JACC: BASIC TO TRANSLATIONAL SCIENCE
VOL. 7, NO. 5, 2022
ISSN 2452-302X

Letters

RESEARCH CORRESPONDENCE

S1P Lyase Inhibition Starting After Ischemia/Reperfusion Improves Postischemic Cardiac Remodeling

Adjunct cardioprotection beyond that conferred by coronary reperfusion in the setting of acute myocardial infarction (AMI) has been a conceptual, experimental, and clinical challenge for many years.[1] Despite promising animal studies, numerous approaches have failed to improve outcomes after AMI in clinical trials, which has been attributed to the already excellent clinical outcome and normalized ejection fraction in AMI patients undergoing timely revascularization.[1] Nevertheless, more than 10% of patients might not benefit from coronary revascularization because of delay of symptom onset and clinical presentation, and a substantial proportion of patients (more than 10%)—eg, latecomers—are not eligible for the standard interventional procedure.[1] Especially in these patients, heart failure with reduced ejection fraction (HFrEF), disability, and mortality are frequent. On the other hand, even the high rate of revascularization does not completely prevent functional impairment of left ventricular function and HFrEF, which has profound socioeconomic impact as well as high morbidity and mortality. Therefore, druggable targets to improve cardiac remodeling in addition to revascularization and independent of initial infarct size are still urgently needed.

Reduced plasma levels of the endogenous bioactive sphingolipid S1P have been linked to the incidence and severity of coronary artery disease, AMI, and HFrEF.[2] Experimentally, administration of S1P or its clinical analogon fingolimod (Gilenya, Novartis) before cardiac ischemia/reperfusion (I/R) has been shown to reduce infarct size and improve cardiac function in mice and pigs.[3,4] Accordingly, high endogenous S1P caused by genetic or pharmacologic inhibition of S1P degradation by the S1P lyase before I/R has also proven beneficial.[5] However, such approaches are not applicable in the clinical situation where drug therapy were initiated during or after revascularization and must decrease reperfusion injury and/or improve cardiac remodeling if it were to be considered truly adjunct. Such drugs are dearly in demand.

In our study, we thus tested whether the administration of the S1P lyase inhibitor 4-deoxypyridoxine (DOP) starting 24 hours after a 30-minute ischemia followed by reperfusion of the left descending artery in mice may fulfill these criteria. Remarkably, DOP treatment (5 mg/kg orally) reduced scar formation by 50% on histomorphometry and improved ejection fraction by 20% on echocardiography 28 days after I/R (**Figure 1**). End-systolic volume was reduced by 23% (control: 47.11 ± 11.06 μL vs DOP: 36.21 ± 7.57 μL; $P = 0.016$), whereas end-diastolic volume was unchanged (control: 70.98 ± 7.69 μL vs DOP: 64.39 ± 10.34 μL; $P = 0.13$). Invasive blood pressure measurements showed no change in afterload (Pmax: control: 82.26 ± 16.70 mm Hg vs DOP: 84.83 ± 0.53 mm Hg; $P = 0.77$; Pmin: control: 56.90 ± 9.84 mm Hg vs DOP: 58.63 ± 0.33 mm Hg; $P = 0.74$; n = 5 not shown).

Remodeling after AMI is a complex process involving inflammation, scar formation, and myocardial adaptation, and it is conceivable that S1P signaling may play a role in these processes. The S1P receptor 1 (S1PR1) is extremely important in mediating all these effects in cardiac endothelial cells, fibroblasts, and myocytes. Because several S1PR1 agonists besides fingolimod (Gilenya), such as ozanimod (Zeposia, Celgene) and siponimod (Mayzent, Novartis), have been recently approved for relapsing multiple sclerosis, they may appear as an attractive and easy-to-implement adjunct drug therapy to improve cardiac performance after revascularization. Understanding the biological S1P signaling pathways leading to a better cardiac recovery after I/R is of utmost relevance for the development of any S1P-based adjunct cardioprotective pharmacologic therapy initiated during or after coronary revascularization.

