Circadian Variation in Serum CrossLaps Concentration Is Reduced in Fasting Individuals

To the Editor:
Accurate assessment of bone resorption may be of significant value for selecting women for antiresorptive therapy, monitoring of therapeutic response in treated individuals, and predicting fracture risk (1). This goal may be facilitated by measurement of biochemical markers of bone metabolism. The Serum CrossLaps™ One Step ELISA measures fragments derived from the C-terminal telopeptide of collagen type I. This assay has been shown to provide a sensitive and specific index of bone resorption (2, 3).

An important issue for the use of biochemical markers is biological variability. This has been reported to be relatively high for specific markers of bone resorption. A recent letter by Wichers et al. (4) reports on the circadian variation in serum CrossLaps concentration in young males. Similar to what has been found for other specific markers of bone resorption, they report a pronounced circadian variation in serum CrossLaps concentration, with a nocturnal peak and a daytime nadir (5, 6). The amplitude of the variation was reported to be 60–66% of the mean values observed over the 24-h observation period. The six study subjects were allowed to eat and drink throughout the experiment.

In this letter, I show that fasting can have a pronounced effect on the circadian variation of markers of bone resorption. Fig. 1 shows the circadian variation in serum CrossLaps concentration in 11 premenopausal women who were subjected to a randomized crossover study. In one part of the study, the women fasted overnight (2200–0800) before initiation of the study, but were then allowed to eat and drink without restriction during the 24-h study period. In the other part of the study, they fasted from 10 h before the study and then 24 h throughout the study. Serum samples were obtained at 3-h intervals throughout the study and measured in the Serum CrossLaps One Step ELISA. The results are shown as the average percentage of the individual mean (± SE) for the two groups (Fig. 1). In fasting individuals, the average variation was ± 13.6%, whereas the variation under nonfasting conditions was ± 34%. The maximum changes from the 24-h mean were 20.3% and 44.8% for fasting and nonfasting women, respectively. Especially pronounced was the change in serum CrossLaps concentration seen in nonfasting women in the period from 0800 to 1100. Wichers et al. (4) also reported a similar pronounced decrease in this time interval for nonfasting men. However, the change in serum CrossLaps concentration in this time interval in fasting women was significantly lower.

From these results, we can conclude that the circadian variation of serum CrossLaps concentration is significantly lower in fasting than in nonfasting individuals. Thus, measurement of serum CrossLaps in morning fasting samples significantly reduces individual variability of the marker compared with measurement of serum samples from nonfasting individuals. Morning samples from individuals who have been fasting overnight are easily obtained in a clinical setting because this practice is used for several other common laboratory measures.

Wichers et al. (4) are right to conclude that control of sampling time is important in reducing individual variability in specific measures of bone resorption, but an equally or more important issue is to obtain samples from fasting individuals.

References

Stephan Christgau
Osteometer Biotech A/S
DK-2730 Herlev, Denmark
E-mail stephan_christgau@osteobio.dk

Premetrological Variation of Thyrotropin, Thyroxine (Non-Protein Bound), and Triiodothyronine Concentrations in Serum

To the Editor:
The premetrological (preanalytical) phase is a recognized potential source of variation (1) that includes the variation attributable to sample collection, handling, centrifugation, and storage conditions. It is widely accepted that premetrological varia-
Table 1. CVs corresponding to premetrological variation at physiological concentrations (CVPM).

<table>
<thead>
<tr>
<th>Serum component</th>
<th>Mean concentration</th>
<th>$s_{\text{w}}^a$</th>
<th>$s_{\text{wM}}^b$</th>
<th>CVPM, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrotrpin</td>
<td>2.00 IU/L</td>
<td>0.077 IU/L</td>
<td>0.055 IU/L</td>
<td>2.7</td>
</tr>
<tr>
<td>Thyroxine (non-protein bound)</td>
<td>18.28 pmol/L</td>
<td>0.557 pmol/L</td>
<td>0.532 pmol/L</td>
<td>0.9</td>
</tr>
<tr>
<td>Triiodothyronine</td>
<td>1.85 nmol/L</td>
<td>0.072 nmol/L</td>
<td>0.071 nmol/L</td>
<td>0.6</td>
</tr>
</tbody>
</table>

$^a$ $s_{\text{w}}$, within-run metrological standard deviation plus premetrological standard deviation.

