Short communication

Influence of physical exercise and relationship with biochemical variables of NT-pro-brain natriuretic peptide and ischemia modified albumin

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Abstract

Background: The diagnostic approach and the clinical management of patients presenting with suspected acute coronary syndrome or cardiac dysfunction are as yet challenging. Although ischemia modified albumin (IMA) and natriuretic peptides were recently proposed for detection of myocardial ischemia and cardiac dysfunction, little information is available on preanalytical and metabolic sources of variability of these markers.

Methods: To establish the influence of a regular endurance training and the relationship with conventional biochemical variables, NT-pro-brain natriuretic peptide (NT-proBNP) and IMA were assayed, along with cardiac troponin T (cTnT), lactate dehydrogenase (LDH), creatine kinase (CK), creatinine and albumin, in 35 sedentary healthy individuals and 50 male professional road cyclists, 12–24 h following the last demanding training session.

Results: Athletes displayed higher values of both LDH (299 ± 61 vs. 257 ± 36 U/l, P = 0.002) and CK (184 ± 123 vs. 115 ± 74 U/l, P = 0.011), and slightly lower concentrations of creatinine (82 ± 12 vs. 87 ± 9 μmol/l, P = 0.044). No athlete or sedentary control displayed cTnT concentrations exceeding the lower sensitivity limit of the assay. As compared to the sedentary controls, main IMA concentration was increased in athletes (100 ± 13 vs. 94 ± 6 KU/l, P = 0.035), whereas that of NT-proBNP appeared significantly decreased (2.8 ± 1.6 vs. 4.3 ± 3.4, P = 0.005). The percentage of subjects displaying values exceeding the upper reference limit for the IMA assay was significantly different between athletes and sedentary controls (50% vs. 7%; P < 0.001). Pearson correlation analysis revealed an inverse association between IMA and albumin in both athletes (r = −0.640; P < 0.001) and sedentary controls (r = −0.583; P = 0.001).

Conclusions: Results of our investigation indicate that a demanding and regular aerobic training regimen, though able to trigger skeletal muscle sufferance, is not associated with any biochemical sign of severe and irreversible chronic cardiac involvement. Moreover, we suggest the adoption of specific IMA diagnostic thresholds following patients’ stratification according to serum albumin concentration and physical activity.

Keywords: Heart failure; Acute coronary syndrome; Physical exercise; Sport; Ischemia modified albumin; Natriuretic peptides

1. Introduction

The diagnostic approach and the clinical management of patients presenting with acute coronary syndrome and cardiac dysfunction are as yet challenging [1]. Over the past decades, several biomarkers were proposed to identify patients with true myocardial ischemia and risk stratification of heart failure. The ischemia modified albumin (IMA) [2] and the natriuretic peptides [3] were recently proposed as reliable markers for early detection of myocardial ischemia and cardiac dysfunction, respectively. During ischemia, the generation of reactive oxygen species influences the metal-
binding capacity of albumin for transition metals, like cobalt. It has been recently hypothesized that IMA generation in vivo might be interpreted as an efficient endogenous signal or mechanism of response to ischemia, preventing myocardial damage or limiting the burden of myocyte necrosis [4]. On this premise, any IMA increase preventing myocardial damage or limiting the burden of endogenous signal or mechanism of response to ischemia, generation in vivo might be interpreted as an efficient cobalt. It has been recently hypothesized that IMA binding capacity of albumin for transition metals, like increase of both BNP and NT-proBNP levels in plasma[8].

2. Materials and methods

To establish the influence of a regular endurance training on cardiovascular function, cardiac troponin T (cTnT), NT-proBNP and IMA, along with lactate dehydrogenase (LDH), creatine kinase (CK), creatinine and albumin, were evaluated in 50 consecutive male professional road cyclists and further compared with 35 consecutive sedentary healthy individuals, matched for age and sex. Athletes reached our center in the middle of the competitive season, during a regular, high-workload period of aerobic training. All subjects recruited to the study gave a preliminary informed consent for being tested and were in a fasted state and athletes had rested for a period of 12–24 h since the last demanding training session or competition. Blood was collected in the morning in vacuum tubes containing no additives (Becton-Dickinson, Oxford, UK). After centrifugation at 1500×g for 10 min at room temperature, serum was separated, stored in aliquots and kept frozen at −70 °C until measurement. cTnT and NT-proBNP were assayed on Elecsys 2010 (Roche Diagnostics GmbH, Mannheim, Germany), whereas IMA, determined by a colorimetric assay (ACB, Ischemia Technologies, Denver, USA), LDH, CK, creatinine and albumin were measured on the Modular System P (Roche Diagnostics GmbH), employing proprietary reagents. The upper reference limit for the IMA assay for this study was established at 100 KU/l, as established in a previous evaluation [18]. Results of measurements and relative distribution of values were compared by Student’s t-test and chi-square analysis. The level of statistical significance was set at p<0.05. Pearson correlation analysis was used to quantify the degree of association between variables from the population studied.

