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Primary mechanical unloading in high-risk myocardial infarction: Perspectives in view of a paradigm shift

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ABSTRACT

The improvement achieved in recent years in early myocardial infarction (MI) mortality poses several new clinical challenges, owing to late consequences of myocardial loss and the significant incidence of heart failure (HF) observed thereafter. A still unaddressed residual reperfusion injury (RI) contributes to final infarct size, acute MI mortality and longer-term HF development. Despite many cardioprotective lines of research in the setting of MI, no treatment has significantly altered clinical practice or convincingly improved outcomes either. Left ventricular mechanical unloading before culprit vessel reopening may reduce RI and prime (biologically and mechanically) the myocardium for reperfusion, thus limiting infarct size and preventing subsequent adverse remodeling. Aim of this review is to summarize key pre-clinical and clinical experiences furnishing a rationale to the approach of mechanical unloading before myocardial reperfusion with a translational outlook on its implications for the management of MI patients.

1. Background and new horizons

The concept of rapid myocardial reperfusion as the primary therapeutic goal in acute myocardial infarction (AMI) has led to development of specific treatment pathways and has changed the natural history of this condition. The improvement achieved in recent years in early AMI mortality poses several new clinical challenges, owing to late consequences of myocardial loss [1,2]. Indeed, AMI survivors are burdened by an incidence of heart failure (HF) as high as 25% and 76% at 1-year and 5-year respectively [3,4]. As myocardial salvage is recognized as a key therapeutic target, efforts in reducing myocardial loss should be primarily directed towards ischemic and reperfusion injury (RI) cut-down. However, patient's delay to presentation still represents a major issue and the significant trend towards reduction in the door-to-balloon time observed in recent years, aimed to limit total ischemic time, did not translate into a parallel in-hospital or 30-day mortality decrease that plateaued at around 5% and 10%, respectively [5–7]. This suggests a still unaddressed residual RI contribution to AMI mortality. Interestingly, despite the recognition of the clinical relevance of RI and the number of treatments trialed, no definitive therapy has been still widely validated and adopted [7,8]. Previously investigated pharmacologic strategies have not shown clear clinical efficacy, likely depending on the efforts made to compress reperfusion delay, that limit the time to wait for drug effect onset, and on the multiple and redundant biologic pathways underpinning RI. On the other hand, non-pharmacologic invasive mechanical support approaches that have favorable pre-clinical and clinical evidence and might be easily deployed, have still not been definitely substantiated and convincingly endorsed [7–9].

Pre-reperfusion mechanical unloading of the left ventricle (LV) during acute AMI (primary unloading) is emerging as a promising cardioprotective therapy. Several lines of pre-clinical research encompassing different animal models of AMI have unveiled the molecular basis of primary unloading biologic effect and highlighted its efficacy in controlled settings, furnishing a solid framework for a clinical trialing of this approach. Aim of this hypothesis-generating review is to summarize the available evidence with a focused view on the translational aspects of this relatively novel concept.

2. Mechanical circulatory support in acute myocardial infarction

To date, in the context of AMI, mechanical circulatory support (MCS) has limited role beyond the setting of cardiogenic shock (CS). In the real-world USpella registry, early initiation of hemodynamic support prior to percutaneous coronary intervention (PCI) with the transvalvular aortic axial-flow Impella pump (Abiomed, Danvers, MA, USA) resulted in improved in-hospital and 30-day survival in refractory CS complicating AMI [10]. In this registry, however, patients with ST-elevation myocardial infarction (STEMI) more likely received post-PCI Impella (87.9%). This trend can easily be explained considering the large adoption of a primary reperfusion strategy in contemporary clinical practice. Interestingly, this latter approach resulted in worse hemodynamics and increased need for mechanical ventilation at the time of

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Table 1
Overview of the principal pre-clinical and clinical experiences of myocardial unloading in myocardial infarction.

