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Editorial

The cell biological basis for primary unloading in acute myocardial infarction

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Early initiation of mechanical circulatory support improves survival in patients with acute myocardial infarction (MI) complicated by refractory cardiogenic shock. In contrast, the potential benefits of mechanical support in MI patients without overt cardiogenic shock remain unclear. In patients with acute anterior ST elevation MI (STEMI), early mechanical support through intra-aortic balloon counterpulsation (IABC) prior to percutaneous coronary intervention (PCI) did not affect infarct size. However, 6 months after the acute event, the exploratory composite endpoint of time to death, shock or new or worsening heart failure was significantly reduced in the IABC + PCI group, raising the intriguing possibility for lasting beneficial effects of early mechanical support in patients with large anterior STEMI [1].

In the current issue of the journal, Baldetti and co-workers [2] provide an interesting and provocative perspective on the potential role of mechanical unloading performed prior to reperfusion in acute MI. This approach, termed primary unloading may exert potent cardioprotective actions. The authors review the published evidence, discuss the highly promising experimental animal studies, and propose the need for new clinical studies to test this new approach. However, the mechanistic basis for the proposed protection remains unclear. Considering the complexities of the cell biological and molecular responses in the ischemic myocardium, how can early mechanical unloading attenuate injury?

1. Effects on ischemic cardiomyocytes and on the microvasculature

Sudden coronary occlusion results in immediate cessation of aerobic metabolism, inducing rapid ATP depletion and accumulation of metabolites. Severe systolic dysfunction occurs within seconds, whereas minutes later early ultrastructural changes are noted in cardiomyocytes. These changes are initially reversible; however with coronary ischemic intervals longer than 15–20 min, an increasing number of cardiomyocytes are unable to preserve their structure and exhibit irreversible changes that lead to their death. It has been suggested that ischemia activates a "wavefront" of death, mediated through stimulation of necrotic and apoptotic pathways, ultimately leading to massive loss of cardiomyocytes in the area at risk. Lowering end-diastolic pressures and volumes through mechanical unloading reduces wall stress, and may protect vulnerable cardiomyocytes from death by limiting metabolic activity [3], or by attenuating mechanosensitive activation of apoptotic signals. Unloading-mediated activation of cytoprotective cascades that inhibit cardiomyocyte apoptosis has also been proposed [4]; however, specific mechanisms remain unclear. Preservation of calcium handling through unloading [5] may also improve contractility. Moreover, reduction in end-diastolic pressures may significantly improve coronary arteriolar flow, resulting in better perfusion of the myocardium, thus amplifying protection. These beneficial effects may significantly reduce the size of the infarct [6,7].

2. Unloading may preserve the cardiac extracellular matrix (ECM) under conditions of stress

Often overlooked, the cardiac ECM network plays a critical role in preserving myocardial structure and function, not only by providing mechanical support, but also by transducing key survival signals in cardiomyocytes. In the ischemic myocardium, rapid release and activation of matrix-degrading proteases generates matrix fragments, termed matrikines [8]. Increased ECM fragmentation has been suggested to trigger inflammation, while promoting cardiomyocyte death under conditions of stress, thus accentuating myocardial dysfunction [9]. Mechanical unloading reduces matrix metalloproteinase (MMP) expression and activity in the ischemic heart [10] and may preserve the ECM network, inhibiting ischemia-induced cell death responses and attenuating inflammatory activation. It should be emphasized that MMPs have numerous substrates in addition to ECM proteins, and may modulate levels and activity of pro-inflammatory chemokines and cytoprotective signals. For example, it has been suggested that lower MMP activity in unloaded hearts may results in decreased degradation of the "cardioprotective" chemokine CXCL12/stromal cell-derived factor (SDF)-1α, promoting cardiomyocyte survival [10]. Considering the

