Letter to the Editor

Comparison of hs-cTnI, hs-cTnT, hFABP and GPBB for identifying early adverse cardiac events in patients presenting within six hours of chest pain-onset

To the Editor:

A recent publication comparing and assessing high-sensitivity cardiac troponin T (hs-cTnT) with heart-type fatty-acid binding protein (hFABP) at presentation in a pooled population of patients included in the FAST II (Fast Assessment of Thoracic Pain) and FASTER I (Fast Assessment of Thoracic Pain by nEuRal networks) studies indicated no incremental value for the diagnosis of myocardial infarction (MI) with the addition of hFABP to hs-cTnT [1]. An additional study in 3 centers in Germany on patients admitted with suspected acute coronary syndrome (ACS) to chest pain units also suggested limited utility of combining another early biomarker (glycogen phosphorylase BB; GPBB) with a sensitive cardiac troponin I (cTnI) assay for the diagnosis of acute MI [2]. However, neither of these studies assessed peak concentrations on early serial measurements (i.e., at presentation and 3 h, and 6 h later) for the diagnosis of MI as recommended by recent guidelines [3] or for predicting other short-term serious cardiac adverse events. Further work is needed here, as the pathophysiological role of GPBB, an enzyme of cellular metabolism, is believed to be released from its binding to glycogen during conditions of ischemia, which is then rapidly moved into circulation within the first hours of chest pain onset [2]. Moreover, hFABP, which is highly concentrated in the myocardium, is also rapidly released into circulation following myocardial injury [4]. Accordingly, to further delineate the role of early biomarkers (i.e., hFABP, GPBB) for identifying short-term serious adverse cardiac events in the presence of either hs-cTnT or hs-cTnI assays, we measured these early biomarkers in samples collected at presentation and 3 h and 6 h later in the emergency department (ED) in an early chest pain population.

The study population has been previously described [5] as well as the performance by the area under the curve (AUC) of hs-cTnI (AUC=0.86) and hs-cTnT (AUC=0.82) assays using the presentation sample for predicting a short-term adverse cardiac event [6]. Briefly, the inclusion criteria in the study were as follows: i) ≥18 years of age, ii) patients with possible ACS symptoms within 6 h before presentation, and iii) a cTnI ordered by an ED physician. On the other hand, patients were excluded if: i) they refused to participate, ii) were referred directly to trauma/surgery, or iii) had an outcome before the initial cTnI result. The study outcomes (composite adverse cardiac events within 72 h after presentation) were: MI, heart failure, serious arrhythmia, refractory ischemic cardiac pain, or death [5,6]. After obtaining research ethics board approval, available serum samples collected at presentation and 3 h and 6 h later in the ED were thawed and analyzed for hs-cTnT (Roche Elecsys 2010) and hs-cTnI (investigational-use only assay; Beckman Coulter Access II) (first thaw) and levels of hFABP and GPBB (second thaw) were measured (Randox Evidence Investigator). Analyses were then performed (with the Analyse-it and GraphPad Prism software) on the peak concentration for each biomarker (n=163 patients) to obtain the AUC (ROC curve analysis with the Delong-Clarke-Pearson method used for comparison), the diagnostic sensitivity, specificity, likelihood ratios (LR), positive predictive value (PPV), and negative predictive value (NPV) calculated using the reported 99th percentile cutoffs for each biomarker (hs-cTnT=14 ng/L [1,6]; hs-cTnI=10 ng/L [6]; hFABP=5.2 μg/L [4]; GPBB=7.88 μg/L [manufacturer]).

The average (standard deviation) age of the study cohort was 62 (15) years with 59% being males. Those patients with an adverse cardiac event (n=21) within 72 h after presentation had significantly higher peak biomarker concentrations as compared to those without an event (n=142) (median hs-cTnT=45 ng/L vs. 7 ng/L, p=0.0001; hs-cTnI=75 ng/L vs. 6 ng/L, p=0.0001; hFABP=4.6 ng/L vs. 2.6 ng/L, p=0.0007; GPBB=16.6 μg/L vs. 13.4 μg/L, p=0.0059; via Mann-Whitney test). ROC curve analyses indicated that hs-cTn, but not hs-TnT, had a significantly higher AUC as compared to either hFABP or GPBB (Fig. 1). When the 99th percentile cutoffs for the peak concentration were applied, only the dual combination of hs-cTnI>99th or GPBB>99th was able to identify all patients with an adverse cardiac event (sensitivity=100%; 95% CI: 82–100), albeit at a lower specificity of 32% (95% CI: 25–41) as compared to either biomarker alone (Table 1). By comparison, the dual combination of hs-cTnI>99th or hFABP>99th did not improve performance above hs-cTnI. Restricting the analysis to only those with a diagnosis of ACS (n=16; MI=11 and refractory ischemic cardiac pain=5) the dual combination of hs-cTnI>99th or GPBB>99th produced a sensitivity of 100% (95% CI: 77–100) with a specificity of 38% (95% CI: 31–47), similar to the performance of hs-cTnI combined with GPBB. On the other hand, for the combination of hFABP>99th with either hs-cTnI>99th or hs-cTnI>99th, the sensitivity for ACS diagnosis was only 81% (95% CI: 56–94).