$^b$ $s_{\text{wM}}$, within-run metrological standard deviation.

Where $s_C^2$ is the analytical variance (within-run metrological variance plus premetrological variance); $x$ and $y$ are the results obtained for different samples from the same individual; and $n$ is the number of individuals.

For each quantity, the metrological within-run variance was calculated as:

$$s_{\text{wM}}^2 = \frac{\sum (z - z')^2}{2n}$$

Where $s_{\text{wM}}^2$ is the metrological within-run variance; $z$ and $z'$ are the replicate results; and $n$ is the number of individuals.

Finally, the premetrological variance was obtained by subtracting $s_{\text{wM}}^2$ from $s_C^2$. The CVs corresponding to premetrological variation, calculated using the mean of the 60 measurements done for each quantity, are shown in Table 1.

For serum thyroxine (non-protein bound) and triiodothyronine, the premetrological variation was negligible; however, for serum thyrotropin, the CV was not null. We conclude that the premetrological CV for thyrotropin measurements should be taken into account when estimating the uncertainty of measurement (3) of this analyte.

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References


Xavier Fuentes-Arderiu*
José María Gonzalez-Alba
Ferran Baltuille-Feiron
Miguel Angel Navarro-Moreno

Servei de Bioquímica Clínica
Ciutat Sanitària i Universitària de Bellvitge
08907 L’Hospitalet de Llobregat
Catalonia, Spain

*Author for correspondence. Fax 34-93-260-7546; e-mail xfa@csub.scs.es.

Response to “Increased Creatine Kinase MB and Cardiac Troponin T with Normal Cardiac Troponin I in Metastatic Alveolar Rhabdomyosarcoma”

To the Editor:

We wish to comment on the case reported recently by Isotalo et al. (1). Two different cardiac troponin I (cTnI) assays were used: the AxSYM (Abbott) and the Opus Plus (Dade Behring). The title of the letter claimed that the cTnI value was normal. This is not consistent with the data presented.

The AxSYM values for cTnI of 1.2 (day 1), 0.8 (day 2), and 1.1 μg/L (2 weeks) are not normal. The limit of detection for the AxSYM is 0.3 μg/L, with a quoted upper reference limit of 0.4 μg/L and an acute myocardial infarction cutoff of 2.0 μg/L (2). The patient’s values fall within the range for detectable and prognostically significant myocardial damage.

The main conclusion that Isotalo et al. (1) make is that the increased cardiac troponin T (cTnT) and creatine kinase MB (CK-MB) concentrations are the result of release from a non-cardiac source related to abnormal expression of these proteins. They did not perform experiments to detect evidence of abnormal cTnT or CK-MB expression in the tumor bi-
opsy. Therefore, we fully agree with the authors that their conclusions were “speculative”. However, we disagree with their discussion. The authors clearly state that the patient had no biochemical evidence of renal failure. However, they go on to describe, in detail, the findings of three conflicting studies that discuss the issue of skeletal muscle expression of cTnT in uremic patients. The reference to these studies in this case presentation implies that the authors are making an association with the issues of cTnT in patients with renal failure. We believe this to be a tenuous link between their limited study and the subject of skeletal muscle expression of cTnT in renal failure. In addition, we feel that they have either misread or misinterpreted two of the references dealing with this subject that they quote (3, 4).

The authors state that “Isoforms of cTnT have been identified in diseased skeletal muscle of chronic renal failure patients by Western blots and highly specific M7 and M11.7 monoclonal antibodies for cTnT (II, 12).” These monoclonal antibodies are the same ones that are used in the [Boehringer Mannheim] second-generation cTnT immunoassay”.