	Study population and MI model	Unloading device and protocol	Final population and design	Results	Comments
Smalling [13]	Population 18 dogs MI model Surgical LAD ligation and reperfusion	Hemopump IABP	Treatment arms Control (n = 6) IABP (n = 6) Hemopump (n = 6)	Hemodynamics: - Hemopump reduced LVESP and LVEDP vs IABP and control -Hemopump slightly increased MBF in the ischemic region Final IS: - Hemopump IS/AAR: 22% - IABP IS/AAR: 27% - Control IS/AAR: 63%	Unloading initiated at ischemia onset has low clinical translational value
Meyns [14]	Population 26 sheep MI model Surgical LAD ligation and reperfusion	Impella Full support: 4.1 l/min Partial support: 2.4 l/min	Treatment arms Group 1 (n = 8): no support (control) Group 2 (n = 6): full support during ischemia and reperfusion Group 3 (n = 6): full support during reperfusion only Group 4 (n = 6): partial support during reperfusion only	Hemodynamics: - Impella increased DAP and MAP (Groups 2, 3, 4) and decreased LVEDP (Groups 2, 3) Final IS: - Impella significantly reduced IS Group 1 IS/AAR: 67.2% Group 2 IS/AAR: 18.1% Group 3 IS/AAR: 41.6% Group 4 IS/AAR: 54% Myocardial oxygen match: - Reduction in MVO_2 in unloading groups - Normal MBF after reperfusion only in fully supported animals (Group 2)	Higher myocardial salvage with unloading during ischemia IS inversely proportional to the degree of unloading
Achour [15]	Population 24 dogs MI model Surgical LAD occlusion and reperfusion	Transvalvular LVAD Maximum flow (2–3 l/min)	Treatment arms Sham procedure (n = 8) LV Assist Pre group (n = 8): unloading started 15′ prior to reperfusion LV Assist Post group (n = 8): unloading started 15′ after reperfusion	Hemodynamics: - Unloading significantly reduced LVEDP and RPP EDWT and MBF: - Less EDWT increase in AAR after reperfusion in the LV Assist Pre group - Higher RMBF in LV Assist Pre group Final IS: - LV Assist Pre significantly reduced IS/AAR Histology: - Increased signs of RI in control group and in LV Assist Post group	Increased myocardial salvage with unloading prior to reperfusion
Tamareille [16]	Population 12 pigs MI model Surgical LAD ligation and reperfusion	A-Med trans-femoral LVAD	Treatment arms MI without unloading (n = 6) MI with unloading (n = 6)	Hemodynamics: - Unloading reduced LVEDP Final IS: - Unloading reduced IS/AAR by 54% vs control - No difference in infarct weight/LV weight Biological pathways: - Unloading reduced ET-1 release - Lower post-reperfusion Ca^{2+} overload in infarct area in unloading group - Lower apoptotic cells in infarct area in unloading group	–
Kapur [17]	Population 15 adult male swine MI model Mid-LAD balloon occlusion (4 acute deaths)	Left atrial-to-femoral artery TandemHeart	Treatment arms Sham procedure (n = 3) MI and reperfusion (n = 4) Primary unloading (n = 4)	Hemodynamics: - Unloading reduced LVEDP vs MI group - Unloading group had higher ESPVR - Unloading reduced circumferential LV strain after reperfusion vs MI group Final IS: - Unloading reduced IS by 42% vs MI group - Unloading reduced CK-MB and TnI release after reperfusion vs MI group Biological pathways: - RISK pathway activation in non-infarcted zone by unloading	First design with 30′-delayed reperfusion (primary unloading)

(continued on next page)

Table 1 (*continued*)