3. Results

Main results of this study are synthesized in Table 1 (values are expressed as mean±standard deviation). As

<table>
<thead>
<tr>
<th></th>
<th>Sedentary controls</th>
<th>Professional road cyclists</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>35</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>29.3±2.6</td>
<td>28.9±2.9</td>
<td>0.580</td>
</tr>
<tr>
<td>Training regimen (h/day)</td>
<td>0.05±0.02</td>
<td>2.95±0.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.87±0.09</td>
<td>0.82±0.12</td>
<td>0.044</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>46.6±2.4</td>
<td>46.1±3.8</td>
<td>0.078</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>257±36</td>
<td>299±61</td>
<td>0.002</td>
</tr>
<tr>
<td>CK (U/l)</td>
<td>115±74</td>
<td>184±123</td>
<td>0.011</td>
</tr>
<tr>
<td>cTnT (ng/ml)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>–</td>
</tr>
<tr>
<td>IMA (KU/l)</td>
<td>94±6</td>
<td>100±13</td>
<td>0.035</td>
</tr>
<tr>
<td>NT-proBNP (pmol/l)</td>
<td>4.3±34</td>
<td>2.8±1.6</td>
<td>0.005</td>
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</tbody>
</table>

Differences are evaluated by Student’s t-test.
Table 2
Pearson correlation analysis between ischemia modified albumin (IMA), NT-pro-brain natriuretic peptide (NT-proBNP) and serum creatinine, albumin, lactate dehydrogenase (LDH), creatine kinase (CK), evaluated in professional road cyclists and matched sedentary healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Sedentary controls</th>
<th>Professional road cyclists</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>NT-proBNP vs. IMA</td>
<td>0.023</td>
<td>0.908</td>
</tr>
<tr>
<td>NT-proBNP vs. CK</td>
<td>0.061</td>
<td>0.762</td>
</tr>
<tr>
<td>NT-proBNP vs. LDH</td>
<td>−0.207</td>
<td>0.301</td>
</tr>
<tr>
<td>NT-proBNP vs. albumin</td>
<td>−0.158</td>
<td>0.430</td>
</tr>
<tr>
<td>NT-proBNP vs. creatinine</td>
<td>0.175</td>
<td>0.383</td>
</tr>
<tr>
<td>IMA vs. CK</td>
<td>0.038</td>
<td>0.852</td>
</tr>
<tr>
<td>IMA vs. LDH</td>
<td>0.114</td>
<td>0.571</td>
</tr>
<tr>
<td>IMA vs. albumin</td>
<td>−0.583</td>
<td>0.001</td>
</tr>
<tr>
<td>IMA vs. creatinine</td>
<td>−0.051</td>
<td>0.800</td>
</tr>
</tbody>
</table>

\( r \) = correlation coefficient.

expected, following the high workload aerobic training, athletes displayed higher values of both CK and LDH. Mean value of serum albumin was nonstatistically different between athletes and sedentary controls, whereas that of serum creatinine was significantly lower in athletes. The concentration of cTnT was always below the lower sensitivity limit of the assay in both athletes and controls. Main IMA concentration was significantly increased in athletes, whereas that of NT-proBNP appeared significantly decreased. In multiple linear regression analysis, higher LDH \((P=0.003)\) and decreased NT-proBNP \((p=0.047)\) values were the only biochemical covariables that significantly discriminated professional athletes from sedentary controls. The percentage of subjects displaying IMA values exceeding our upper reference limit (100 KU/l) was significantly different between athletes and controls (50% vs. 7%; \(P<0.001\)). No athlete or sedentary control exhibited values exceeding the age- and sex-specific NT-proBNP diagnostic threshold recommended by the manufacturer (>14.8 pmol/l). Pearson correlation analysis between the biochemical variables tested is shown in Table 2. Beside an inverse association between IMA and albumin in both athletes \((r=-0.640; \ P<0.001)\) and sedentary controls \((r=−0.583; \ P=0.001)\), no additional significant correlation could be observed. After stratifying the population according to the albumin threshold of 46 g/l, mean IMA concentrations below or above this arbitrary threshold appeared significantly different in both sedentary controls \((99±4 \ vs. 91±4 \ KU/l; \ P<0.001)\) and professional athletes \((106±14 \ vs. 93±8 \ KU/l; \ p<0.001)\).

