High-sensitive cardiac troponin after CPAP in obstructive sleep apnoea: the adjusted analytical change limit (adjACL) for small variations at low concentrations

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Interpreting change in cardiac troponin after CPAP in OSA is challenging, especially since the lower the troponin concentration, the higher the analytical imprecision. In such cases, the adjusted analytical change limit (adjACL) should be used. https://bit.ly/3eaHcuq

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To the Editor:

Even below the 99th percentile upper reference limit (99PURL), elevated high-sensitive cardiac troponin concentration (hs-cTn) is associated with increased cardiovascular risk [1]. However, the lower the troponin concentration, the higher the analytical imprecision [2]. It is unclear to what extent a change in hs-cTn (Δhs-cTn) is significant between the limit of detection (LOD) and the 99PURL. Recently, Lui *et al.* [3] compared, through a randomised control trial, the effect of 8 weeks of continuous positive airway pressure (CPAP) on Δhs-cTnI in subjects with moderate-to-severe obstructive sleep apnoea (OSA) and hypertension. They showed a statistically significant variation compared to untreated subjects (adjusted mean difference $-1.74\ ng{\cdot}L^{-1}$; p=0.006). The adjusted mean hs-cTnI decreased from 5.6 to $4.8\ ng{\cdot}L^{-1}$ (−14.3%) after CPAP, and increased from 7.9 to $8.5\ ng{\cdot}L^{-1}$ (+7.6%) in the control group. These values are above the LOD of $1.2\ ng{\cdot}L^{-1}$, but are close to the limit of quantification of $5\ ng{\cdot}L^{-1}$ (hs-cTnI reagent kit 3P25, Abbott, Chicago, IL, USA). From a diagnostic standpoint, at the individual scale, the reference change value (RCV) concept assumes that the change between two serial results is significant if greater than the sum of the variations for each result. These variations are mostly analytical (analytical coefficient of variation, CVa) and biological (intra-individual, CVi) [2]. Considering two serial results, the RCV is equal to $Z\times((CVa_1^2+CVi_1^2)+(CVa_2^2+CVi_2^2))^{1/2}$, with Z=1.96 for a probability of change of 95%. Considering only analytical imprecision, which mainly depends on assay methods and analysers, as the minimal unavoidable variation, and applying it to serial results, the adjusted analytical change limit (adjACL) is equal to $\pm1.96\times(CVa_1^2+CVa_2^2)^{1/2}$ [4]. To test whether the Δhs-cTnI observed after 8 weeks of CPAP was greater than the adjACL of hs-cTnI, we used CVa for hs-cTnI concentrations ranging from 50 to $1\ ng{\cdot}L^{-1}$ (mean imprecision profile), provided in the supplementary data from [2], and measured on an Architect Abbott analyser, as did Lui *et al.* [3]. The regression equation of the best-fit curve was CVa=3.997+(28.17/hs-cTnI) (figure 1). Applying this formula on serial hs-cTnI means of 5.6 and $4.8\ ng{\cdot}L^{-1}$ (before and after CPAP), the adjACL was ±26.2%. Hence, at such low concentrations, the Δhs-cTnI of −14.3% is within the adjACL, meaning that the effect of CPAP is not great enough to decrease troponin more than analytical variability. According to this model, a decrease from 5.6 to at least $4.0\ ng{\cdot}L^{-1}$ (Δhs-cTnI $\leqslant$−28.6%, *i.e.* out of adjACL ±28.0%) would have been considered as significantly due to CPAP, at least in part. As expected, Δhs-cTnI of the control group (7.9 to $8.5\ ng{\cdot}L^{-1}$, +7.6%) remains within the adjACL, calculated at ±20.6%. As demonstrated, the closer the concentrations are to the

LOD, the greater the imprecision. This regression model reflects real analytical imprecisions for low ranges of hs-cTnI in the laboratory, with concentrations of 10%CV and 20%CV at 4.7 and 1.8 $ng \cdot L^{-1}$ [5]. Another analytical consideration is lot-to-lot bias between hs-cTnI reagents and/or calibrators, which can occur over weeks and could partly bias the mean difference of $-1.74\ ng \cdot L^{-1}$ observed by Lui *et al.* [3]. Illustrating this, Wu *et al.* [6] recently showed for Abbott hs-cTnI a lot-to-lot bias at low ranges (below $5.4\ ng \cdot L^{-1}$) between -1.7 to $+2.3\ ng \cdot L^{-1}$. A large difference of $2.5\ ng \cdot L^{-1}$ between two successive lots was even observed (from 4.7 to $7.2\ ng \cdot L^{-1}$), leading the authors to conclude that "a total analytic error $<3.5\ ng \cdot L^{-1}$ for long-term studies with hs-cTnI concentrations $<10\ ng \cdot L^{-1}$ could prevent erroneous reporting of results" [7]. This bias is advantageously considered in the adjACL, since it is also determined over the course of weeks.