JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 79, NO. 1, 2022

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Intramyocardial Hemorrhage

The Final Frontier for Preventing Heart Failure Post-Myocardial Infarction*

Colin Berry, MBChB, PhD,[a,b] Borja Ibáñez, MD, PhD[c]

Incident heart failure following acute myocardial infarction (MI) is a preventable therapeutic target. Adverse left ventricular remodeling, which is the pathophysiological substrate for left ventricular systolic dysfunction and heart failure, develops insidiously, even in patients with seemingly successful myocardial reperfusion following primary percutaneous coronary intervention (PCI) (1). In fact, primary PCI for acute ST-segment elevation myocardial infarction (STEMI) routinely achieves normal antegrade coronary artery blood flow in >90% of cases; yet, imaging evidence shows failed myocardial reperfusion, manifesting as microvascular obstruction (2) and myocardial hemorrhage (2-4), in approximately 50% and 40%, respectively. Microvascular obstruction (MVO) is independently associated with an increased likelihood of death and heart failure, independent of the size of infarction (5).

Myocardial hemorrhage is caused by severe reperfusion injury within ischemic myocardium leading to disruption of vascular integrity and extravasation of erythrocytes (6,7). MVO, revealed by cardiac magnetic resonance imaging (CMR), may diminish, and in some cases, resolve (2). The extravasation of red blood cells releases hemoglobin degradation products that are toxic (8). Localization of iron degradation products promote persisting inflammation and fibrosis, limiting infarct healing and promoting adverse left ventricular remodeling and worse clinical outcomes in the longer term (9).

The time course of MVO and myocardial hemorrhage in post-MI patients is now reasonably well understood. MVO is an upstream problem and almost always precedes myocardial hemorrhage, which would not be expected to occur in its absence (2,10). Acute microvascular dysfunction (obstruction) may recover or persist and evolve into irreversible myocardial hemorrhage (2). Carrick et al (11) undertook a longitudinal clinical study of the temporal evolution of myocardial infarct pathologies using serial contrast-enhanced cardiovascular CMR at 4 time points after primary PCI (4-12 hours, 3 days, 10 days, and 7 months) in an unselected series of STEMI survivors. The main findings were as follows: 1) the overall incidence of myocardial hemorrhage was 43%; and 2) approximately one-quarter of the patients had evidence of myocardial hemorrhage 4-12 hours post-MI, hemorrhage detection increased progressively with 20% new cases at 3 days compared with 4-12 hours, and hematoma persisted at 10 days and 7 months in 37% and 13% patients, respectively (**Figure 1**). Myocardial hemorrhage was associated with sustained reductions in left ventricular ejection fraction and adverse left ventricular remodeling from baseline through 7 months. Based on these observations, myocardial hemorrhage appears to increase progressively after reperfusion with a primary hyperacute phase <12 hours post-MI culminating in a peak 3 days later. The interval between days 1 and 3, potentially a phase of secondary hemorrhage, suggests that there may be a therapeutic window to prevent hemorrhage should targeted therapies become available in the future.

SEE PAGE 35

In this issue of the *Journal*, Liu et al (12) provide a translational clinical study of myocardial injury in relation to the occurrence of intramyocardial

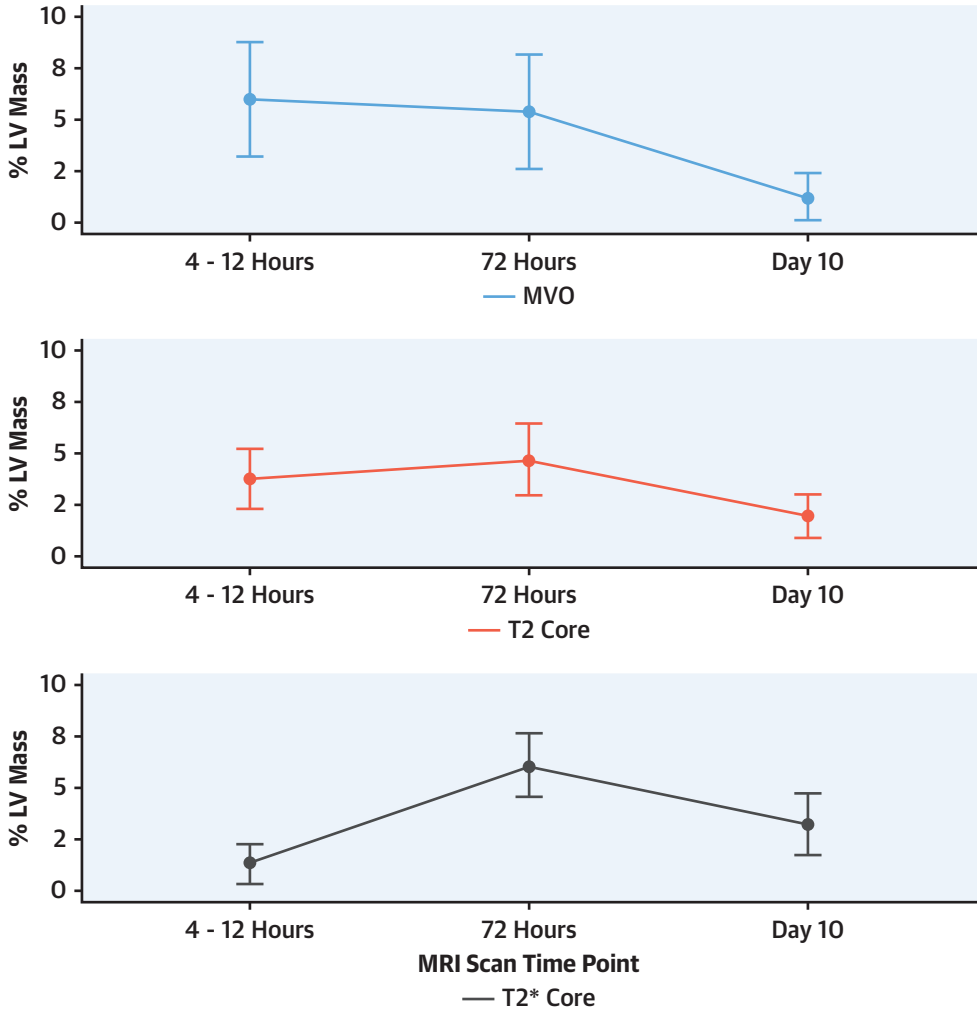
*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the [a]British Heart Foundation Research Centre of Excellence, University of Glasgow, Glasgow, Scotland; [b]West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, Scotland; and the [c]Centro Nacional de Investigaciones Cardiovasculares, IIS-Hospital Universitario Fundación Jiménez Díaz, and CIBERCV, Madrid, Spain.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2021.11.002

