Title

Redox Paradox: Can Hypoxia Heal Ischemic Hearts?

Journal

Developmental Cell, 39(4)

ISSN

1534-5807

Authors

Guimarães-Camboa, Nuno

Evans, Sylvia M

Publication Date

2016-11-01

DOI

10.1016/j.devcel.2016.11.007

Peer reviewed

HHS Public Access

Author manuscript

Dev Cell. Author manuscript; available in PMC 2017 August 08.

Published in final edited form as:

Dev Cell. 2016 November 21; 39(4): 392–394. doi:10.1016/j.devcel.2016.11.007.

Redox Paradox: Can Hypoxia Heal Ischemic Hearts?

Nuno Guimarães-Camboa[1] and **Sylvia M. Evans**[1,2,3,*]

[1]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California at San Diego, La Jolla, CA 92093, USA

[2]Department of Medicine, University of California at San Diego, La Jolla, CA 92093, USA

[3]Department of Pharmacology, University of California at San Diego, La Jolla, CA 92093, USA

Abstract

Adult cardiomyocytes are largely thought to lack proliferative and therefore regenerative potential. Reporting in *Nature*, Nakada et al. (2016) find that a hypoxic regime reduces mitochondrial metabolism and promotes proliferation in adult mouse cardiomyocytes, resulting in increased regeneration following myocardial infarction. These findings suggest the potential to transform post-MI care.

Damage to the heart following blockage of blood flow—known as ischemic injury or myocardial infarction (MI)—is a fundamental human health problem. A major impediment to recovery from MI is the fact that adult mammalian cardiomyocytes appear to largely lack proliferative capacity. Interestingly, adult zebrafish cardiomyocytes do proliferate. In studies using this system, hypoxia has been shown to induce de-differentiation, cell cycle re-entry, and proliferation (Jopling et al., 2012). Mounting evidence suggests that hypoxia, and resulting differences in cellular redox state, can also influence mammalian cardiomyocyte proliferation. Expression of hypoxia-inducible factor (HIF) 1 alpha is required for proliferation of a subset of cardiomyocytes that reside within a hypoxic niche (Guimarães-Camboa et al., 2015). Other work has also identified a small population of adult mouse cardiomyocytes that retain proliferative capacity and are labeled by a transgene that suggests they reside within a hypoxic niche (Kimura et al., 2015). Relatedly, perinatal oxidative stress and consequent DNA damage is potentially a major contributor to cardiomyocyte cell-cycle withdrawal in the first place (Puente et al., 2014). Now, new work from the Sadek group suggests that exposing adult mice to an extreme hypoxic environment can promote cardiac regeneration, suggesting a potential direct therapeutic application of these fundamental principles (Nakada et al., 2016).

In the study by Nakada et al. (2016), adult mice were subjected to a gradual (1% per day) decrease in ambient oxygen concentration, going from 20.9% to 7% oxygen within 2 weeks, and were then kept at 7% oxygen for 2 weeks (Figure 1A). As a comparison, 7% oxygen is similar to conditions on the summit of Mount Everest (Peacock, 1998). Hearts from animals subjected to hypoxia showed, as predicted from previous studies (Kobs et al., 2005),

*Correspondence: syevans@ucsd.edu, http://dx.doi.org/10.1016/j.devcel.2016.11.007.

pulmonary hypertension accompanied by hypertrophy of the right ventricle (RV), as compared to normoxic control hearts. Decreased mitochondrial content with corresponding changes in metabolites, decreased radical oxygen species (ROS), and decreased DNA damage were also observed in hypoxic hearts. These findings are consistent with the known hypoxia-induced switch in energy metabolism, from mitochondrial oxidative phosphorylation to glycolysis (Guimarães-Camboa et al., 2015). Under these conditions, the authors observed significantly decreased size of cardiomyocytes within the left ventricle (LV). They also saw increased cardiomyocyte proliferation, as assessed by BrdU labeling and antibodies to phospho-histone H3 and Aurora B kinase, although whether this increase was in RV or LV cardiomyocytes was not specifically mentioned. Statistically significant ($p < 0.05$) increases or decreases were observed in mononucleated and binucleated cardiomyocytes, respectively. Because it is thought that mononucleated myocytes might be more amenable to cell cycle re-entry, this observation suggests the presence of a greater number of myocytes capable of proliferation (Kimura et al., 2015). Lastly, isolation of cardiomyocytes from whole hearts followed by counting suggested a 75% increase in total cardiomyocyte number in hypoxic hearts. Altogether, from these findings in hypoxemic animals, the authors concluded that their hypoxic regimen resulted in increased proliferation of normally recalcitrant adult cardiomyocytes.