	Study population and MI model	Unloading device and protocol	Final population and design	Results	Comments
Wei [35]	Population 16 adult sheep MI model Apical MI due to permanent coronary artery ligation	Impella 5.0	Treatment arms Sham procedure (n = 4) MI without unloading (n = 6) MI with unloading (n = 6)	Hemodynamics: Impella unloaded 43.6 ± 13.2% of CO Final IS and adverse remodeling: - Unloading decreased IS - Smaller increase in LVEDV and LVESV in unloading group - Better LVEF preservation in unloading Biological pathways: - Perilesional CHP preservation with unloading - Lower perilesional SR damage with unloading	–
Kapur [19]	Population 14 adult male swine MI model Mid-LAD angioplasty occlusion and reperfusion	Impella CP	Treatment arms Sham procedure (n = 3) MI and reperfusion (n = 5) Primary unloading (n = 5)	Hemodynamics: - Primary unloading reduced LVSV, LVSW, LVEDP, LVEDV, LV wall stress, while supporting MAP Final IS: - Primary unloading significantly reduced IS/AAR by 43% compared to primary reperfusion Biological pathways: - Primary unloading promotes cardioprotective signaling (SDF-1α/CXCR4) - Primary unloading reduces myocardial apoptosis	Myocardial levels of SDF-1α/CXCR4 inversely correlated with final IS
Saku [40]	Population 23 dogs MI model Surgical LAD ligation and reperfusion	LV apex-to-left femoral artery LVAD p-LVAD (partial unloading) t-LVAD (total unloading)	Treatment arms Control (n = 8) p-LVAD (n = 5) t-LVAD (n = 5)	Hemodynamics: - Unloading decreased LVSW - Unloading reduced LVEDP Final IS: - Unloading reduced final IS Myocardial oxygen consumption: - Unloading increased CS oxygen saturation - Unloading decreased PVA - Unloading decreased MVO_2	Hemodynamic and cardioprotective effects were higher in the t-LVAD group
Saku [18]	Population 20 dogs MI model Surgical LAD ligation	Impella CP p-Impella (partial unloading) t-Impella (total unloading)	Treatment arms Sham (n = 5) MI without unloading (n = 5) p-Impella (n = 5) t-Impella (n = 5)	Hemodynamics: - Unloading reduced LVEDP - LVESE was higher in unloading - t-Impella preserved LVEF Final IS: - Unloading reduced final IS HF parameters: - NT-proBNP was lower in unloading	Hemodynamic and cardioprotective effects were higher in the t-Impella group
Esposito [20]	Population 19 adult male swine MI model Mid-LAD balloon occlusion	Impella CP	Treatment arms Sham (n = 3) Group 1 (n = 4): MI and reperfusion Group 2 (n = 4): 15′ unloading before reperfusion Group 3 (n = 4): 30′ unloading before reperfusion Group 4 (n = 4): unloading 30′ after reperfusion	Hemodynamics: - Reduced LVEDP at 28-day in unloading - Higher LVSW at 28-day in unloading Final IS: - Lower final acute IS in Group 3 - Lower final IS at 28-day in unloading Biological pathways: - Mitochondrial protection activation in Group 3 - Lower SDF-1α degradation by MMP-2 and MMP-9 in Group 3 - Lower levels of pro-apoptotic proteins in Group 3 HF parameters: - Lower NT-proBNP levels at 28-day in Group 3 - Lower levels of AR markers at 28-day in unloading	Only a strategy of 30′ unloading prior to reperfusion showed positive effects

Table 1 (*continued*)

	Study population and MI model	Unloading device and protocol	Final population and design	Results	Comments
Clinical trials					
DTU Pilot Trial [36]	Population 50 patients with acute anterior STEMI Primary endpoint 30-day final IS at CMR (efficacy) and MACCE (safety) Additional safety endpoints - BARC bleedings grade ≥2 - Vascular access site complications	Impella CP Flow 2.8 ± 0.4 l/min	Treatment arms Prolonged primary unloading (n = 25): unloading started 30′ before reperfusion Immediate primary unloading (n = 25): unloading started immediately prior to reperfusion	Final IS: - IS/LVmass not statistically different between the two groups (13.1 ± 11.3% vs 15.3 ± 11.5%) - IS was reduced in those with an ST-segment sum elevation >6 mm MACCE: - Similar rates between the two groups (12% vs 8%) Additional safety endpoints: - BARC bleedings grade ≥2 16% - Vascular access site complications 4%	Average Impella CP insertion and activation time 15.4 ± 8.4′ Average door-to-balloon time 84.4 ± 27.6′ 30-day CMR not available for nearly 20% of patients

PCI, with detrimental effects on prognosis. On the opposite, despite longer door-to-balloon times, STEMI patients who received pre-PCI Impella showed better outcomes.

The only randomized evidence on MCS in patients with large AMI without overt CS is limited to the disappointing results of the CRISP AMI study, that investigated the role of intra-aortic balloon pump (IABP) as an adjunct to percutaneous myocardial revascularization in this scenario [11]. Interestingly, in this study approximately 10% of patients who underwent primary reperfusion crossed over to rescue IABP due to hypotension and CS, raising concerns about possible early injury after primary PCI in large anterior AMI.

