JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 18, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.09.010

REVIEW TOPIC OF THE WEEK

Mechanisms Contributing to the Progression of Ischemic and Nonischemic Dilated Cardiomyopathy

Possible Modulating Effects of Paracrine Activities of Stem Cells

Anita A. Kelkar, MD, MPH,* Javed Butler, MD, MPH,† Erik B. Schelbert, MD, MS,‡ Stephen J. Greene, MD,§ Arshed A. Quyyumi, MD,* Robert O. Bonow, MD,§ Ira Cohen, MD, PhD,† Mihai Gheorghiade, MD,§ Michael J. Lipinski, MD,‖ Wei Sun, PhD,‖ Dror Luger, PhD,‖ Stephen E. Epstein, MD‖

ABSTRACT

Over the past 1.5 decades, numerous stem cell trials have been performed in patients with cardiovascular disease. Although encouraging outcome signals have been reported, these have been small, leading to uncertainty as to whether they will translate into significantly improved outcomes. A reassessment of the rationale for the use of stem cells in cardiovascular disease is therefore timely. Such a rationale should include analyses of why previous trials have not produced significant benefit and address whether mechanisms contributing to disease progression might benefit from known activities of stem cells. The present paper provides such a reassessment, focusing on patients with left ventricular systolic dysfunction, either nonischemic or ischemic. We conclude that many mechanisms contributing to progressive left ventricular dysfunction are matched by stem cell activities that could attenuate the myocardial effect of such mechanisms. This suggests that stem cell strategies may improve patient outcomes and justifies further testing.
(J Am Coll Cardiol 2015;66:2038–47) © 2015 by the American College of Cardiology Foundation.

Over the past 1.5 decades, numerous stem cell trials have been performed in patients with cardiovascular disease, using both autologous and allogeneic stem cells, numerous stem cell types, and various strategies to administer the stem cells. Although many individual studies reported encouraging signals, these were all phase 1 or 2 studies with appropriately small numbers of patients, and their conclusions must therefore be considered preliminary. In an attempt to increase statistical robustness, a recent meta-analysis assessing the results of all randomized clinical trials of stem cell therapy for patients with acute myocardial infarction (AMI) was performed, demonstrating no net

From the *Cardiology Division, Emory University, Atlanta, Georgia; †Stony Brook University, Stony Brook, New York; ‡Cardiology Division, University of Pittsburgh, Pittsburgh, Pennsylvania; §Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and the ‖MedStar Heart and Vascular Institute, MedStar Washington Hospital Center, Washington, DC. Dr. Quyyumi has served as a consultant to and has stock options with CardioCell. Dr. Cohen has received research support from the National Institutes of Health. Dr. Gheorghiade has served as a consultant to Novartis, Bayer, Takeda, Jenssen, Cardicell, and Steth; and has relationships with Abbott, Astellas, AstraZeneca, Cardiorentis, Corthera, Cytokinetics, CytoPherx, Debiopharm, Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Intersection Medical, Inc., Johnson & Johnson, Medtronic, Merck, Ono Pharma, Otsuka, Palatin Technologies, Pericor Therapeutics, Protein Design, Sanofi, Sigma Tau, Solvay, Sticares InterACT, and Trevena Therapeutics. Dr. Butler has received research support from the National Institutes of Health and the European Union; and is a consultant to Amgen, Bayer, Cardiocell, Celladon, Medtronic, Novartis, Takeda, Trevena, and Zensun. Dr. Schelbert has received contrast material from Bracco Diagnostics, donated for research purposes. Dr. Cohen has a research agreement with Servier for development of an atrial fibrillation drug. Dr. Epstein has served as a consultant to, served on the scientific advisory board of, and has equity interests in CardioCell. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 6, 2015; revised manuscript received August 24, 2015, accepted September 2, 2015.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

beneficial effects on outcomes, except for a small improvement in ejection fraction (1). A major review of patients with heart failure (HF) yielded similar conclusions (2).

Given these results, a reassessment of the rationale for the use of stem cells in cardiovascular disease is timely. There are powerful arguments for concluding that stem cell-based mechanisms exist that might be therapeutically efficacious, thereby making continued pursuit of stem cell strategies for treating cardiovascular disease reasonable. Such a rationale would have to include the likely mechanisms contributing to progression of the disease and the potential influences, if any, of stem cells on such mechanisms. The present paper is intended to provide such a rationale, focusing on the patient with HF and left ventricular (LV) systolic dysfunction, whether nonischemic cardiomyopathy (NICM) or ischemic cardiomyopathy (ICM).