Following these observations, the authors tested whether a similar hypoxic regimen could affect functional cardiac outcomes after MI (Figure 1B). One week post-MI, experimental mice underwent a gradual reduction of oxygen to 7%. After 2 weeks of 7% oxygen, tissues were collected for histological analyses, or mice were gradually transferred to normal atmospheric oxygen (a 2% daily increase in oxygen for 1 week) before physiological assessment of contractile function. Resulting analyses of hypoxemic animals relative to normoxic controls demonstrated statistically significant decreases in fibrotic scar, enhanced re-vascularization of the ischemic area, increased proliferation of healthy myocytes remote to the ischemic region, and an improvement in cardiac function, as indicated by ejection fraction calculated from echocardiographic M-mode measurements of minor axis dimensions. Altogether, the authors conclude that rather severe hypoxic treatment can increase adult cardiomyocyte proliferation at baseline and that a similar hypoxic treatment can promote cardiac regeneration post-MI, in part by promoting cardiomyocyte proliferation.

Although these provocative findings are of great potential interest and clinical impact, there are some caveats to the conclusions drawn that perhaps merit attention and further inquiry. Accurate assessment of adult cardiomyocyte proliferation is notoriously challenging, owing to complexity of smaller, more proliferative, and tightly packed non-myocyte populations in the heart. Thus, as first pointed out by Loren Field’s group, it is generally preferable to utilize a cardiomyocyte nuclear marker to more accurately identify cells (Hirai et al., 2016; Soonpaa et al., 2013), something that was not done in this study. There are also other potentially confounding factors in interpreting the results. Although the substantial increase in the number of isolated ventricular cardiomyocytes from hypoxemic hearts might be consistent with increased myocyte proliferation, another possibility is that hypoxia-induced changes in extracellular matrix could affect yields of cardiomyocytes following isolation. Furthermore, there are likely to be complicated physiological consequences of pulmonary

hypertension induced by hypoxic treatment. The increase in pulmonary vascular resistance and acute pulmonary hypertension in the setting of hypoxemia may reduce forward flow from the right to the left heart, essentially unloading the left ventricle. A similar phenomenon has been observed with right ventricular failure and low right ventricular output states, with unloading and atrophy of left ventricular myocytes (Hardziyenka et al., 2011). With respect to the latter, it is interesting to note that Nakada et al. (2016) observed smaller left ventricular myocytes in hypoxemic hearts throughout the left ventricle at baseline and within the remote zone post-MI. Unloading of the left ventricle may result in lower wall stress, reduced ventricular dilatation, and apparent improved contractile function, when assessed by M-mode measurements as performed in the study by Nakada et al. (2016). Whether hypoxemic animals developed RV hypertrophy subsequent to MI was not reported. If that was the case, geometric alterations consequent to RV hypertrophy might also affect the M-mode measurements. In this respect, it is important to note that M-mode measurements of minor axis dimensions do not necessarily reflect global LV function (ejection fraction).

Finally, experimentally induced MI is a complex model, subject to tremendous variability of injury size. Nakada et al. (2016) did not mention whether hypoxic treatment resulted in increased mortality post-MI. If that was the case, examination of only surviving hypoxic animals might bias the data from hypoxic animals toward those with smaller infarcts. Altogether, the results of the study are intriguing and open the way for future work in this area to explore the potential role of hypoxia in promoting mammalian heart regeneration. The results raise the appealing clinical prospect of mitigating consequences of myocardial infarction in humans by transferring, for controlled periods of time, patients to hypobaric chambers in the immediate aftermath of an ischemic episode. However, prior to being applicable in humans, these findings need to be further validated in mouse models, as well as in other mammalian animal models.

References

Guimarães-Camboa N, Stowe J, Aneas I, Sakabe N, Cattaneo P, Henderson L, Kilberg MS, Johnson RS, Chen J, McCulloch AD, et al. Dev Cell. 2015; 33:507–521. [PubMed: 26028220]

Hardziyenka M, Campian ME, Reesink HJ, Surie S, Bouma BJ, Groenink M, Klemens CA, Beekman L, Remme CA, Bresser P, Tan HL. J Am Coll Cardiol. 2011; 57:921–928. [PubMed: 21329838]

Hirai M, Cattaneo P, Chen J, Evans SM. Circ Res. 2016; 118:916–919. [PubMed: 26987912]