We disagree with this representation of the findings of the report by Ricchiuti et al. (3). In this report, positive immunoreactive bands were found with M11.7 in <45% of the samples measured, and <4.5% were found with M7. The bands did not correspond to the adult cTnT isoform. The authors specifically state that the intact adult cardiac isoform is not detected in skeletal muscle by the antibodies in the Roche assay.

The study by McLaurin et al. (4) demonstrated immunoreactive bands in four of five muscle samples from renal failure patients. However, the cTnT antibody in this study was JS-2 from Lakeland Biochemical, which is no longer available, and not the M7 or the M11.7 antibody, as stated by Isotalo et al. (1). The finding of Isotalo et al. has no relationship with cTnT expression in renal failure, and the specific citation of the Roche/Boehringer Mannheim antibodies M7 and M11.7 is inaccurate.

Isotalo et al. (1) also state that Haller et al. (5) were “unable to demonstrate cTnT mRNA expression in skeletal muscle...". This study clearly demonstrated, with control data, the absence of cTnT mRNA and cTnT protein, using two different experimental formats: Western blot and immunohistochemistry. It should also be stated that the study by Haller et al. (5) was in contrast to the two other references (3, 4).

The case presented by Isotalo et al. (1) was potentially interesting but incomplete. If tissue analysis of the tumor had been performed at the protein or molecular level, this would have contributed greatly to the subject of expression of cTnT in non-cardiac tissue.

We also would like to offer a possible explanation as to the causes of these high circulating concentrations of all three markers of myocardial damage. The patient received three cycles of doxorubicin, but the authors did not state the dosages (1). For nearly three decades, reports have appeared that describe the fatal cardiotoxic effects of this drug (6–8). Results from human subjects (9) and animal models of doxorubicin-induced myopathies (10, 11) have shown that these myopathies are directly related to serum concentrations of cTnT. It has even been suggested that monitoring of serum cTnT may be used to assess the severity of doxorubicin-related myocyte damage as an alternative to invasive procedures such as endomyocardial biopsy. The claim by Isotalo et al. (1) that the cTnI concentrations were not increased in this patient suggests that cTnI is not a sensitive enough marker to detect drug-induced cardiac damage, whereas CK-MB and cTnT may be.

References


Salim Fredericks* Paul O. Collinson2 David W. Holt2

2 Cardiological Sciences
Analytical Unit
St. George’s Hospital Medical School
Cranmer Terrace
London SW17 0RE, UK

3 Department of Chemical Pathology
St. George’s Hospital
Blackshaw Road
London SW17 0QT, UK

*Author for correspondence. Fax 44-208-767-9687; e-mail frederic@sghms.ac.uk.

The authors of the Letter cited above reply:

To the Editor:

We appreciate the interest that Fredericks et al. have shown in our letter (1). As mentioned previously, our
patient was a 53-year-old man with metastatic alveolar rhabdomyosarcoma who had increased cardiac markers detected after he developed atypical chest pain while being managed for deep venous thrombosis and inguinal lymph node metastases. In our letter, we erroneously stated that the patient’s AxSYM cTnI values were normal when in fact we should have stated that cTnI values were below the cutoff value for acute myocardial infarction (AMI; ≈2.0 μg/L). In addition to being below the cutoff for AMI, our patient’s cardiac troponin I (cTnI) values were within the 95th percentile of cTnI for non-AMI patients (≈2.4 μg/L), as described by Apple et al. (2).

It is unfortunate that Fredericks et al. have either disregarded or misunderstood our previous discussion regarding cTnT expression and chronic renal failure (1). Ricciuti et al. (3) have clearly demonstrated cTnT isoform expression in skeletal muscle from patients with chronic renal disease. Fredericks et al. cannot dismiss this expression of skeletal muscle cTnT isoforms. Although this cTnT isoform expression does not produce false-positive results in the second-generation Boehringer Mannheim cardiac troponin T (cTnT) assay (3), the discovery that skeletal muscle may re-express cTnT isoforms under certain conditions is significant. The study by McLaurin et al. (4) also confirmed cTnT expression in skeletal muscle from hemodialysis patients by use of Western blots and J5-2 antibodies. We erroneously stated that they had used M7 and M11.7 antibodies for their immunologic detection of cTnT.

