data are in agreement with previous reports dealing with the higher affinity of Hp 2-2, compared with Hp 1-1, for the CD163 receptor on macrophages. The more efficient uptake of the multimeric Hp molecules is reflected in the serum concentrations of free Hb.

The observed differences in free Hb between Hp phenotypes could help to explain the previously reported differences in oxidative stress markers among Hp phenotypes (3, 10).

In conclusion, we observed a marked relationship between free Hb concentrations in serum and Hp phenotypes. These findings further support the view of multimeric Hp forms in the clearance of the free Hb. In this regard, the Hp polymorphism is another caveat in the interpretation of free Hb values.

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Na Na¹
Jin Ouyang¹
Youri E.C. Taes²
Joris R. Delanghe²*

¹ Department of Chemistry
Beijing Normal University
Beijing, People’s Republic of China

² Laboratory Clinical Chemistry
Ghent University Hospital
Ghent, Belgium

*Address correspondence to this author at: Laboratory Clinical Chemistry, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium. Fax: 32-9-240-4985; e-mail joris.delanghe@UGent.be.

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Beliefs in Cardiac Troponin Testing

To the Editor:

In a recent editorial, Panteghini (1) asks whether there is a need to revise evidence-based beliefs regarding the currently recommended design of troponin immunoassays as a consequence of our recent and previous reports (2–4) on the occurrence of circulating anti-troponin antibodies, which can significantly distort patient results in existing cardiac troponin I (cTnI) assays. In response to some of the statements in the editorial, we wish to make some clarifying comments.

It is evident from our studies (5) that autoantibodies interfere most severely with the measurement of cTnI when the antibody combinations most frequently favored by commercial manufacturers are used. However, within the so-called stable mid fragment area (amino acids 30–110), some epitope combinations are less prone to this interference than others. Nevertheless, we do maintain that the present IFCC recommendation for antibody selection (6) clearly becomes inadequate in individuals with high titers of anti-troponin autoantibodies.

Panteghini (1) asserts that troponin testing would never have become the cornerstone for diagnosis of myocardial infarction (MI) if there had been false-negative results in a large proportion of patients. This statement is a misrepresentation of what we are claiming. Despite many methodologic difficulties, immunoassays for cardiac troponins have been extensively implemented in clinical routine and have replaced the other biochemical markers, particularly creatine kinase MB. This is mainly attributable to the fact that cardiac troponins are not usually found in the large majority of healthy persons by state-of-the-art analytical techniques. However, it is important that one acknowledges that with the adoption of the new definition of MI (7), which was spurred largely by the troponin assays themselves, the number of patients classified as having an MI has increased by an estimated 20%–30% (8, 9). In hindsight, these additional patients would have been false negatives in the pre-troponin era, i.e., missed by the evidenced-based belief of that time.

Against this background it may be wise not to categorically rule out the possibility that even today, with the multiple generations of troponin tests commercially available, cases of myocardial injury can be overlooked. This is a sound approach for reasons of general scientific caution, but is particularly pertinent considering the extensive analytical difficulties and challenges in troponin assay methodologies that we have witnessed over the past 10 to 15 years.

In fact, it has recently been demonstrated (10, 11) that troponin assays with high analytical sensitivity do not necessarily show equivalent performance in detecting minor cardiac injuries. These injuries, although not acutely fatal, are still important to detect because patients showing even minor leakages of troponins represent a group with increased short- and long-term risks for future adverse cardiac events. Neither should we forget the frequently acknowledged circumstance that 1%–2% of chest pain patients who are sent home have a subsequent MI and adverse outcomes (12).

Panteghini (1) also finds it difficult to understand that disturbing auto-
antibodies do not necessarily give rise to false negatives but may produce only partial inhibition. It is important that this misconception be rectified. Autoantibodies are characterized by their concentration (titer), their binding specificity (mono- or polyspecific), and their affinity (with variable on- and off-rate constants). Their inhibiting effect on the formation of the 2-site immunoassay complex is dependent on the same qualities of the immunoreagents used. The net effect is not an all-or-none or irreversible situation, but a result of at least 2 competing reactions that follow the law of mass action. Autoantibodies will have their highest inhibiting effect early during the release of troponins from the injured myocytes. As troponin release continues, the inhibiting effect will be gradually overcome.

According to our results (4, 13), one of the most noteworthy consequences of circumventing the inhibiting effect on cTnI assays by careful selection of assay design is unhindered recognition of the small and/or early cTnI releases in chest pain patients. The troponins have generally been considered markers of high specificity but with a relatively slow release. By combining high analytical sensitivity with assay designs that circumvent the interference from autoantibodies, we are confident that the troponins will be suitable as early markers similar to myoglobin, but with a superior specificity.

Regarding the doubts that Panteghini (1) still harbors in his editorial about the validity and importance of our findings, we do understand that changes in the official recommenda-

tions from regulatory bodies call for additional independent studies investigating large patient cohorts to determine the overall significance of troponin autoantibodies in differently designed, widely used immunoassays. Meanwhile, our priorities will continue to be investigations of mechanisms for anti-troponin antibody formation, further characterization of the fine specificities of the autoantibodies and their effect on assays of cTnI as well as troponin T (14), and exploration of possible correlations to cardiac disease etiologies. We also believe that closely related to this is the development of analytical tools with further improved detection limits. This will serve to promote the troponins toward their full clinical potential as cardiac markers.

References

Susann Eriksson* Kim Pettersson
Department of Biotechnology University of Turku Turku, Finland

*Address correspondence to this author at: Department of Biotechnology, University of Turku, Tykitöökatu 6A, FIN-20520 Turku, Finland. Fax 358-2-333-8050; e-mail susann.eriksson@utu.fi.

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