Chronic Heart Failure
Opportunities for a Bridge Between China and the United States

Yingnan Bai, Piero Anversa, Junbo Ge

Death by heart failure (HF) is a terrible long agony that does not spare celebrities. Poets who wrote about broken hearts, from Samuel Taylor Coleridge to Robert Frost, Edgar Allan Poe, and Pablo Neruda, and Hollywood stars who played on the stage or created characters experiencing heartache from Barbara Stanwyck to Bing Crosby, Alfred Hitchcock, and Elizabeth Taylor died of chronic heart disease. The beautiful description of the sadness of love by Tagore, perhaps the greatest writer in modern Indian literature, evokes the dramatic experience of patients with advanced HF and pulmonary edema:

Suddenly a wild wave
Broke over my heart’s shores
And drowned all language.

Rabindranath Tagore was a poet, philosopher, artist, playwright, composer, and novelist. Tagore was India’s first Nobel laureate; he won the Nobel Prize for Literature in 1913. The beautiful description of the sadness of love by Tagore,1 perhaps the greatest writer in modern Indian literature, evokes the dramatic experience of patients with advanced HF and pulmonary edema:

Suddenly a wild wave
Broke over my heart’s shores
And drowned all language.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, China (Y.B., J.G.); and Departments of Anesthesia and Medicine, Division of Cardiovascular Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA (Y.B., P.A.).

Correspondence to Junbo Ge, MD, Institute of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, China. E-mail ge.junbo2@zs-hospital.sh.cn or Piero Anversa, MD, Division of Cardiovascular Medicine, Departments of Anesthesia and Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115. E-mail panversa@partners.org


Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.113.302124

7 million have a history of a previous cerebral ischemic event, and 2 million have experienced myocardial infarction. Moreover, there are 92.4 million adults in China with diabetes mellitus and 148.2 million with prediabetes mellitus,5,6 with a higher frequency in individuals aged ≥60 years. The number of patients with HF is 4.2 million7 but will increase rapidly, paralleling the striking increase in 2 major risk factors for HF, aging, and diabetes mellitus. Thus, cardiovascular disease is severely affecting the health of Chinese today, mimicking the dramatic situation in the United States and Europe.

China has undergone a profound transformation from a rural to an urban lifestyle; overwhelmingly crowded cities, constructions occurring all over with impressive skyscrapers and huge condominium, and stores and restaurants with products and cuisine from throughout the world, have had an unquestionable impact on Chinese culture and daily routine. Shanghai is a typical example of the extraordinary revolution that has occurred in modern China; today, walking in downtown Shanghai is strikingly similar to walking in downtown Manhattan. A nice, comfortable feeling for one of the authors who lived for 35 years in the upper eastside of Manhattan, but a rather disturbing medical reality at the Institute of Cardiology, Zhongshan Hospital, Fudan University. There, the number of patients seen per day for cardiac problems is in the thousands. The waiting room is a large auditorium.

In the past 3 years, outpatient office visits at the Institute of Cardiology, Zhongshan Hospital numbered 316,577, 354,194, and 315,813, respectively. Among these patients, 11,245 were admitted to the hospital with coronary artery disease, and >300 were diagnosed with HF for the first time each year. On the basis of the data collected by the Shanghai Investigation Group,7 in 2000, coronary artery disease was the predominant cause of HF, comprising 55.7% of the cases, whereas hypertension accounted for 13.9%, rheumatic valve disease for 8.9%, and idiopathic dilated cardiomyopathy for 7.5%. In the United States, cardiovascular procedures increased by 28% from 2000 to 2010 with a total cost $312.6 billion in 2009,2 and a similar phenomenon may occur in China. These staggering numbers portend a dire outlook of the magnitude of the problem that modern China is facing, a problem that may reach enormous proportion in a few years and represents a veritable time bomb. The economic growth of the country and largest cities has been paralleled by a similar increase in cardiovascular diseases, currently the major cause of death in China1 and in the Western world.2

Because of the major political and economical role that China has in the world, common strategies need to be developed with other industrialized countries and the United States, in particular, to alleviate the burden of this public health problem. A collective effort should be made to identify novel
therapies that have the potential to modify the onset and evolution of cardiovascular diseases worldwide.

The improved clinical management of HF has extended the lifespan of this patient population; the quality of life, however, is far from optimal and rehospitalization is a recurrent event that reflects the inability to control the process and the inexorable progression of the underlying disease. What has been accomplished successfully is to delay the effects of the multiple variables responsible for negative ventricular remodeling, thereby enabling patients with HF to live longer; however, what has not yet been done is to reverse the disease, restoring, at least in part, the structural and functional integrity of the failing heart. Standard-of-care management, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, aldosterone antagonists, and diuretics with dosing and schedule tailored for maximal benefit, has not been able to cure HF. There is no question that we need better insights into the fundamental mechanisms that determine the anatomic and functional manifestations of advanced HF.