Skeletal muscle cTnT expression is not restricted to patients with chronic renal disease; it has also been described in the skeletal muscle of patients with Duchenne muscular dystrophy (5). It is clear that Fredericks et al. fail to understand the significance of skeletal muscle cTnT re-expression with respect to our patient. If “diseased” skeletal muscle can re-express an immature, fetal phenotype, as manifested by cTnT re-expression (3), it is very reasonable, and in fact logical, to expect that neoplasms with features of skeletal muscle differentiation may also express cTnT isoforms. In addition, anaplastic tumors are genetically unstable, and because of lack of differentiation, they may elaborate proteins that are not usually expressed by their benign tissue counterparts.

With respect to possible doxorubicin cardiac toxicity, our patient had no clinical evidence of cardiomyopathy. Our patient received a total doxorubicin dose of 180 mg/m². Histologic evidence of myocardial toxicity has been identified in endomyocardial biopsies of patients who have been treated with total doxorubicin doses as small as 250 mg/m² (6). The risk of doxorubicin-induced cardiomyopathy is dose dependent (7,8), with cardiomyopathy developing in 30% of patients once total doxorubicin doses of 550 mg/m² have been attained (8). It is unlikely that our patient would have ever developed a doxorubicin-induced cardiomyopathy, considering his relatively small total dose of doxorubicin.

In addition to overt cardiomyopathy, it has been suggested that patients treated with doxorubicin may also develop subclinical cardiac toxicity, as evidenced by increased serum troponins, cTnT and cTnI, and cardiac uptake of radiolabeled antimyosin antibodies (7,9–11). Lipshultz et al. (9) studied 15 children with acute lymphoblastic leukemia who underwent doxorubicin chemotherapy and demonstrated increases in cTnT post anthracycline chemotherapy. None of these patients showed significant increases in creatine kinase (CK), CK-MB, or myoglobin. Anthracycline-treated patients of Missov et al. (11) had postanthracycline cTnI increases attributed to subclinical myocyte toxicity, also with no significant increases in CK-MB or myoglobin. Despite the suggestion by Fredericks et al., our patient’s sustained increased CK concentrations and his grossly disproportionate increase in CK-MB are inconsistent with both doxorubicin-induced cardiac toxicity and acute cardiac ischemia. A CK concentration of 1364 U/L, a CK-MB mass of 1047 μg/L, a remarkable CK-MB index of 77, and a cTnT concentration of 2.49 μg/L post tumor radiotherapy, cannot be explained by toxic doxorubicin therapeutic effects, especially considering that these markers were measured 5 months after the patient’s last chemotherapy cycle. In addition, our patient had a CK-BB of 25 U/L before his radiotherapy. Ongoing tumor necrosis, especially post radiotherapy, and increased tumor mitotic activity with high neoplastic cell turnover more likely explain these increased values. An association between our patient’s biochemical results and doxorubicin-induced cardiotoxicity seems inconceivable. In our experience, disproportionate increases in CK-MB in relation to total CK, along with the detection of substantial quantities of CK-BB, cannot be explained by a cardiac source.

References
10. Lipshultz SE, Grenier MA, Colon SD. Doxorubi-
We examined two methods for cell isolation as applied to three types of specimens before detection of tumor cells by immunocytochemistry or RT-PCR (5).