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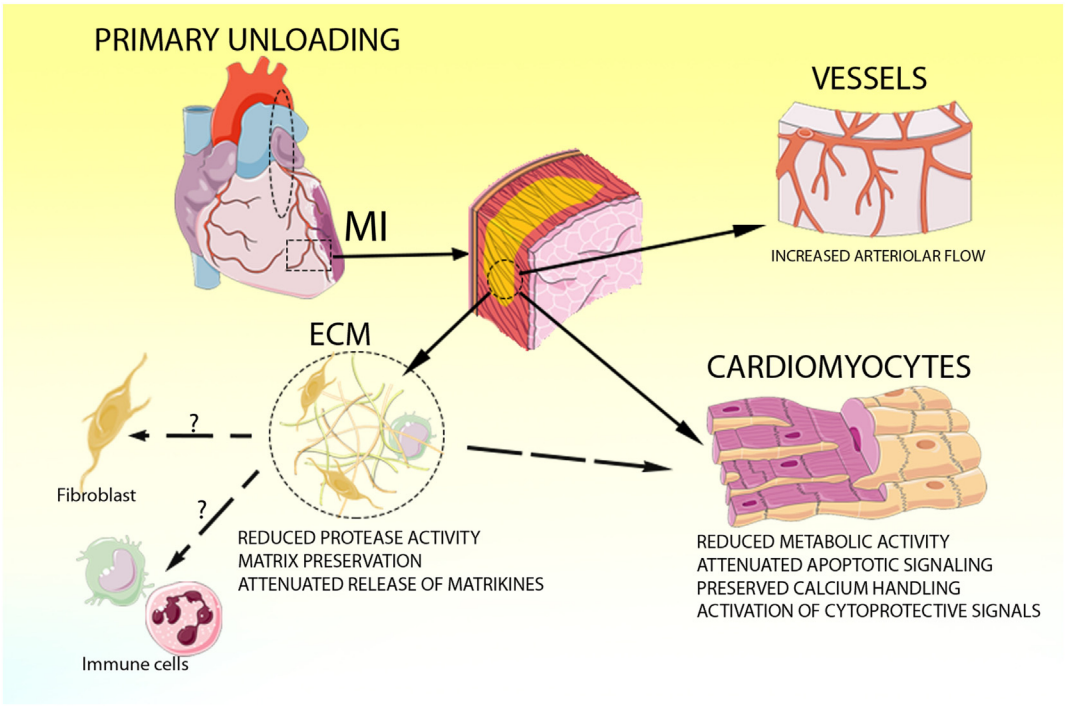

Fig. 1. Cellular mechanisms remediating the proposed protective effects of primary unloading in the infarcted heart. Cardiomyocytes, vessels, and the extracellular matrix (ECM) may be the main targets of primary unloading. Reduced end-diastolic pressures may improve coronary arteriolar flow, increasing perfusion. In addition to an increase in blood supply, unloading may also reduce demand by decreasing left ventricular wall stress, thus attenuating metabolic activity in cardiomyocytes. Unloading may reduce infarct size, by decreasing activation of mechanosensitive pro-apoptotic pathways, and by stimulating cytoprotective signals. Primary unloading may also inhibit matrix metalloproteinase (MMP) expression and activity, preserving the cardiac ECM, and reducing generation of pro-inflammatory matrix fragments (matrikines). In addition to ECM proteins, MMPs also process cytokines and chemokines. Thus, decreased MMP activity may exert protective actions by modulating the cytokine milieu in the infarcted heart. Although direct effects of unloading on resident cardiac fibroblasts and immune cells cannot be excluded, the timing and brief duration of the intervention may limit any consequences on the inflammatory and reparative response.

wide range of injurious and protective mediators processed by MMPs, the relative significance of this very specific pathway is unclear. Unloading may also act by modulating levels of matricellular proteins, macromolecules that do not play a major direct structural role, but enrich the ECM following injury and regulate signaling responses.

3. Does early unloading affect immune and reparative responses following infarction?

Mechanosensitive signaling has been implicated in activation of immune cells, and plays a critical role in stimulating both reparative and fibrogenic actions of cardiac fibroblasts. To what extent early mechanical unloading may act by modulating phenotype and function of macrophages or interstitial cells remains unclear. Effects of primary unloading on these cells may be relatively limited due to the early timing of the intervention. In the infarcted myocardium, recruitment of inflammatory leukocytes occurs in response to cardiomyocyte necrosis, whereas myofibroblast activation follows, after the peak of the inflammatory reaction. Thus, infarct macrophages and myofibroblasts are unlikely direct targets of an early and brief mechanical support intervention.