4. Discussion

Although acute coronary syndrome and heart failure are the most frequent pathologies in western countries, diagnostic approach and differential diagnosis are as yet challenging [1]. Identification of preanalytical sources of variability is essential to avoid pitfalls in laboratory testing and becomes pivotal for the management of patients in the acute care setting, admitted with suspected cardiac pathologies. It was earlier determined that the adoption of sex-, race- and age-related reference limits is essential for clinical interpretation of results of natriuretic peptides measurement, and relative thresholds should be selected according to these demographic variables. Moreover, as renal failure is a potential cause of elevated BNP and NT-proBNP, even in the absence of left ventricular dysfunction, diagnostic thresholds of these markers should be preferably stratified according to renal function [19]. As for the natriuretic peptides, selection of accurate IMA diagnostic thresholds influences the efficient diagnosis of myocardial ischemia and prediction of cardiac outcomes [20]. Peculiarly, results of IMA measurements should be interpreted considering preanalytical sources of variations, such as the physical activity [18]. To our knowledge, this is the first study attempting to establish whether a regular and demanding aerobic physical exercise in highly trained athletes may influence baseline NT-proBNP serum concentrations, as earlier investigations focalized mainly on healthy untrained individuals or patients with established heart failure. IMA and NT-proBNP levels were additionally related to conventional biochemical parameters, which are supposed to mirror renal (creatinine), liver (albumin) and muscle (CK, LDH) function. In agreement with previous investigations, we confirm that IMA generation might be slightly increased 12–24 h following a demanding physical exercise, in a percentage up to 50% of athletes subjected to a regular and demanding aerobic training (Fig. 1). Nevertheless, such an increase is on overall moderate, as most of these values are still comprised within the interval 100–115 KU/l. No significant association could be observed between IMA and conventional markers of muscular injury (Table 2). Therefore, increased IMA generation appears more justifiable with a transitory ischemic condition of the skeletal muscle during a vigorous training regimen, rather than with irreversible muscular damage or necrosis. Unfortunately, we cannot provide data on exercise ECG testing, dobutamine stress echography or scintigraphy. Therefore, although unmeasurable concentrations of cTnT at 24–48 h postexercise rule out irreversible myocardial injury as the primary cause of increased IMA generation in athletes, the possibility of a reversible cardiac ischemia cannot be definitively excluded.

Owing to heterogeneity in study design, clinical setting and timing of blood sampling after exercise, controversial observations emerged from IMA measurement in athletes [21–23]. Some previous investigations already showed a characteristic biphasic IMA response to strenuous exercise. In the first-period postexercise, there is a transient reduction, which has been primarily related to increased lactate generation and hemoconcentration. It has been demonstrated that increased lactate in the specimen generates an analytical interference on ACB testing; in particular, as lactate concentrations increased, IMA values decreased [22]. Accordingly, hemoconcentration increases several plasma
The acute and transient postexercise albumin reduction might be responsible for a fixed amount of cobalt added to albumin, acute values. As the ACB test quantifies the nonbound portion of the physiologic range produce an opposite change of IMA proteins, including albumin, and changes in albumin within the physiologic range produce an opposite change of IMA values. As the ACB test quantifies the nonbound portion of the physiologic range produce an opposite change of IMA proteins, including albumin, and changes in albumin within the physiologic range produce an opposite change of IMA values. As the ACB test quantifies the nonbound portion of the physiologic range produce an opposite change of IMA proteins, including albumin, and changes in albumin within the physiologic range produce an opposite change of IMA values.

Mechanic and neurohumoral stimulation of the heart, along with ventricular myocyte stretch in response to ventricular volume expansion, appear so far the main causes for equimolar increase of both BNP and NT-proBNP levels in plasma [25]. In a recent investigation, Kragelund et al. identified NT-proBNP as a marker of increased risk of left ventricular systolic dysfunction in patients with stable coronary artery disease [26]. Exercise-induced ischemia, or its associated regional wall-motion abnormalities, trigger the release of natriuretic peptides; measurement of plasma levels of both NT-proBNP and BNP before and immediately after symptom-limited exercise can help to distinguish patients with and without ischemia of cardiac origin with a high degree of accuracy [27]. There is as yet controversy on the potential onset of myocardial damage and diastolic left ventricular dysfunction following strenuous endurance exercise. Acute and significant postexercise increase of natriuretic peptides was observed in healthy men immediately after a marathon running [28,29].

Fig. 1. NT-pro-brain natriuretic peptide (NT-proBNP) and ischemia modified albumin (IMA) values distribution in sedentary healthy controls and professional road cyclists. The central horizontal line indicates the mean value.

Although these results are partially in agreement with those of Scharhag et al., the difference in NT-proBNP values reached a marginal statistical significance as a probable consequence of the greater number and the more homogenous training profile of the endurance athletes enrolled in our study. This finding is also consistent with a short half-life in plasma which, along with undetectable cTnT levels since the last competition or demanding training session, demonstrating that NT-proBNP concentrations are slightly lower when compared to a sedentary untrained population.
cardiac remodeling in well-trained endurance athletes, we can see that the evidence that no athlete or sedentary control displayed NT-proBNP values exceeding the age- and sex-specific upper reference limit of the assay, providing a reliable explanation for the discrepancies observed with previous investigations, especially those that have measured BNP instead of NT-proBNP.

NT-proBNP is established as a reliable diagnostic and prognostic marker in patients with suspected heart failure. Chronic elevations of natriuretic peptides are a useful biochemical tool to identify and monitor cardiac dysfunction. It has been earlier suggested that a vigorous physical activity might elicit cardiovascular complications not present at rest, mainly due to hemodynamic and electrophysiological changes brought about by exercise in the susceptible individual [17]. In agreement with earlier investigations, we provide evidence that a demanding and regular aerobic training regimen, though able to trigger some apparent skeletal muscle injury, is not associated with any biochemical sign of severe and irreversible chronic cardiac involvement and NT-proBNP may be a useful tool to discriminate between physiological and pathological cardiac remodeling in well-trained endurance athletes [31,32].

References


