Procalcitonin and the Early Diagnosis of Infective Endocarditis

Christian Mueller, MD; Peter Huber, MD; Gerd Laifer, MD; Beat Mueller, MD; André P. Perruchoud, MD

Background—Variability in the clinical presentation of infective endocarditis (IE) makes the diagnosis a clinical challenge. We hypothesized that serum procalcitonin, a marker of systemic bacterial infection, might be helpful in its diagnosis.

Methods and Results—We conducted a prospective cohort study in 67 consecutive patients admitted to the hospital with the suspicion of IE or in whom the suspicion arose during the hospital course. IE was diagnosed by an interdisciplinary team that included an infectious disease specialist and a cardiologist who applied the Duke criteria. IE was confirmed in 21 patients. Procalcitonin was significantly higher in patients with IE (median 6.56 ng/mL) than in those with other final diagnoses (median 0.44 ng/mL, \( P<0.001 \)). The area under the receiver operating characteristic curve that used procalcitonin to predict IE was 0.856 (95% CI 0.750 to 0.962), compared with 0.657 (95% CI 0.511 to 0.802) for C-reactive protein. The optimum concentration of procalcitonin for the calculation of positive and negative predictive accuracy as obtained from the receiver operating characteristic curve was 2.3 ng/mL. With this cutoff, the test characteristics of procalcitonin were as follows: sensitivity 81%, specificity 85%, negative predictive value 92%, and positive predictive value 72%. Multiple logistic regression analysis revealed that procalcitonin was the only significant independent predictor of IE on admission (OR 1.52, 95% CI 1.07 to 2.15, \( P=0.018 \)).

Conclusions—Procalcitonin may be a valuable additional diagnostic marker in patients with suspected IE. (Circulation. 2004;109:1707-1710.)

Key Words: hormones • endocarditis • infection • diagnosis

Despite advances in antimicrobial therapy and enhanced ability to diagnose and treat complications, infective endocarditis (IE) continues to carry a high risk of morbidity and mortality.\(^1-3\) The incidence of IE is rising. IE now represents the fourth-leading cause of life-threatening infectious disease syndromes.\(^1\) Rapid diagnosis and initiation of effective treatment are essential to good patient outcome. Unfortunately, variability in the clinical presentation of IE makes the diagnosis a clinical challenge.

The diagnostic strategy currently recommended by the American Heart Association and others was proposed in 1994 (Duke criteria).\(^3,4\) In general, the diagnosis of IE requires typical microorganisms grown from at least 2 separate blood cultures and evidence of endocardial involvement. Application of the Duke criteria in clinical practice requires expertise and time. Accordingly, a simple blood test that would help predict the presence or absence of IE in suspected cases would be highly desirable.

Circulating calcitonin precursors, including procalcitonin, have been proposed as potential markers and mediators of systemic bacterial infections.\(^5\) We hypothesized that IE, an intravascular infection with continuous bacteremia, would result in significantly higher procalcitonin levels than other systemic infections or noninfectious disorders with similar clinical presentation.

Methods

Patient Population

This study was performed from May 1999 through February 2001 at the University Hospital Basel, Basel, Switzerland. All adult patients who were consecutively admitted with the suspicion of IE or in whom the suspicion arose during the hospital course were enrolled in the study. Patients included in this study exhibited clinical symptoms such as fever, chills, exhaustion, loss of appetite, and night sweats. The differential diagnosis of IE had to be stated specifically in the referral letter, in the initial medical summary, or in the specialist statement of the infectious disease consultant to qualify for inclusion. IE was diagnosed by an interdisciplinary team that included an infectious disease specialist and a cardiologist who applied the Duke Criteria\(^1\) and the modified Duke Criteria after April 2000.\(^4\) The study was performed according to the principles of the Declaration of Helsinki. Informed consent was obtained from all participating patients.