While an estimate of 25% of patients with AMI develops early, in-hospital HF, it should be kept in mind that AMI survivors are also at high risk of late adverse remodeling [4]. This holds particularly true for extensive AMI. Cardiac magnetic resonance studies have identified the infarct size (IS) area as the leading determinant of adverse remodeling, HF and cardiovascular events after AMI [12]. Notably, despite the overall lack of benefit observed with MCS in the CRISP AMI study, on exploratory analysis, the 6-month composite endpoint of death, shock, and HF was significantly lower in the IABP group [11]. These findings hint at a potential benefit of mechanical unloading in terms of adverse remodeling prevention in high-risk extensive AMI.

3. Primary unloading to reduce final infarct size

More than 20 years ago, a pioneering study by Smalling et al. first demonstrated reduction in final IS with the use of a trans-valvular axial-flow left ventricular assist device (LVAD) in AMI animal models [13]. To date, a number of other invasive MCS has been tested in primary unloading and the benefits (in terms of IS reduction) appear consistent across all these experiences, whatever the device implanted [14–18]. In 2013, a pre-clinical study by Kapur et al. using the percutaneous left atrium-to-femoral artery centrifugal-flow pump TandemHeart (Cardiac Assist, Pittsburgh, PA, USA) demonstrated a significant reduction in IS by histology in swine anterior AMI models treated with reperfusion and mechanical unloading of the LV, as compared to those treated with reperfusion alone [17]. Notably, this was the first study to propose an experimental design encompassing 30-minute of unloading (primary unloading) prior to revascularization (delayed reperfusion), a concept that was later reappraised and confirmed in a similar

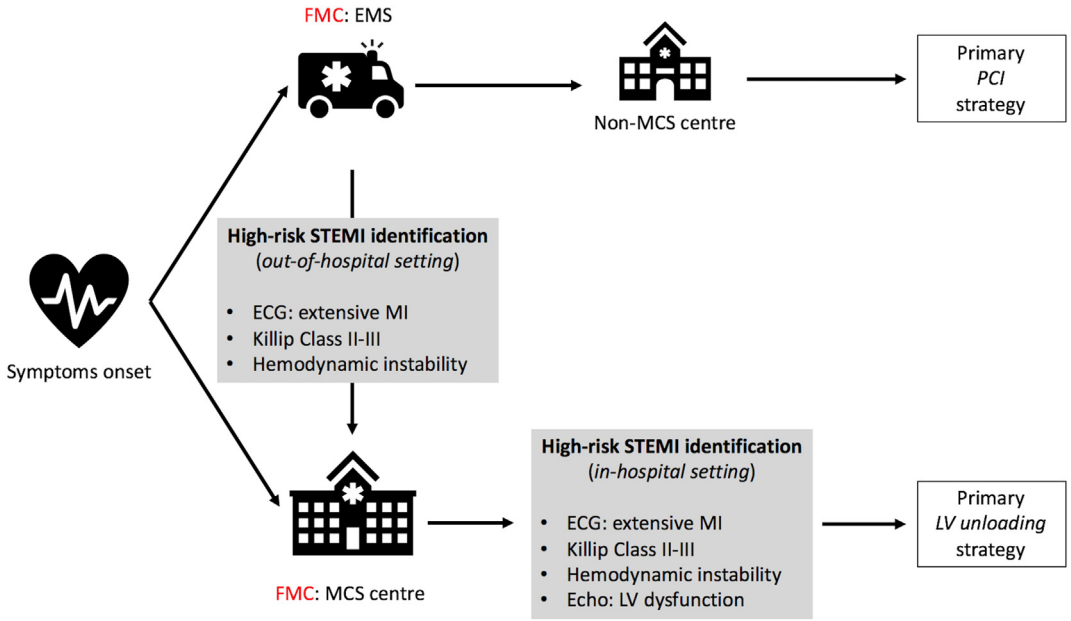

Fig. 1. Hypothetical "hub-and-spoke" organization of emergency medical service to guarantee access to a MCS-capable hospital to patients eligible to primary unloading treatment. Gray boxes summarize simple "red flags" features to identify high-risk patients.