FIGURE 1 Time-Course of MVO and IMH After Primary PCI



Time course of microvascular obstruction and intramyocardial hemorrhage Reflected by T2- and T2* within the infarct core (2).
IMH = intramyocardial hemorrhage; LV = left ventricular; MRI = magnetic resonance imaging; MVO = microvascular obstruction; PCI = percutaneous coronary intervention.

hemorrhage. They studied cardiac troponin kinetics in 70 patients treated by primary PCI for acute STEMI, and 70% had evidence of myocardial hemorrhage by T2* CMR criteria. They then assessed the effects of myocardial hemorrhage on ischemic burden using a canine experimental model of myocardial ischemia/reperfusion injury and serial assessments of troponin and MI size using time-lapse imaging. In the clinical study, the investigators found that troponin following primary PCI peaked earlier (12 hours vs 24 hours; $P < 0.05$) and was higher in patients with hemorrhage ($P < 0.01$). In hemorrhagic animals, reperfusion led to an endo-epicardial wave front of necrosis that was not observed in nonhemorrhagic cases ($P < 0.001$). MI size and salvage were not different at 1-hour post-reperfusion in animals with and without hemorrhage; however, within 72 hours of reperfusion, a 4-fold greater loss in salvageable myocardium was evident in hemorrhagic MIs ($P < 0.001$). This paralleled observations in the clinical study, with larger MIs occurring in hemorrhagic cases ($P < 0.01$). The investigators concluded that myocardial hemorrhage is a determinant of MI size, drives MI expansion after reperfusion, and compromises myocardial salvage.

We applaud the investigators for providing new, mechanistic insights into a difficult clinical problem that has an unmet therapeutic need. Only through mechanistic studies that are transferable to the clinic

can therapeutic targets be identified. The authors executed elegant experimental imaging with serial scans. To avoid the limitations of edema as a surrogate of area-at-risk (AAR) (13), they acquired ^{13}N-ammonia positron emission tomography studies during coronary occlusion. It is noteworthy that animals that were defined as having hemorrhagic infarction based on the CMR scan at 3 days already had a much larger MI size at 24 hours. Previous experimental studies have demonstrated that hemorrhage at 24 hours is still not large (certainly much smaller than at days 3-4 postreperfusion) (14). Therefore, it is difficult to completely dissect the impact of hemorrhage per se (vs MI size) on adverse remodeling. It might be the case that more severe ischemia/reperfusion events are associated with large MI sizes and higher degree of hemorrhage. Considering some of the potential limitations of this paper, the prevalence of myocardial hemorrhage (70%) was higher compared with prior studies implying a level of selection bias in the population. Further, future research should assess the validity of T2* for accurate sizing of intramyocardial hemorrhage, including at different time points, because T2* decay is influenced by the breakdown products of hemoglobin which evolve over time.

In conclusion, intramyocardial hemorrhage represents the final frontier for preventing heart failure post-MI. It is readily detected using CMR, and clinical research of novel therapeutic approaches (15,16) merits prioritization.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Berry has received research funding from the British Heart Foundation grant (RE/18/6134217), Chief Scientist Office, EPSRC (EP/R511705/1, EP/S030875/1), European Union (754946-2), Medical Research Council (MR/S018905/1), and UKRI (MC/PC/20014); and is employed by the University of Glasgow, which holds consultancy and research agreements for his work with Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Causeway Therapeutics, Coroventis, Genentech, GlaxoSmithKline, HeartFlow, Menarini, Neovasc, Siemens Healthcare, and Valo Health. Dr Ibanez is supported by the European Commission (ERC-CoG grant Nº 819775) and by the Spanish Ministry of Science and Innovation (MCN; 'RETOS 2019' grant Nº PID2019-107332RB-I00). The CNIC is supported by the ISCIII, the Ministry of Science and Innovation, and the Pro CNIC Foundation. CNIC is a Severo Ochoa Center of Excellence.