Amin Polzin, MD†
Lisa Dannenberg, MD†
Marcel Benkhoff, MSc

Maike Barcik, MSc
Petra Keul, PhD
Carolin Helten, MD
Tobias Zeus, MD
Malte Kelm, MD
*Bodo Levkau, MD

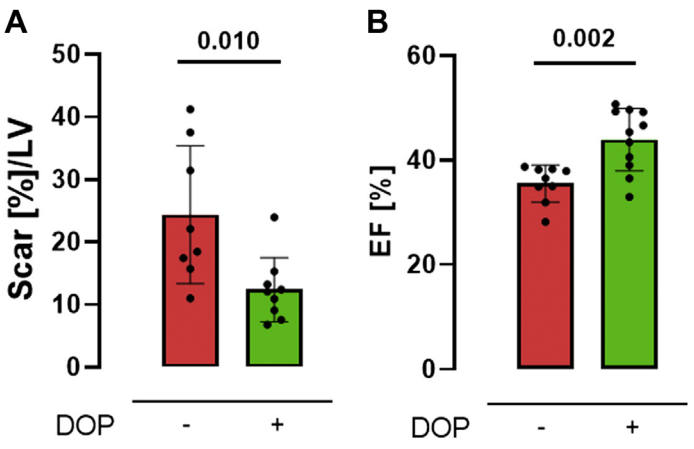
*Institute of Molecular Medicine III
Heinrich Heine University
Universitätsstrasse 1
40225 Düsseldorf, Germany
E-mail: bodo.levkau@med.uni-duesseldorf.de

https://doi.org/10.1016/j.jacbts.2022.03.009

†Drs Polzin and Dannenberg contributed equally to this work. This work was supported by the Forschungskommission of the Medical Faculty of the Heinrich Heine University (29-2019 to Dr Dannenberg and 18-2019 to Dr Polzin) and by the German Research Foundation (LE 940/7-1 to Dr Levkau, PO 2247/2-1 to Dr Polzin, and SFB1116 to Drs Polzin and Levkau). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The study complied with all national requirements for the care and use of laboratory animals. The authors thank Stefanie Becher for experimental support.

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.

FIGURE 1 DOP Treatment Starting After Coronary Reperfusion Prevents Adverse Cardiac Remodeling at 28 Days After Ischemia/Reperfusion in the Mouse



DOP treatment starting 24 hours after ischemia/reperfusion improves long-term remodeling measured by **(A)** scar formation measured by Picro-Sirius Red (control: 24.37% ± 11.01% vs DOP: 12.36% ± 5.13%; $P = 0.010$); and **(B)** ejection fraction on echocardiography (control: 35.52% ± 3.54% vs 43.94% ± 5.94%; $P = 0.002$); unpaired Student's *t-test*. DOP = 4-deoxypyridoxine; EF = ejection fraction; LV = left ventricle.

REFERENCES

1. Heusch G. Critical issues for the translation of cardioprotection. *Circ Res*. 2017;120:1477–1486.

2. Polzin A, Piayda K, Keul P, et al. Plasma sphingosine-1-phosphate concentrations are associated with systolic heart failure in patients with ischemic heart disease. *J Mol Cell Cardiol*. 2017;110:35–37.

3. Theilmeier G, Schmidt C, Herrmann J, et al. High-density lipoproteins and their constituent, sphingosine-1-phosphate, directly protect the heart against ischemia/reperfusion injury in vivo via the S1P3 lysophospholipid receptor. *Circulation*. 2006;114:1403–1409.

4. Santos-Gallego CG, Vahl TP, Goliasch G, et al. Sphingosine-1-phosphate receptor agonist fingolimod increases myocardial salvage and decreases adverse postinfarction left ventricular remodeling in a porcine model of ischemia/reperfusion. *Circulation*. 2016;133:954–966.

5. Bandhuvula P, Honbo N, Wang GY, et al. S1P lyase: a novel therapeutic target for ischemia-reperfusion injury of the heart. *Am J Physiol Heart Circ Physiol*. 2011;300:H1753–H1761.