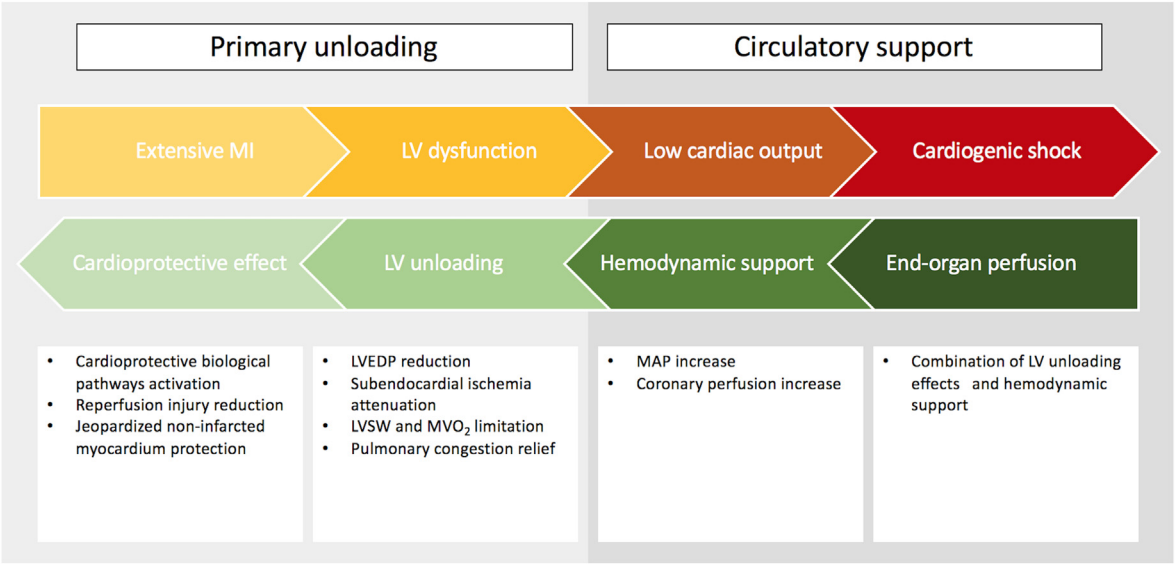

Fig. 2. Cardioprotective and hemodynamic effects of LV unloading across a worsening spectrum of cardiac compromise. Upper arrow represents the vicious cycle of an extensive AMI leading to overt CS: reversal or prevention of this unfavorable evolution is attained by LV unloading (lower arrow). Gray boxes summarize pathophysiological mechanisms subtending therapeutic effect of LV unloading.

experimental setting [19]. Adding strength to the translational value of this approach, a recent experiment by Esposito et al. demonstrated that 30 min of LV unloading before reperfusion using the Impella device led to an acute IS reduction of approximately 50%, corresponding to a 28-day LV scar size reduction in a swine model of anterior AMI [20]. This study furnished a mechanistic link between the acute cardioprotective effect (IS reduction) and the later-onset HF prevention (scarsize reduction).

From a pathophysiological perspective, primary unloading provides a "mechanical priming" of the ischemic myocardium: LV pressure-volume loops recorded with LV unloading during AMI, show lower end-diastolic volumes and pressures, and lower total cardiac stroke work. This limits oxygen consumption, optimizes hemodynamics and reduces the detrimental, pro-ischemic compressive effect of elevated LV end-diastolic pressures on subendocardial arterioles [17,19,21–23].