In the past 20 years, our understanding of cardiac pathophysiology has changed dramatically. For nearly a century, the heart has been considered a postmitotic organ unable to replace dying cardiomyocytes. This view, however, has recently been challenged and, despite ongoing controversy, a pool of resident cardiac stem cells (CSCs) that can acquire the cardiomyocyte, vascular smooth muscle, and endothelial cell lineages has been identified in the human heart. Stem cells have a high propensity for cell division and this property is maintained throughout the lifespan of the organ and organism. These concepts form the foundation of a new paradigm of the heart in which multipotent CSCs are implicated in the constant turnover of myocytes, endothelial cells, smooth muscle cells, and fibroblasts. Activated CSCs translocate to areas of injury where they grow and differentiate making myocardial regeneration a feasible reality. Theoretically, in a manner comparable with hematopoietic stem cells, which repopulate and completely reconstitute the ablated bone marrow, CSCs may rebuild the injured myocardium, improving the function of a severely diseased heart. In addition to CSCs, several other adult stem cells offer promise for clinical application, including mononuclear bone marrow cells, mesenchymal stromal cells, and CD34-positive cells (Figure). A recent meta-analysis strongly supports the concept that various classes of bone marrow cells interfere with left ventricular dysfunction, infarct size, ventricular remodeling, and mortality in patients with ischemic heart disease. Although in some studies little or no improvement in clinical outcome has been observed, the overwhelming majority of data are consistent with a sustained beneficial effect of this experimental therapeutic approach.

In China, the stem cell program has been suspended and correctly so in view of the fact that inappropriate control and regulations failed to protect patients from the implementation of therapies that were either dangerous or not properly established and validated in the required preclinical studies. The fantasy in the general population is that stem cells may cure any form of degenerative diseases and chronic illness where there is currently little or no hope. Charlatans have been very successful in selling ineffective stem cell products to desperate individuals searching for a potential miracle and the reacquisition of health lost suddenly or during a period of many years. The exploitation of the term stem cells has reached incredible levels with patients travelling thousands of miles to find charlatans abusing them and collecting enormous medical fees.

The extraordinary social and economic progress in China has been accompanied by a remarkable medical progress. Despite some inevitable difficulties and instances of questionable scientific rigor, a young generation of Chinese scientists is emerging who will soon have a major impact on the country and our community. The time has come for highly qualified laboratories in China and in the United States to join forces and address important health-related problems in a collaborative effort. With this strategy, a critical mass of scientists may be created to study adult stem cells in a coordinated manner, the only stem cells that can be used as a clinical therapy in the near future. Patients with HF cannot wait much longer and patients with advanced HF have little time left. The clinical application of adult stem cells, such as autologous CSCs, mononuclear bone marrow cells, and bone marrow–derived and adipose-derived mesenchymal stromal cells, is a disruptive treatment that needs to be tested. A fundamental advantage of the adult human heart is that it is largely protected from the development of primary malignant neoplasms. In addition, none of the cells used thus far in multiple clinical trials have been reported to cause tumor formation. Other strategies, such as embryonic stem cells, induced pluripotent stem cells, and reprogramming of fibroblasts into functionally competent cardiomyocytes is far from being ready for clinical use.

Importantly, the ultimate clinical objective is myocardial regeneration; by definition, this implies the coordinated reconstitution of cardiomyocytes and coronary resistance arteries and arterioles, together with capillary profiles. This goal can be achieved by implementing multipotent adult stem cells, which can create a progeny composed of parenchymal cells and coronary vessels. Alternatively, the delivered cells may release a variety of growth factors, which activate a pool of resident primitive cells capable of differentiating into the various cardiac cell lineages. With either protocol, the newly formed structures need to integrate with the recipient myocardium to contribute to global ventricular performance.

---

**Figure. Adult human stem cells.** Culture of c-kit-positive cardiac stem cells (A, green), CD105-positive bone marrow mesenchymal stromal cells (B, red), and CD34-positive bone marrow cells (C, yellow). Nuclei are stained by 4',6-diamidino-2-phenylindole (DAPI; A–C, blue).
possibly attenuating chamber dilation and increasing wall thickness, major anatomic determinants of negative cardiac remodeling and HF.

Investments by the Chinese government and the United States, under the current regulations of the Food and Drug Administration and its Chinese equivalent, may help scientists of both countries to understand the complex pathogenesis of HF and advance the use of adult stem cells in the treatment of this devastating syndrome. In the context of HF, our knowledge of the biology and mechanisms of action of stem cells are relatively poor and a major attempt needs to be made to define the basic properties of these powerful primitive cells. Despite these uncertainties, stem cell therapy is one of the very few new medical options that have the potential to reverse HF and materially improve the prognosis of this patient population.

Disclosures

None.

References

Chronic Heart Failure: Opportunities for a Bridge Between China and the United States
Yingnan Bai, Piero Anversa and Junbo Ge

doi: 10.1161/CIRCRESAHA.113.302124
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/113/4/362

An erratum has been published regarding this article. Please see the attached page for:
/content/117/12/e132.full.pdf

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the
Editorial Office. Once the online version of the published article for which permission is being requested is
located, click Request Permissions in the middle column of the Web page under Services. Further information
about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/
In the article by Bai et al, “Chronic Heart Failure: Opportunities for a Bridge Between China and the United States,” which appeared in the August 2, 2013, issue of the journal (Circ Res. 2013;113:362-364. DOI: 10.1161/CIRCRESAHA.113.302124), a correction was needed.

Piero Anversa, MD, discloses that he is a member of Analogous, LLC.

The author regrets this omission.

This correction has been made to the current online version of the article, which is available at http://circres.ahajournals.org/content/113/4/362.full