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How is cardiac troponin released from cardiomyocytes?

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Cardiac-specific troponin I (cTnI) and cardiac-specific troponin T (cTnT) are released following cardiac injury and are the preferred diagnostic biomarkers when acute myocardial infarction (MI) is suspected. Because cardiomyocytes are filled with sarcomeres that start to contract and consume adenosine triphposhate (ATP) whenever Ca^{2+} enters the cell, cardiomyocytes are more prone to undergo necrosis compared with other cells. In early studies, it was noted that other cell types such as endothelial cells and fibroblasts survived although all cardiomyocytes showed contraction band necrosis after 2 h of cardiac ischaemia followed by reperfusion in dogs.[1] As the cTnI:cTnT complex binds tightly to the cardiac sarcomere, its release is dictated by local proteolysis, which separates cTnI from cTnT (*Figure 1A* and *B*). As cTnI has no affinity for the sarcomere on its own, its degradation products are more quickly released compared with cTnT that remains bound[2] and is for the most part degraded locally together with the insoluble material in the necrotic cardiomyocyte.[3] For that reason, cTnI reaches much higher plasma levels compared with cTnT following MI with reperfusion.

Cardiac troponin elevations are also observed in conditions without obvious necrotic cardiac damage. Striking examples are the transient troponin elevations seen following strenuous exercise and after ischaemia lasting only a few minutes.[4] Early experiments on isolated rat hearts before the troponin era show that only 5% of the creatine kinase released following limited ischaemia could be explained by the few necrotic cardiomyocytes that were found.[5] In these instances, cTnT and cTnI are often elevated to similar levels.

Possible mechanisms involved in protein release from cardiomyocytes subjected to sublethal stress include bursting and resealing of small membranous blebs formed in response to cell swelling and active exocytosis (*Figure 1C*). A recent study shows that cardiac myocytes can release large extracellular vesicles derived from autophagy which have been termed 'exopheres' containing mitochondria and sarcomere fragments. Cardiomyocytes appear to exocytose exopheres to get rid of damaged mitochondria and sarcomere proteins as part of its normal maintenance, and this process is enhanced in cardiomyocytes during conditions of cardiac stress.[6] Conceivably, this autophagy mediated exocytosis can then result in release of sarcomere proteins like troponin into the circulation that will be higher after sublethal stress but never-the-less present under normal conditions.

An appreciation of the mechanisms through which cTn is released from cardiomyocytes will help clinicians to interpret elevated cTn in acute MI and other clinical settings associated with cardiac stress.

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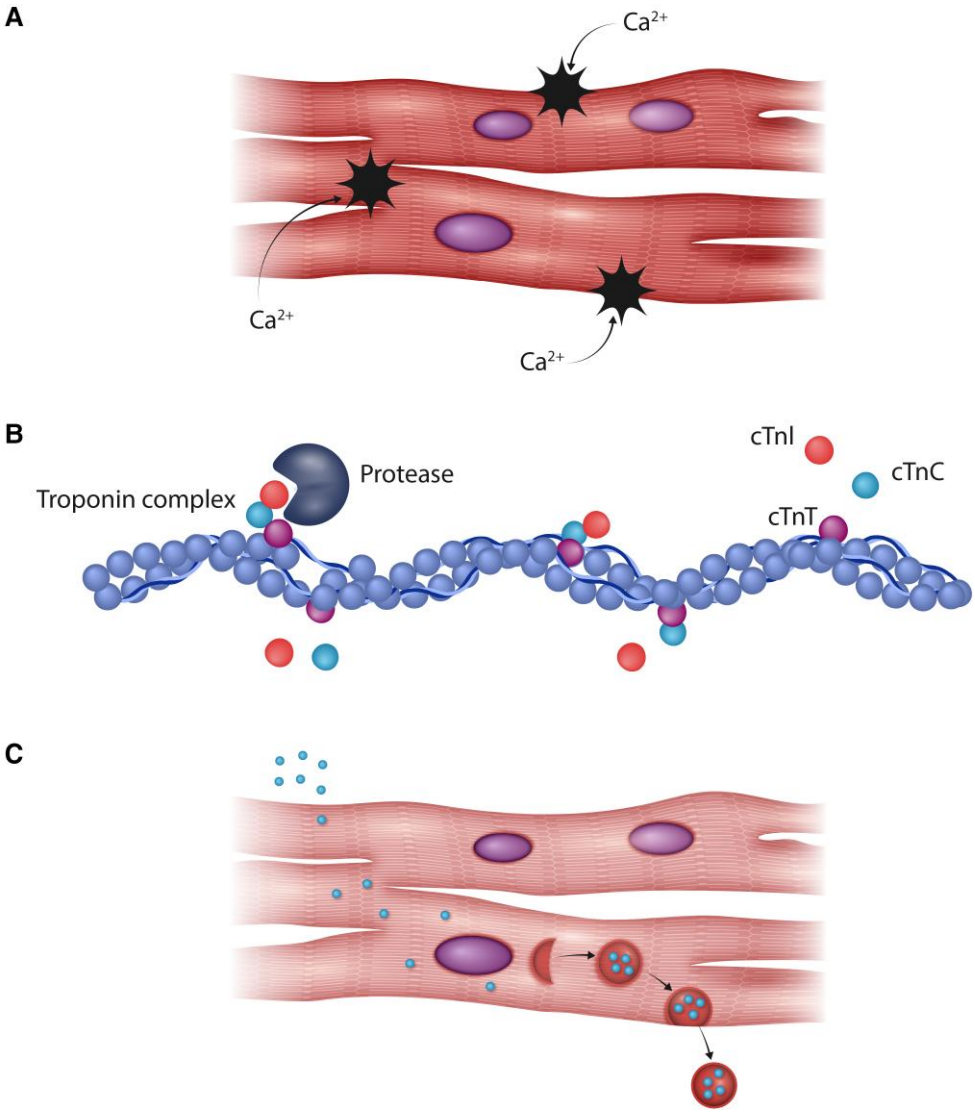