4. Conclusions

From a theoretical mechanistic perspective, primary unloading of the infarcted heart would be expected to stimulate pro-survival responses in cardiomyocytes, while improving myocardial perfusion and preserving the cardiac ECM (Fig. 1). Some of the proposed effects are supported through experimental evidence in animal models. Obviously, the current evidence is insufficient to support primary unloading as an effective adjunctive strategy in high-risk patients with acute MI. Both robust clinical studies and well-executed mechanism-oriented experimental investigations are needed to test the effectiveness of this promising new therapeutic approach.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] M.R. Patel, R.W. Smalling, H. Thiele, H.X. Barnhart, Y. Zhou, P. Chandra, D. Chew, M. Cohen, J. French, D. Perera, E.M. Ohman, Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial, JAMA 306 (2011) 1329–1337.
[2] L. Baldetti, A. Beneduce, F. Pappalardo, Primary mechanical unloading in high-risk myocardial infarction: perspectives in view of a paradigm shift, Int. J. Cardiol. (2019)https://doi.org/10.1016/j.ijcard.2019.05.042 pii: S0167-5273(19)31391-9 (epub ahead of print).
[3] B.R. Weil, F. Konecny, G. Suzuki, V. Iyer, J.M. Canty Jr., Comparative hemodynamic effects of contemporary percutaneous mechanical circulatory support devices in a porcine model of acute myocardial infarction, J. Am. Coll. Cardiol. Intv. 9 (2016) 2292–2303.
[4] S. Tamareille, H. Achour, J. Amirian, P. Felli, R.J. Bick, B. Poindexter, Y.J. Geng, W.H. Barry, R.W. Smalling, Left ventricular unloading before reperfusion reduces endothelin-1 release and calcium overload in porcine myocardial infarction, J. Thorac. Cardiovasc. Surg. 136 (2008) 343–351.
[5] X. Wei, T. Li, B. Hagen, P. Zhang, P.G. Sanchez, K. Williams, S. Li, G. Bianchi, H.S. Son, C. Wu, C. DeFilippi, K. Xu, W.J. Lederer, Z.J. Wu, B.P. Griffith, Short-term mechanical unloading with left ventricular assist devices after acute myocardial infarction conserves calcium cycling and improves heart function, J. Am. Coll. Cardiol. Intv. 6 (2013) 406–415.
[6] K. Saku, T. Kakino, T. Arimura, G. Sunagawa, T. Nishikawa, T. Sakamoto, T. Kishi, H. Tsutsui, K. Sunagawa, Left ventricular mechanical unloading by total support of Impella in myocardial infarction reduces infarct size, preserves left ventricular function, and prevents subsequent heart failure in dogs, Circ. Heart Fail. 11 (2018), e004397.

[7] N.K. Kapur, V. Paruchuri, J.A. Urbano-Morales, E.E. Mackey, G.H. Daly, X. Qiao, N. Pandian, G. Perides, R.H. Karas, Mechanically unloading the left ventricle before coronary reperfusion reduces left ventricular wall stress and myocardial infarct size, Circulation. 128 (2013) 328–336.
[8] N.G. Frangogiannis, The extracellular matrix in myocardial injury, repair, and remodeling, J. Clin. Invest. 127 (2017) 1600–1612.
[9] I. Russo, M. Cavalera, S. Huang, Y. Su, A. Hanna, B. Chen, A.V. Shinde, S.J. Conway, J. Graff, N.G. Frangogiannis, Protective effects of activated myofibroblasts in the pressure-overloaded myocardium are mediated through Smad-dependent activation of a matrix-preserving program, Circ. Res. 124 (2019) 1214–1227.
[10] M.L. Esposito, Y. Zhang, X. Qiao, L. Reyelt, V. Paruchuri, G.R. Schnitzler, K.J. Morine, S.K. Annamalai, C. Bogins, P.S. Natov, R. Pedicini, C. Breton, A. Mullin, E.E. Mackey, A. Patel, E. Rowin, I.Z. Jaffe, R.H. Karas, N.K. Kapur, Left ventricular unloading before reperfusion promotes functional recovery after acute myocardial infarction, J. Am. Coll. Cardiol. 72 (2018) 501–514.<!–