By definition, the most conspicuous difference between ICM and NICM is the existence of atherosclerotic lesions of the epicardial coronary arteries in patients with ICM and the absence of such lesions in patients with NICM. This leads to 1 major difference in the initiation of the cardiomyopathic process and its progression to HF: most patients with ICM have had 1 or more previous clinically-recognized or clinically-silent myocardial infarctions (MIs), with the development of progressive remodeling and LV dysfunction occurring consequent either to an initial large injury to the LV or to smaller, repeated injuries occurring over time. Such a mechanism does not exist in NICM.

Despite this difference, disease progression in ICM can occur, even when the initial infarct does not result in severe LV dysfunction, and conversely, many patients with large infarcts do not develop such progression (3,4). These findings raise the possibility that a given patient may experience progressive deterioration of LV function on the basis of additional mechanisms independently of MI, which may be shared by patients with ICM and with NICM.

Another abnormality shared by both ICM and NICM patients, which might provide an important therapeutic target, is the presence of dysfunctional but viable myocardium. Patients with ICM invariably have areas of myocardial scar, usually extensive, whereas patients with NICM either do not or have it to a lesser extent. Bello et al. (5) observed, using cardiac magnetic resonance imaging, that whereas all patients with ICM had myocardial scar, only 12% of patients with NICM did so. Importantly, both ICM and NICM patients had areas of myocardial dysfunction due not to scar, but to dysfunctional *viable* myocardium (DVM).

Although more common and extensive in patients with NICM, DVM provides a potential target for therapeutic interventions in both ICM and NICM. If the dysfunctional tissue consists of viable rather than scarred myocardium, LV function can presumably be improved. **Figure 1**, adapted from Bello et al. (5), demonstrates these concepts—that LV ejection fraction can be improved, that the magnitude of improvement is related to the percent of the LV that is dysfunctional but viable, and that DVM is present in both ICM and NICM.

The concept of DVM may also help direct which patients may benefit most from stem cell therapy. As the stage of HF that may be considered too late for stem cell therapy is unclear, the presence of DVM may help guide the identification of those patients with the most potential to benefit.

The potential of any therapy, including stem cells, to improve outcomes in ICM or NICM is related not only to its effects on restoring function to DVM, but also to its capacity to improve processes that contribute to

ABBREVIATIONS AND ACRONYMS

ECM = extracellular matrix

HF = heart failure

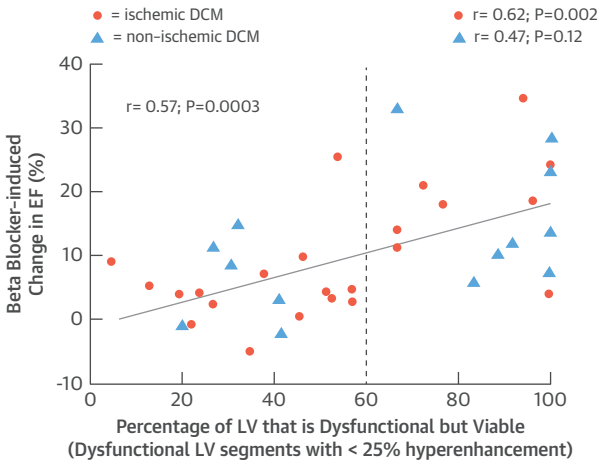
ICM = ischemic cardiomyopathy

MMP = matrix metalloproteinase

MSC = mesenchymal stem cells

NICM = nonischemic cardiomyopathy

FIGURE 1 Ischemic or Nonischemic DCM: Identification of Dysfunctional But Viable Myocardium and Relation to Beta-Blocker–Induced Increase in EF



Dysfunctional myocardium refers to myocardium that is dysfunctional in the absence of delayed hyperenhancement by magnetic resonance imaging. The magnitude of improvement in LV EF that occurs following initiation of beta-blocker therapy is directly related to the percent of the LV that is dysfunctional, but still viable. Importantly, although compared with patients with ischemic cardiomyopathy, those with nonischemic cardiomyopathy have greater portions of the LV that are dysfunctional. However, viable, dysfunctional myocardium is present in both groups. Adapted with permission from Bello et al. (5). DCM = dilated cardiomyopathy; EF = ejection fraction; LV = left ventricle.