Figure 1 Release of cardiac troponin. **(***A*) When large membrane defects allow uncontrolled Ca^{2+} entry, the sarcomeres in cardiomyocytes contract and result in contraction band necrosis. (*B*) The troponin complex is cleaved by proteases in necrotic cardiomyocytes, so that cardiac-specific troponin T, cardiac-specific troponin I, and cTnC are separated. As cardiac-specific troponin T and its degradation products bind to insoluble thin filaments, it is for the most part retained in the sarcomere, whereas cardiac-specific troponin I fragments are released into the circulation. (*C***)** Possible non-necrotic release mechanisms include transient membrane defects and active autophagosome mediated exocytosis of sarcomere components in the form of exophers.

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Data availability

Data available on request from the authors.

References

1. Jennings RB. Historical perspective on the pathology of myocardial ischemia/reperfusion injury. *Circ Res* 2013;**113**:428–438.
2. Starnberg K, Fridén V, Muslimovic A, Ricksten S-E, Nyström S, Forsgard N, Lindahl B, Vukusic K, Sandstedt J, Dellgren G, Hammarsten O. A possible mechanism behind faster clearance and higher peak levels of cardiac troponin I compared with troponin T in patients with acute myocardial infarction. *Clin Chem* 2020;**66**:33–341.
3. Kragten JA, Hermens WT, van Dieijen-Visser MP. Cardiac troponin T release into plasma after acute myocardial infarction: only fractional recovery compared with enzymes. *Ann Clin Biochem*. 1996;**33**:314–323.
4. Arnadottir A, Pedersen S, Bo Hasselbalch R, Goetze JP, Friis-Hansen LJ, Bloch-Munster AM, Skov Jensen J, Bundgaard H, Iversen K. Temporal release of high-sensitivity cardiac troponin T and I and copeptin after brief induced coronary artery balloon occlusion in humans. *Circulation* 2021;**143**:1095–1104.
5. Huser M, Stegemann E, Kammermeier H. Is enzyme release a sign of irreversible injury of cardiomyocytes? *Life Sci* 1996;**58**:545–550.
6. Nicolas-Avila JA, Lechuga-Vieco AV, Esteban-Martinez L, Sanchez-Diaz M, Diaz-Garcia E, Santiago DJ, Rubio-Ponce A, Li JL, Balachander A, Quintana JA, Martínez-de-Mena R, Castejón-Vega B, Pun-García A, Través PG, Bonzón-Kulichenko E, García-Marqués F, Cussó L, A-González N, González-Guerra A, Roche-Molina M, Martin-Salamanca S, Crainiciuc G, Guzmán G, Larrazabal J, Herrero-Galán E, Alegre-Cebollada J, Lemke G, Rothlin CV, Jimenez-Borreguero LJ, Reyes G, Castrillo A, Desco M, Muñoz-Cánoves P, Ibáñez B, Torres M, Ng LG, Priori SG, Bueno H, Vázquez J, Cordero MD, Bernal JA, Enríquez JA, Hidalgo A. A network of macrophages supports mitochondrial homeostasis in the heart. *Cell* 2020;**183**:94–109.e123.