Origin of Cardiac Troponin T Elevations in Chronic Kidney

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Plasma concentrations of cardiac troponins, the preferred biomarkers for the diagnosis of acute myocardial infarction, are often persistently elevated in patients with chronic kidney disease (CKD). The origin of these elevations is unknown: Is it the heart, by increased release, or the kidneys, by decreased renal elimination? In clinical practice, this equivocal view on troponin elevations in patients with reduced glomerular clearance underlies countless clinical discussions among physicians and may delay rapid initiation of adequate treatment when these patients present with chest pain.

In the present study, we aimed to discriminate between increased cardiac release and reduced renal elimination as the main process underlying this phenomenon. Specifically, we used the recently demonstrated rhythmic diurnal oscillation pattern of troponin T as a model to assess the contribution of impaired renal elimination to persistently elevated cardiac troponin levels in patients with CKD.[1] The diurnal troponin T rhythm is characterized by gradually decreasing concentrations throughout daytime and rising concentrations during nighttime.[1] If decreased renal clearance, and not increased production, is the key driver of elevated troponins in patients with CKD, the increased half-life and subsequent accumulation of cardiac troponin T will fade its diurnal rhythm.[2]

To test this hypothesis, we conducted hourly blood sampling over 1 full day (24 hours) in 44 individuals: 20 reference subjects (16 male, 4 female; median estimated glomerular filtration rate [eGFR] 82.8 mL·min^{-1}·1.73 m^{-2} [68.0–92.7 mL·min^{-1}·1.73 m^{-2}]) and 24 subjects with impaired renal function (eGFR <60 mL·min^{-1}·1.73 m^{-2}; 17 male, 7 female; median eGFR, 18.3 mL·min^{-1}·1.73 m^{-2} [14.2–32.2 mL·min^{-1}·1.73 m^{-2}]). All included subjects had detectable cardiac troponin T concentrations (median concentration reference group, 14.1 ng/L [10.4–20.6 ng/L] versus 20.5 ng/L [18.0–24.6 ng/L] in subjects with impaired renal function; P=0.009). With the use of cosinor rhythmometry, diurnal troponin T curves were fitted and expressed as deviation (percent) from their 24-hour mesor troponin concentration. Cardiac troponin T concentrations over the day in the reference subjects fitted a cosinor model (Figure, A; individual curves[1]: range R^2=0.23–0.91; all P<0.001). Next, we used a validated mathematical framework on the dynamics of diurnal rhythms to examine the hypothetical effect of prolonged elimination times caused by impaired renal function on the rhythmic oscillation of cardiac troponin T. This model is extensively described elsewhere.[2] As depicted in Figure, B, an 80% decrease in renal elimination (based on the eGFR in the CKD group) would theoretically reduce the cardiac troponin T amplitude on the group level from 12% to 8%. Finally, to examine whether the predicted faded rhythm was evident in subjects who actually have an 80% decreased renal elimination rate, the diurnal troponin T rhythm was analyzed in 24 participants with impaired renal function. In Figure, C, we demonstrate identical cosinor patterns for all subjects with amplitudes similar to those observed in the reference group (12.0±0.5% versus 11.4±0.5%; P=0.53), excluding a major

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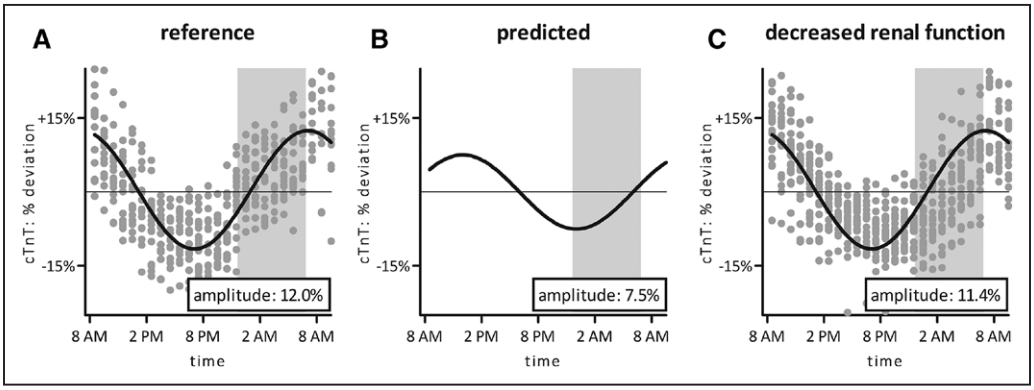

Figure. The effect of decreased estimated glomerular filtration rate (eGFR) on the diurnal rhythm of cardiac troponin T (cTnT).
The diurnal rhythm of cTnT. **A**, All individual data points and cosine curve on the group level of the reference population. **B**, The mathematically predicted cosine curve for a group with an 80% decrease in eGFR. **C**, All individual data points and cosine curve on the group level for the group with decreased renal function.

role for impaired renal elimination as the main cause of persistently elevated cardiac troponin T levels in CKD. The observed rhythm was not abrogated by the use of loop diuretics, nor was the circadian pattern of cardiac troponin T correlated with the circadian pattern of 24-hour blood pressure measurements, cortisol, thyroid-stimulating hormone, or testosterone (data not shown). Meanwhile, the amplitude of cystatin C, an analyte that also has a diurnal rhythm and with an established renal elimination route, was significantly faded among subjects with decreased renal function compared with the reference group. Its mathematically predicted amplitude in subjects with impaired renal function matched the observed amplitude in these subjects, supporting the validity of the mathematical model (amplitude cystatin c reference group, 3.9±0.2% versus 1.7±0.2% in subjects with impaired renal function; $P<0.001$; mathematically predicted amplitude, 2%).

Although we cannot exclude small amounts of renal elimination of cardiac troponin T,[3] the nonfading diurnal rhythm in subjects with decreased eGFR implies that diminished renal clearance with subsequent accumulation of troponin is not the key driver of high troponin levels in CKD. Accordingly, our findings strongly suggest that factors other than renal elimination, most likely increased release of cardiac troponins from the heart as a result of (subclinical) myocardial injury, contribute to elevated troponin T levels in subjects with CKD. This is in line with epidemiological evidence showing strong and robust associations between decreased renal function and cardiovascular risk.[4,5]

In conclusion, our results indicate that impaired renal elimination is not the main driver behind persistently elevated cardiac troponin T levels and emphasize the importance of extensive diagnostic workup in all patients with elevated cardiac troponin concentrations, regardless of their eGFR.

The present study was carried out according to the principles of Helsinki, approved by the Institutional Review Board and Ethics Committee, and registered at ClinicalTrials.gov (Unique identifiers: NCT02091427 and NCT02210897). All participants provided written informed consent.

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DISCLOSURES

None.

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FOOTNOTES

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