We analyzed 254 samples consisting of 90 bone marrow aspirates, 104 granulocyte colony-stimulating factor-mobilized stem cell samples harvested at steady-state hemopoiesis, and 60 venous blood samples. Samples were from patients with high-risk breast cancer (n = 237), large bowel cancer (n = 13), gastric cancer (n = 2), ovarian cancer (n = 1), and salivary gland cancer (n = 1). Samples were assigned without conscious bias to nucleated cell separation either by ficoll centrifugation (30 min at 400g without brake) or by ammonium chloride-mediated red cell lysis (RCL). For RCL samples were diluted 1:10 with RCL buffer (155 mmol/L NH4Cl, 10 mmol/L KHCO3, 0.1 mmol/L EDTA), incubated for 3–5 min, and centrifuged. Washed cells were counted and subjected to cytopsin.

For immunocytochemistry, cells of the isolated fraction were spun onto slides, using a centrifuge from Heticch. A median of two slides (1–3) were prepared from each sample. Cytokeratin-positive cells were detected with antibody KL1 (Coulter-Immunotech). The median cell count examined was 2 × 10^6 (mean, 1.85 × 10^6) with a range from 1 × 10^6 to 1 × 10^5. Labeled cells were detected by a biotinylated secondary antibody and a streptavidin-alkaline phosphatase procedure. Breast cancer cell lines MCF-7 and MDA-MB453 were used as positive controls, and nucleated cells from non-cancer patients were used as negative controls. Slides were evaluated by light microscopy, and positive cells were counted (2).

For RT-PCR, messenger RNA was measured in 2 × 10^6 nucleated cells from 89 samples (bone marrow, n = 38; leukapheresis, n = 19; and peripheral blood, n = 32) as described previously (4).

Data were analyzed using the computer software WinSTAT (Kalmia). For the comparison of two groups, the Mann–Whitney U-test was used. To compare the tumor cell count detected in different samples, the relative tumor cell count per 10^6 cells examined was calculated.

Tumor cells were detected in more bone marrow samples after RCL compared with ficoll centrifugation (P = 0.045; Table 1). For blood samples, a similar but nonsignificant trend was seen (42% vs 31%). Surprisingly, there were no differences between RCL and ficoll centrifugation for leukapheresis samples or for tumor cell detection by CK19 RT-PCR.

Similarly, the number of tumor cells identified/10^6 cells was higher after RCL for all 254 samples (P = 0.05) and for bone marrow aspirations (P = 0.05). For venous blood samples and apheresis samples, nonsignificant trends were seen (Table 1).

The present data are derived from

### Table 1. Nominal results.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Separation method</th>
<th>No. of samples</th>
<th>Positive, %</th>
<th>P</th>
<th>Mean TC^a</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>RCL</td>
<td>154</td>
<td>51</td>
<td>0.02</td>
<td>1.3</td>
<td>2.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>RCL</td>
<td>56</td>
<td>55</td>
<td>0.05</td>
<td>2.0</td>
<td>4.0</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>FIC</td>
<td>34</td>
<td>44</td>
<td></td>
<td>1.3</td>
<td></td>
<td>2.1</td>
</tr>
<tr>
<td>Leukapheresis</td>
<td>RCL</td>
<td>86</td>
<td>44</td>
<td>0.49</td>
<td>0.9</td>
<td>1.3</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>FIC</td>
<td>18</td>
<td>44</td>
<td></td>
<td>1.2</td>
<td></td>
<td>2.1</td>
</tr>
<tr>
<td>PB</td>
<td>RCL</td>
<td>12</td>
<td>42</td>
<td>0.25</td>
<td>1.1</td>
<td>1.7</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>FIC</td>
<td>48</td>
<td>31</td>
<td></td>
<td>0.9</td>
<td></td>
<td>1.8</td>
</tr>
<tr>
<td>PCR samples</td>
<td>RCL</td>
<td>21</td>
<td>43</td>
<td>0.49</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FIC</td>
<td>68</td>
<td>43</td>
<td></td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^a Significances were calculated using the Mann–Whitney U test.

^b TC, tumor cells per 10^6 cells investigated; RCL, red cell lysis; FIC, ficoll centrifugation; PB, peripheral blood; NA, not applicable.
clinical samples. The alternative of working with dilutions of cell lines suffers from a major disadvantage because circulating tumor cells vary widely in size, shape, weight, and antigen expression, whereas tumor cells from cultured lines are very homogeneous in these variables. Thus, the results from such a model system may not predict results with clinical specimens (6).

