancy. However, it has been demonstrated that prostatic ischemia and infarction may also produce marked elevations of PSA. Prostatic infarction has been described in situations associated with presumed pelvic ischemia, such as cross-clamping of the aorta for aortic or iliac surgery or ruptured aortic aneurysms. Hagood et al observed marked elevations of serum PSA levels after cardiac surgery and extracorporeal cardiopulmonary bypass. Although several factors may contribute to elevated PSA levels in this postoperative setting, evidence strongly suggests intraoperative prostatic ischemia to induce epithelial cell damage of the prostate gland, leading to a concomitant increase in PSA serum concentrations.

The purpose of the present study was to investigate the effect of prolonged CPR on serum levels of PSA, AP, and PAP. We could demonstrate that prolonged CPR is followed by a marked increase in PSA, AP, and PAP serum levels in up to 50% of patients. In fact, peak serum concentrations of PSA (55.0 ± 108.2 μg/L) were comparable to those found in patients with an advanced clinical stage of prostate cancer. Seven days after CPR, elevated PSA levels were still present in 3 of 12 patients (25%). Because the study period was limited to the first 7 days after CPR, we cannot answer the question of at what time elevated PSA serum levels in the remaining 3 patients returned to baseline values. It seems likely, however, that complete normalization of initially marked elevated levels may even require up to 2 to 3 weeks.

Because serum levels of PSA, AP, and PAP were in the normal range at baseline and reversible increases in serum concentrations were observed only in male subjects, it is reasonable to assume that prolonged CPR induces pelvic ischemia, leading to epithelial cell damage of the prostate gland. Increased PSA, AP, and PAP levels may therefore represent markers for ischemic prostatic cell damage during CPR. To further support this hypothesis, we investigated the relationship between prostatic markers and serum lactate, which represents a well-established parameter for global tissue hypoperfusion. In fact, lactate levels were not only higher in nonsurvivors than survivors but also were highly correlated to PSA, AP, and PAP serum levels.

Most striking was the finding that patients who died had higher maximum serum levels of PSA, AP, and PAP than patients who survived (Table 2). There was even a strong association between peak serum levels of prostatic markers and neurological outcome. Accordingly, patients with good functional neurological recovery exhibited lower peak serum levels of PSA, AP, and PAP than patients with poor neurological outcome.

Because neurological outcome after circulatory arrest is known to relate inversely to the degree and duration of global ischemia, one would have expected a positive correlation between peak serum levels of PSA, AP, and PAP and time...
until ROSC. In our study, however, we could not observe a correlation between peak serum levels of prostatic markers and time until ROSC. This somewhat surprising finding might be explained by the fact that circulatory and neurological responses after CPR are also determined by various prearrest and intra-arrest factors, such as patient age, underlying disease, extent and quality of basic/advanced life support, and the cumulative dose of inotropic agents applied.12

Although we could observe a relation of peak serum levels of PSA, AP, and PAP to overall mortality and neurological outcome, the number of patients in our study is too small to define the value of PSA as prognostic marker after CPR. In fact, our study was designed primarily to identify the effect of prolonged CPR on serum levels of prostatic markers. One could argue that urethral catheterization may also have contributed to elevated serum levels in this study. In 2 patients, however, blood samples were obtained before and after urethral catheterization, and no effect on PSA, AP, and PAP serum levels was observed. Moreover, it was shown previously that neither atraumatic urethral catheterization nor flexible or rigid cystoscopy is likely to produce any meaningful change in PSA level.1,6

In conclusion, our results demonstrate that prolonged CPR is frequently associated with a significant increase of PSA, AP, and PAP levels. Therefore, PSA, AP, and PAP serum levels should not be used as markers for prostate malignancy during the first weeks after CPR, rendering invasive urological examinations inappropriate during that time. Further studies are warranted to investigate whether these markers may serve as additional prognostic parameters for survival and neurological outcome after CPR.

References
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