Jopling C, Suñé G, Faucherre A, Fabregat C, Izpisua Belmonte JC. Circulation. 2012; 126:3017–3027. [PubMed: 23151342]

Kimura W, Xiao F, Canseco DC, Muralidhar S, Thet S, Zhang HM, Abderrahman Y, Chen R, Garcia JA, Shelton JM, et al. Nature. 2015; 523:226–230. [PubMed: 26098368]

Kobs RW, Muvarak NE, Eickhoff JC, Chesler NC. Am J Physiol Heart Circ Physiol. 2005; 288:H1209–H1217. [PubMed: 15528223]

Nakada, Y., Canseco, DC., Thet, S., Abdisalaam, S., Asaithamby, A., Santos, CX., Shah, A., Zhang, H., Faber, JE., Kinter, MT., et al. Nature. 2016. Published online October 31 2016 http://dx.doi.org/10.1038/nature20173

Peacock AJ. BMJ. 1998; 317:1063–1066. [PubMed: 9774298]

Puente BN, Kimura W, Muralidhar SA, Moon J, Amatruda JF, Phelps KL, Grinsfelder D, Rothermel BA, Chen R, Garcia JA, et al. Cell. 2014; 157:565–579. [PubMed: 24766806]

Soonpaa MH, Rubart M, Field LJ. Biochim Biophys Acta. 2013; 1833:799–803. [PubMed: 23142641]

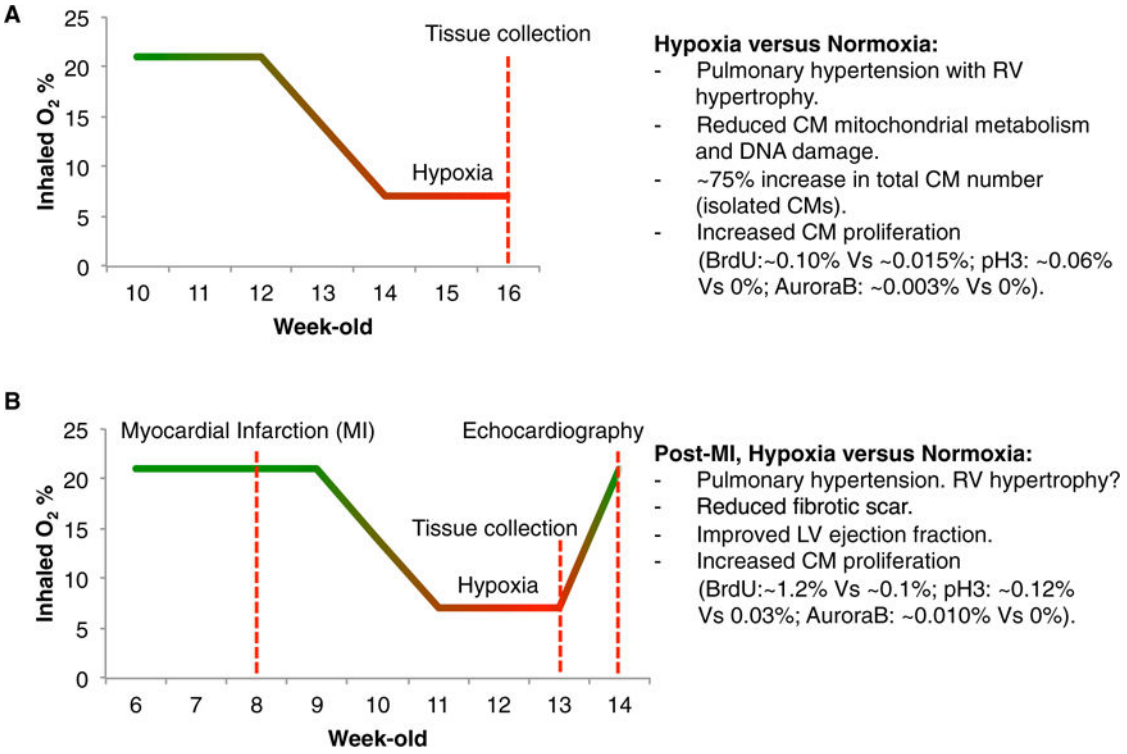

Figure 1.

Graphical Representation of Experimental Design and Summary of Differences between Hypoxic and Control Hearts, Reported by Nakada et al.

(A) Wild-type animals.

(B) Wild-type animals post-MI. Abbreviations: BrdU, Bromodeoxyuridine; CM, cardiomyocyte; LV, left ventricle; pH3, phospho-histone 3; RV, right ventricle.