ADDRESS FOR CORRESPONDENCE: Prof Colin Berry, BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, 126 University Place, University of Glasgow, Glasgow G12 8TA, Scotland, United Kingdom. E-mail: colin.berry@glasgow.ac.uk.

REFERENCES

1. Carrick D, Haig C, Rauhalammi S, et al. Pathophysiology of LV remodeling in survivors of STEMI: inflammation, remote myocardium, and prognosis. *J Am Coll Cardiol Img*. 2015;8(7):779–789.

2. Carrick D, Haig C, Ahmed N, et al. Myocardial hemorrhage after acute reperfused ST-segment-elevation myocardial infarction: relation to microvascular obstruction and prognostic significance. *Circ Cardiovasc Imaging*. 2016;9(1):e004148.

3. Ganame J, Messalli G, Dymarkowski S, et al. Impact of myocardial haemorrhage on left ventricular function and remodelling in patients with reperfused acute myocardial infarction. *Eur Heart J*. 2009;30(12):1440–1449.

4. Reinstadler SJ, Stiermaier T, Reindl M, et al. Intramyocardial haemorrhage and prognosis after ST-elevation myocardial infarction. *Eur Heart J Cardiovasc Imaging*. 2019;20(2):138–146.

5. de Waha S, Patel MR, Granger CB, et al. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. *Eur Heart J*. 2017;38(47):3502–3510.

6. Higginson LA, White F, Heggtveit HA, Sanders TM, Bloor CM, Covell JW. Determinants of myocardial hemorrhage after coronary reperfusion in the anesthetized dog. *Circulation*. 1982;65(1):62–69. https://doi.org/10.1161/01.cir.65.1.62. PMID: 7053289.

7. Payne AR, Berry C, Kellman P, et al. Bright-blood T(2)-weighted MRI has high diagnostic accuracy for myocardial hemorrhage in myocardial infarction: a preclinical validation study in swine. *Circ Cardiovasc Imaging*. 2011;4(6):738–745. https://doi.org/10.1161/CIRCIMAGING.111.965095

8. Rifkind JM, Mohanty JG, Nagababu E. The pathophysiology of extracellular hemoglobin associated with enhanced oxidative reactions. *Front Physiol*. 2015;5:500.

9. Carberry J, Carrick D, Haig C, et al. Persistent iron within the infarct core after st-segment elevation myocardial infarction: implications for left ventricular remodeling and health outcomes. *J Am Coll Cardiol Img*. 2018;11(9):1248–1256.

10. Wang G, Yang HJ, Kali A, Cokic I, Tang R, Xie G, Yang Q, Francis J, Li S, Dharmakumar R. Influence of myocardial hemorrhage on staging of reperfused myocardial infarctions with T2 cardiac magnetic resonance imaging: insights into the dependence on infarction type with ex vivo validation. *J Am Coll Cardiol Img*. 2019;12(4):693–703.

11. Carrick D, Haig C, Ahmed N, et al. Temporal evolution of myocardial hemorrhage and edema in patients after acute ST-segment elevation myocardial infarction: pathophysiological insights and clinical implications. *J Am Heart Assoc*. 2016;5(2):e002834.

12. Liu T, Howarth AG, Chen Y, et al. Intramyocardial hemorrhage and the "wave-front" of reperfusion injury compromising myocardial salvage. *J Am Coll Cardiol*. 2022;79(1):35–48.

13. Fernandez-Jimenez R, Barreiro-Perez M, Martin-Garcia A, et al. Dynamic edematous response of the human heart to myocardial infarction: implications for assessing myocardial area at risk and salvage. *Circulation*. 2017;136:1288–1300.

14. Rossello X, Lopez-Ayala P, Fernandez-Jimenez R, et al. R2 prime (R2') magnetic resonance imaging for post-myocardial infarction intramyocardial haemorrhage quantification. *Eur Heart J Cardiovasc Imaging*. 2020;21:1031–1038.

15. García-Ruiz JM, Galán-Arriola C, Fernández-Jiménez R, et al. Bloodless reperfusion with the oxygen carrier HBOC-201 in acute myocardial infarction: a novel platform for cardioprotective probes delivery. *Basic Res Cardiol*. 2017;112(2):17.

16. Fernández-Jiménez R, Galán-Arriola C, Sánchez-González J, et al. Effect of ischemia duration and protective interventions on the temporal dynamics of tissue composition after myocardial infarction. *Circ Res*. 2017;121(4):439–450.

KEY WORDS microvascular obstruction, myocardial hemorrhage, primary PCI