Blood Sampling and Laboratory Methods

During the initial venipuncture for routine blood sampling on admission, an additional blood sample was obtained from each patient. All procalcitonin assays were processed at our central laboratory. Procalcitonin samples were centrifuged and immediately

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Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>All Patients (n=67)</th>
<th>IE (n=21)</th>
<th>No IE (n=46)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>49±20</td>
<td>45±19</td>
<td>51±20</td>
</tr>
<tr>
<td><strong>Female gender</strong></td>
<td>27 (40)</td>
<td>7 (33)</td>
<td>20 (43)</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous IE</td>
<td>6 (9)</td>
<td>5 (24)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>23 (34)</td>
<td>9 (43)</td>
<td>14 (30)</td>
</tr>
<tr>
<td>Intravenous drug abuse</td>
<td>22 (33)</td>
<td>10 (48)</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Fever</td>
<td>57 (85)</td>
<td>21 (100)</td>
<td>36 (78)</td>
</tr>
<tr>
<td>Taking antibiotics at presentation</td>
<td>17 (25)</td>
<td>6 (29)</td>
<td>11 (24)</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart murmur</td>
<td>48 (72)</td>
<td>17 (81)</td>
<td>31 (67)</td>
</tr>
<tr>
<td>Systolic murmur</td>
<td>44 (66)</td>
<td>14 (67)</td>
<td>30 (65)</td>
</tr>
<tr>
<td>Diastolic murmur</td>
<td>10 (15)</td>
<td>6 (29)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Vascular phenomena*</td>
<td>6 (9)</td>
<td>5 (24)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Laboratory findings on admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count, ×10^9/μL</td>
<td>12.6±6.5</td>
<td>15.4±5.5</td>
<td>11.3±6.5</td>
</tr>
<tr>
<td>Percentage neutrophiles</td>
<td>78±17</td>
<td>85±9</td>
<td>75±18</td>
</tr>
<tr>
<td>Platelet count, ×10^9/μL</td>
<td>273±153</td>
<td>236±123</td>
<td>289±162</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.6±2.5</td>
<td>10.9±2.5</td>
<td>11.8±2.5</td>
</tr>
<tr>
<td>C-reactive protein, mg/L, median</td>
<td>100</td>
<td>146</td>
<td>77</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>44–205</td>
<td>53–230</td>
<td>31–159</td>
</tr>
<tr>
<td>Procalcitonin, ng/mL, median</td>
<td>0.61</td>
<td>6.56</td>
<td>0.44</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.17–3.63</td>
<td>2.57–12.48</td>
<td>0.13–1.20</td>
</tr>
<tr>
<td><strong>Findings during hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood culture positive</td>
<td>50 (75)</td>
<td>21 (100)</td>
<td>29 (63)</td>
</tr>
<tr>
<td>Echocardiogram positive for IE†</td>
<td>10 (19)</td>
<td>10 (59)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or n (%).
P value for comparison of patients with IE compared with patients with no IE.
*Vascular phenomena include arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway’s lesions.
†Defined as follows: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic valve.

Statistical Analysis

We compared differences in concentration of procalcitonin between patients ultimately diagnosed with IE and those with no IE. We used a multiple logistic regression model to test for independent predictors of IE on admission. All baseline characteristics shown in the Table were tested in univariate analysis. Those variables in univariate analysis with a probability value below 0.05 were entered in the multivariate model. A receiver operator characteristic (ROC) curve was constructed to assess the sensitivity and specificity of procalcitonin throughout the concentrations to detect IE. The optimum concentration of procalcitonin for the calculation of positive and negative predictive accuracy was obtained from the ROC analysis. Statistical analyses were performed with SPSS/PC (version 11.0, SPSS Inc).

Results

A total of 67 patients with the suspicion of IE were evaluated during the study period. IE was confirmed in 21 patients (Table). Among the baseline patient characteristics, history of IE, history of fever, diastolic heart murmur on auscultation, vascular phenomena, white blood cell count, C-reactive protein, and procalcitonin were associated with the final diagnosis of IE. The cardiac structures involved were the aortic (n=9), mitral (n=5), pulmonic (n=2), and tricuspid (n=7) valves, as well as ventricular septal defect (n=1). The causative organisms included Staphylococcus aureus (n=10), S aureus plus streptococci (n=3), Viridans streptococci (n=3), and Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus intermedius, and Staphylococcus epidermidis (n=1 for each). In 46 frozen and stored at −70°C. Assays were performed in batches at the end of the study period. The interdisciplinary team was blinded to the procalcitonin values. The circulating procalcitonin level was measured by use of an assay based on time-resolved amplified cryptate emission (TRACE) technology (Kryptor-PCT). The analytical sensitivity of the quantitative test method is 0.02 ng/mL, and the functional assay sensitivity is 0.06 ng/mL. Kryptor-PCT is based on a sheep polyclonal anti-calcitonin antibody and a monoclonal anti-calcitonin sequence of calcitonin precursor molecules. A particle enhanced turbidimetric immunoassay technique was used for the determination of C-reactive protein level (Dade Behring Inc).
patients, other disease was diagnosed, including sepsis due to *S. aureus* (n=5), other sepsis (n=4), septic deep vein thrombosis (n=2), erysipelas/phlegmona/fasciitis (n=5), viral infection (n=5), pneumonia (n=4), arthritis (n=3), fever of undetermined cause without evidence of IE during 3-year follow-up (n=3), lymphoma/malignancy (n=2), and abscess (n=2), as well as heart failure with gastroenteritis, perimyocarditis, cardiogenic shock, arteritis temporalis, osteomyelitis, pancytopenia, Wegner’s granulomatosis, diverticulitis, sinusitis, degeneration of the aortic valve of unknown cause, and unclear syndrome (n=1 for each).