Notably, beyond a myocardial "mechanical priming", MCS also guarantees a "biologic priming". In animal models of anterior AMI and reperfusion, pre-revascularization unloading reduced RI ultrastructural markers as compared to sham procedures or post-reperfusion unloading [15]. Experimental pre-clinical data shed light on the biologic pathways underlying primary unloading cardioprotective effect. In acute myocardial ischemia, endothelin-1 (ET-1) release may be triggered by a combination of endothelial cells ischemic disruption and myocardial mechanical stretch [24,25] and is a potent mediator of RI phenomenon [26–28]. Primary unloading has been shown to reduce myocardial release of ET-1 resulting in smaller IS [16]. In this experiment, unloading group also had attenuated post-reperfusion intracellular Ca^{2+} level rise in ischemic regions as compared to control groups. Prevention of Ca^{2+} overload and modulation of Ca^{2+}-mediated cell death programs [29–32] may thus account for the observed myocardial salvage effect. In acutely infarcted myocardium, primary unloading strategy was demonstrated to maintain elevated levels of the stromal derived factor-1α (SDF-1α) and of its receptor CXCR4 with resultant increased phosphorylation of the downstream cardioprotective reperfusion injury salvage kinases (RISK) proteins ERK, Akt and GSK-3β [19,20]. These effects were ascribed to lower levels of MMP-2, MMP-9 and DPP-4 proteases involved in SDF-1α/CXCR4 complex degradation, rather than to increased expression of either SDF-1α or CXCR4 [20]. Net biologic result of these phenomena is reduction of pro-apoptotic signals and enhanced myocytes survival [19,20]. Mechanisms subtending the reduction of MMPs expression observed with primary unloading have not been extensively studied, but similar findings have been reported in failing ventricles during chronic LVAD support [33,34]; a combination of reduced myocardial stretch, attenuation of inflammatory RI, preservation of coronary perfusion and changes in myocardial redox state are likely involved.

Interestingly, unloading effects extend beyond infarcted myocardium and experimental data show preservation of normal Ca^{2+} handling proteins (SERCA-2α, NCX-1 and phospholamban pentamer) expression levels and normalization of Ca^{2+} cycling events in perilesional myocardium [35]. Non-infarcted myocardium also shows higher levels of the phosphorylated ERK and Akt proteins suggesting activation of further cardioprotective pathways if mechanical unloading precedes reperfusion in experimental models [17].

In summary, LV primary unloading (whatever the device employed) may be beneficial through a 2-hit mechanism: first, it may reduce ventricular wall stress and promote collateral blood flow (limiting myocardial ischemia); second, it may activate cardioprotective signaling that, after a 30-min mechanical conditioning, may enable the myocardium to receive reperfusion without further injury. This combined mechanical and biologic effect may confer to this strategy advantage over other treatments targeting one molecular signaling cascade at a time and may turn also synergistic with other pharmacologic and non-pharmacologic cardioprotective treatments [9]. These findings have high clinical translational value and, if confirmed in humans, may dramatically alter current management of STEMI.

4. Primary unloading in translation: from bench to bedside

The first attempt to trial a primary unloading strategy in a clinical setting was the TandemHeart to Reduce Infarct Size (TRIS) trial (NCT02164058). Notably, this trial had zero patient enrollment as operators were reluctant to participate in a study requiring trans-septal delivery of a Tandem cannula into the left atrium during an anterior STEMI, delaying time to reperfusion. This reflects the deep-rooted notion of rapid reperfusion to reduce final IS.

Among different available MCS devices the percutaneous, transfemoral Impella device is easier to deploy as compared to other MCS devices and may thus be better suited for the STEMI setting in an effort to compress total ischemic time. Building on these premises, the phase 1 multicenter randomized clinical trial DTU-STEMI Pilot randomized 50 patients with anterior STEMI without CS to either LV unloading with

immediate reperfusion or LV unloading with a 30-minute delay to reperfusion. LV unloading was obtained with the Impella CP pump. Study results demonstrated that primary LV unloading is feasible without jeopardizing the benefits of reperfusion: a 30-minute delay to reperfusion on the platform of LV unloading did not increase IS with no significant differences in IS at 3–5 days or 30-day follow-up [36]. This is particularly relevant considering that in AMI, for every 30-minute delay in reperfusion, transmural necrosis risk increases by 37% and 1-year mortality increases by 7.5% [37,38]. Interestingly, in this trial patients with the largest ST-segment sum elevation (>6 mm) had a statistically significant reduction in IS with unloading plus delayed reperfusion compared to unloading plus immediate reperfusion (44% vs 59%, $p = 0.04$) reinforcing the concept that patients with the largest area at risk may receive the greatest benefit from a primary unloading approach. Of note, this trial also implicitly assessed operators' compliance with a study design protocolling 30 min of unloading before reperfusion.