The lower detection rate and lower counts of cancer cells after ficoll centrifugation suggest a significant loss of cancer cells during processing of marrow samples. However, the possibility of antigen loss during ficoll centrifugation needs consideration in future studies. For leukapheresis samples, by contrast, there was no difference in the nominal detection rate (44%), and the yield of detected tumor cells was slightly, although not significantly, higher after ficoll separation. This could be attributable to the lower presence of erythrocytes in apheresis samples, specimens with extremely high white-cell counts, than in marrow or blood samples.

For PCR detection, the separation protocol had no influence on the detection rate. Culture experiments revealed that it is not always possible to culture viable cells from samples that are tumor cell-positive by other methods. One could hypothesize that RT-PCR also detected free mRNA liberated from apoptotic cancer cells, but this must be demonstrated.

We conclude that separation of nucleated cells by RCL from marrow or blood samples is superior to ficoll separation for the immunochemical detection of cancer cells, but that neither technique offers a clear advantage for leukapheresis samples or for RT-PCR analysis of any of these sample types.

We thank Anita Badbaran for excellent technical assistance and the Deutsche Krebshilfe for the support of the clinical trial.

References


William Krüger*
Roman Jung
Nicolaus Krüger
Kai Gutensohn
Walter Fiedler
Michael Neumaier
Fritz Jänicke
Christoph Wagener
Axel R. Zander

1 Bone Marrow Transplantation Center, 2 Department of Clinical Chemistry, 3 Blood Transfusion Service, 4 Department of Oncology/Hematology, and 5 Department of Gynecology and Obstetrics, University-Hospital Eppendorf Martinistrasse 52 20246 Hamburg, Germany

*Address correspondence to this author at: Einrichtung für Knochenmarktransplantation, Abteilung Hämatologie/Onkologie, Universitäts-Krankenhaus Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. Fax 49-40-42803-3795; e-mail krueger@uke.uni-hamburg.de.

Is Lipoprotein(a) Cholesterol a Significant Indicator of Cardiovascular Risk?

To the Editor:

In the July 1999 issue of Clinical Chemistry, Seman et al. (1) present reference ranges and prevalence data for lipoprotein(a) cholesterol [Lp(a)-C], based on the examination of offspring and spouses of participants of the Framingham Heart study. These data will be potentially useful provided that the determination of Lp(a)-C is included in routine cardiovascular risk assessment in the future.

Seman et al. (1) measured Lp(a)-C by nonspecifically trapping Lp(a) with a lectin and subsequently determining cholesterol enzymatically. They claim that their method, in contrast to immunoassays for Lp(a), was not sensitive to the genetic size polymorphism of apolipoprotein(a) [apo(a)]. This, however, has not been demonstrated conclusively. Thus, to date, there are no data available as to whether the apo(a) size polymorphism affects the binding of Lp(a) to the lectin matrix.

In 1995, we published a method to measure Lp(a)-C using a two-step procedure: (a) we first removed lipoproteins with a density <1.006 g/L by preparative ultracentrifugation; and (b) we then detected Lp(a) by electrophoresis of the infranate and subsequent cholesterol staining (2). In addition, we evaluated a commercially available agarose gel electrophoresis method that separated HDL, LDL, VLDL, and Lp(a) in one run (3, 4). Both of these methods are completely independent of the apo(a) size polymorphism, and they have the additional advantage that LDL-cholesterol (LDL-C) is already “corrected” for Lp(a)-C.