Procalcitonin was significantly higher in patients with IE (median 6.56 ng/mL) than in patients with other final diagnoses (median 0.44 ng/mL, *P*<0.001; Figure). The area under the ROC curve that used procalcitonin to predict IE was 0.856 (95% CI 0.750 to 0.962). In comparison, the area under the ROC curve that used C-reactive protein to predict IE was considerably lower: 0.657 (95% CI 0.511 to 0.802). Procalcitonin was 1.06 ng/mL (median; interquartile range 0.28 to 3.17 ng/mL) in patients with non-IE bacterial infections (n=22) and 0.07 ng/mL (median; interquartile range 0.05 to 0.31 ng/mL) in patients with viral infections (n=5). Procalcitonin was 1.06 ng/mL (median; interquartile range 0.43 to 2.88 ng/mL) in patients with *S. aureus* sepsis (n=5) versus 4.81 ng/mL (median; interquartile range 3.02 to 12.93 ng/mL) in patients with *S. aureus* IE (*P*=0.021; n=13).

The optimum concentration of procalcitonin for the calculation of positive and negative predictive accuracy as obtained from the ROC curve was 2.3 ng/mL. With this cutoff, the test characteristics of procalcitonin were as follows: sensitivity 81%, specificity 85%, negative predictive value 92%, and positive predictive value 72%. Multiple logistic regression analysis revealed that procalcitonin (as a continuous variable) was the only significant independent predictor of IE on admission (OR 1.52, 95% CI 1.07 to 2.15, *P*=0.018).

**Discussion**

This study tested the diagnostic performance of procalcitonin in a consecutive patient cohort with presumed IE. We found that procalcitonin was significantly higher in patients with IE than in patients with other final diagnoses. In addition, procalcitonin was the only significant independent predictor of IE on admission in multivariate analysis. The area under the ROC curve that used procalcitonin to predict IE was 0.856 (95% CI 0.750 to 0.962). This accuracy is comparable to that of B-type natriuretic peptide in the emergency diagnosis of heart failure.6 These findings suggest that procalcitonin may be a valuable additional diagnostic marker in the diagnosis of IE. Obviously, our observations need to be confirmed in further studies before definite recommendations can be made regarding the use of procalcitonin for the diagnosis of IE in general and the optimal cutoff value of procalcitonin in particular. The diagnosis of IE will continue to require a high level of suspicion, careful patient history, dedicated physical examination, and blood cultures in all patients. The procalcitonin level was found to be 0.19 ng/mL (range 0.10 to 1.22 ng/mL) in healthy subjects.8

Lamas and Eykyn7 suggested the addition of a high C-reactive protein level as a minor criterion for the diagnosis of IE. Several studies in different clinical settings have shown that procalcitonin may be a more accurate marker of systemic bacterial infection than C-reactive protein.5 Previous experience with procalcitonin in patients with IE is limited. Procalcitonin has been reported to be significantly higher in patients with IE than in healthy controls.5,9

In the present study, the presence of underlying heart disease did not predict IE. This finding is supported by data from a 1-year survey in France that showed that there was no previously known heart disease in 47% of cases.10 This changing profile of IE renders its diagnosis even more difficult. The current use of resources in the diagnosis of IE is suboptimal. Evidence of IE was detected on echocardiography in only 43% (8.6%) of 500 consecutive patients in a recent study.11 Our data suggest that the use of procalcitonin values
may help to improve the resource utilization of diagnostic imaging. In conclusion, procalcitonin may be a valuable additional diagnostic marker in patients with suspected IE.

References
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