The present analyses indicate that measuring either hs-cTnI or hs-cTnT at presentation and 3 and 6 h later in the ED and interpreting them based on guideline cutoffs (i.e., 99th percentile) cannot identify all patients that will experience an adverse cardiac outcome over the short-term. These data reinforce the need for clinical judgment in assessing low-risk patients presenting early after pain onset, irrespective of the cTn concentration obtained within the first 6 h in the ED. Moreover, these data also suggest that different hs-cTn assays may have different clinical characteristics. For instance, by ROC curve comparison only the hs-cTnI assay and not the hs-cTnI assay was superior to either hFABP or GPBB for diagnosing a short-term adverse cardiac event. A possible explanation may be the higher analytical sensitivity of the hs-cTnI assay as compared to the hs-cTnT assay as evidenced by more individuals with detectable concentrations in either a healthy reference population [7] or a stable high-risk population [8,9]. Additional studies should clarify what, if any, clinical differences exist between hs-cTnI assays in this setting.

Finally, the combination of GPBB, but not hFABP, with hs-cTnI assays appears to identify more patients at risk for short-term adverse
cardiac events. The ability to rule out any adverse cardiac event by 6 h as demonstrated by this dual combination needs to undergo subsequent testing in different and larger ED chest pain populations, and in comparison with other emerging biomarkers with possible roles in acute cardiac care [10]. The present data, although pilot in nature, does open the door to multimarker approaches for identifying ED patients at high-risk for a short-term cardiac outcome, even in the era of hs-cTn assays.

Conflict of interest

PK has received grants/consultant fees/honorariums from Abbott Diagnostics, Beckman Coulter, Randox Laboratories, and Roche Diagnostics. He is listed as an inventor on patents filed by McMaster University related to laboratory testing in acute cardiac care.

Acknowledgments

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References


Table 1
Clinical characteristics of the biomarkers using the 99th percentile cutoffs for identifying an adverse cardiac event within 72 h after presentation in patients with early ACS symptom onset.

<table>
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<tr>
<th></th>
<th>hs-cTnI</th>
<th>hs-cTnT</th>
<th>hFABP</th>
<th>GPBB</th>
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<td>Sensitivity</td>
<td>86%</td>
<td>81%</td>
<td>43%</td>
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<td>(59–92)</td>
<td>(24–64)</td>
<td>(45–83)</td>
<td>(65–96)</td>
<td>(59–93)</td>
<td>(82–100)</td>
<td>(76–99)</td>
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<tr>
<td>Specificity</td>
<td>63%</td>
<td>73%</td>
<td>80%</td>
<td>58%</td>
<td>65%</td>
<td>54%</td>
<td>65%</td>
<td>32%</td>
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<td>PPV</td>
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<td>30%</td>
<td>24%</td>
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<td>21%</td>
<td>26%</td>
<td>25%</td>
<td>19%</td>
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<tr>
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<td>96%</td>
<td>90%</td>
<td>92%</td>
<td>96%</td>
<td>96%</td>
<td>100%</td>
<td>98%</td>
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<tr>
<td>(95% CI)</td>
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<td>(91–99)</td>
<td>(84–95)</td>
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<td>0.29</td>
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Fig. 1. ROC curve analysis for the peak concentration of hs-cTnI, hs-cTnT, hFABP, and GPBB for identifying an adverse cardiac event within 72 h.

Contrast                  p-value
Peak hFABP v Peak GPBB   0.5344
Peak hFABP v Peak hs-cTnT 0.0680
Peak hFABP v Peak hs-cTnI 0.0044
Peak GPBB v Peak hs-cTnT  0.1080
Peak GPBB v Peak hs-cTnI  0.0136
Peak hs-cTnT v Peak hs-cTnI 0.0617
Colleen R. Shortt  
Departments of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada

Andrew Worster  
Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Stephen A. Hill  
Departments of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada

Peter A. Kavsak  
Departments of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada

Corresponding author at: Hamilton Regional Laboratory Medicine Program, Juravinski Hospital and Cancer Centre (Core Lab Section), 711 Concession Street, Hamilton, ON, Canada.  
Tel.: +1 905 521 2100; fax: +1 905 575 2581.  
E-mail address: kavsakp@mcmaster.ca.

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