The DTU-STEMI Pilot Trial preludes the DTU-STEMI Pivotal Trial, aimed to test whether LV unloading and delayed reperfusion reduces myocardial damage compared to current standard of care. An overview of previous pre-clinical studies, along with relevant clinical experience is summarized in Table 1 [13–20,35,36,39,40].

5. Patient selection, risk stratification and logistic considerations

For practical purposes high-risk AMI is often used interchangeably with extensive AMI definition. Historically, attempts to identify patients with extensive AMI included ECG estimation of myocardium at risk based on the extent of ST-segment elevation or the sum of elevation [41]. In a trial comparing primary thrombolytic therapy, primary thrombolytic therapy with rescue PCI and primary PCI in extensive AMI patients, only subjects with a total ST-segment elevation and depression of at least 1.5 mV were included [42]. In the DTU Pilot trial patients with an ST-segment sum elevation >6 mm had a statistically significant reduction in IS with unloading plus delayed reperfusion. However, a crude 12-lead ECG based assessment may be misleading: as an example, in anterior AMI both anteroseptal (ST-elevation in V1-V3 leads) and extensive anterior (ST-elevation extending to V5-V6) presentations may subtend similar myocardial area at risk [43,44]. Echocardiography (provided it does not delay catheterization laboratory activation) may overcome some of these limitations furnishing direct visualization of jeopardized myocardium and rapidly provide hemodynamic, valvular function and mechanical AMI complications assessment. Coronary angiography may further refine risk stratification in light of angiographic findings.

We recognize that no unequivocal definition of high-risk AMI exists in literature and strict definitions may have limited applicability in real-world complex clinical scenarios. In the Authors opinion “high-risk AMI” should be reserved for patients with a high probability of extensive AMI and related short-term serious complications including: initial hemodynamic decompensation, congestive pulmonary edema, sustained and poorly tolerated ventricular arrhythmias. While in a strict primary unloading perspective this definition should better precede diagnostic coronary angiography, in a more comprehensive notion, also patients with high a priori probability of myocardial no-reflow and greater IS, including those with longer ischemia time and with a high thrombotic burden might be considered “high-risk AMI”.

In this perspective several healthcare considerations arise. To date, implantation of MCS is often limited to tertiary centers, therefore a “hub-and-spoke” organization of emergency medical service should hypothetically be warranted (Fig. 1). However, inherent device-related complications (vascular access site injury or bleeding and hemolysis) and their cost stand against an indiscriminate use of this resource. Optimization of the biologic and economic cost-effectiveness of primary unloading strategy may thus call for risk stratification at time of AMI diagnosis. A clinical, electrocardiogram-based and fast echocardiographic rule-in approach, may be considered at time of emergency service triage to select patients who will gain the most from a primary LV unloading, as the expected IS reduction and clinical benefit is likely higher with a larger myocardial area at risk. Indeed, a hemodynamically stable extensive AMI patient with significant probability of large myocyte loss, severe LV dysfunction, low cardiac output and CS may particularly benefit from a primary unloading approach: first, the amount of salvaged myocardium will be quantitatively higher with more myocardium at risk; second, the MCS will prevent the vicious cycle of hemodynamic deterioration (Fig. 2). In line with this hypothesis, patients with the largest ST-segment sum elevation from the DTU Pilot trial met the endpoint of IS reduction with a primary unloading strategy. In addition, as final IS (along with LVEF) is a strong prognostic factors of long-term adverse remodeling and HF development [12,45], reduction in final AMI extent may have late positive effects.

In conclusion, the clinical benefit obtained with a primary unloading strategy in high-risk AMI may be ascribed to reduced final IS with 1) aversion of hemodynamic destabilization in the short-term and 2) prevention of the longer-term adverse remodeling process.

6. Conclusions

Notwithstanding optimism for a potentially new technology addressing cardioprotection in AMI, caution is warranted considering possible risks (related to device implantation and to reperfusion deferral) and uncertain benefits (with the only available trial holding neutral results) before striding on towards widespread implementation of such an approach.

With this background, there is an unmet need for strong evidence supporting primary LV unloading in AMI. Should this treatment be validated in robust clinical studies, the shaping theory of mechanical unloading may turn into a valuable therapeutic option and be the starting point for a profound paradigm shift in AMI management.

Declaration of Competing Interest

None of the Authors has relevant conflicts of interest to disclose.

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