Immunoassays for Lp(a) differ widely from each other regarding their sensitivity to the apo(a) genetic polymorphism. Probably the least sensitive ones are enzyme-linked immunosorbent assays that use capture antibodies against apo(a) and detection antibodies against apoB (5, 6). To increase the accuracy and comparability of Lp(a) mass assays, an IFCC standard will soon be available in which the Lp(a) concentration is expressed in mmol/L. This standard will not, however, eliminate the problem that Lp(a) mass determinations are affected by the apo(a) polymorphism because it will be used in...
connection with assays of varying architecture that are themselves influenced by the size of apo(a). In addition, the current cutoff values of the National Cholesterol Education Program (NCEP) guidelines already account for the bias of LDL-C by Lp(a)-C (7). The question, however, of whether quantification of Lp(a) in terms of cholesterol will be preferable over immunoassays will probably not be answered on the basis of methodical considerations only. Instead, this will depend on the ability of this marker to identify subjects at an increased risk for coronary artery disease (CAD) better than Lp(a) protein determination performed by methods independent of the apo(a) size polymorphism. From this point of view, we miss in the publication by Seman et al. (1) the discussion of our reports, in which we measured Lp(a)-C directly using electrophoretic techniques (2, 4).

Using our combined ultracentrifugation and electrophoresis assay, we performed a case-control study that included 399 female and male subjects. Lp(a) mass was determined using a Behring nephelometer, using a polyclonal antibody (Instar). This method was standardized with a commercial calibrator (Immuno) (2). In that study, both Lp(a)-C and Lp(a) mass concentrations were significantly higher in patients with CAD demonstrated by coronary angiography than in healthy controls ($P < 0.05$). The odds ratios were 1.71 (95% confidence interval, 1.024–2.855) and 1.59 (95% confidence interval, 1.019–2.481) for Lp(a)-C and Lp(a) mass, respectively, suggesting that both methods have similar discrimination power. This was confirmed by virtually identical ROC curves. These data are very similar to the results of Seman et al. (1), who reported an adjusted odds ratio for Lp(a)-C of 2.293 in men.

Interestingly, in our study, the ratio of Lp(a)-C to Lp(a) mass tended to be lower in CAD patients than in controls ($P = 0.097$). The nephelometric assay used in this study was sensitive to the apo(a) size polymorphism, with larger apo(a) isoforms producing higher signals than smaller ones. Cross-sectional studies have shown that CAD patients possess smaller apo(a) isoforms than healthy individuals. Because our nephelometric Lp(a) immunoassay is influenced by the size of the apo(a) antigen, this would produce an increased Lp(a)-C/Lp(a) mass ratio in CAD patients if the amount of cholesterol per particle was not different between CAD and controls. However, the opposite was observed (2). This raises the question of whether Lp(a) particles from patients with CAD contain less cholesterol molecules, similar to atherogenic “small, dense” LDL particles (8). Regarding the average percentage of cholesterol content in Lp(a) particles, the averages (29.1% and 26.7%) we found in our studies (2, 4) are in good agreement with the average (27.5%) presented by Seman et al. (1). Seman et al. now have the data to answer the interesting question of whether the composition of Lp(a) is of predictive significance because they measured Lp(a) mass in addition to Lp(a)-C in a subset of 1000 samples, using an immunoassay that is not biased by the apo(a) polymorphism. If they are able to reproduce our finding suggesting the existence of small, dense Lp(a) particles, then the simultaneous assessment of Lp(a)-C and Lp(a) mass might represent a valuable tool to assess the contribution of Lp(a) to an individual’s risk of CAD.

References


Matthias Nauck*
Winfried März
Heinrich Wieland

University Hospital Freiburg
Department of Clinical Chemistry
Hugstetter Strasse 55
D-79106 Freiburg i. Br., Germany

*Author for correspondence. Fax 49-761-270-3444; e-mail manauk@med1.ukl.uni-freiburg.de.

Correction

On page 2130 of the article by V. Ricchiuti and F. S. Apple, entitled “RNA Expression of Cardiac Troponin T Isoforms in Diseased Human Skeletal Muscle” (Clin Chem 1999;45:2129–35), the correct sequence for the human skeletal muscle troponin (sTnT) reverse primer should be: 5‘-GTT TCA GCT TCG CCA TCA GGT CGA ACT-3‘.

The authors apologize for the error.