The role of coronary microvascular disorder in congestive heart failure

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COMMON CAUSES OF heart failure are coronary heart disease (coronary artery atherosclerosis), hypertension, cardiomyopathy, and heart valve disease (4). Accordingly, the most common models of heart failure are coronary arterial occlusion, temporally (partially) or permanently (completely); aortic constriction or high-salt feeding; gene-deficient and knockout models; and mitral, aortic regurgitation (10). Each model of heart failure has its pros and cons versus the respective human condition. Left anterior descending artery ligation is the most widely used model; however, in the myocardial infarction model, distal myocardial tissue to the occlusion site was almost normal, especially in rodent animals, even a couple of months postocclusion (7). Aortic constriction offers a good model for myocyte hypertrophy in mice, rats, swine, and dogs. However, the occurrence of congestive heart failure (CHF) post-aortic constriction depends on the degree of aortic stenosis and the overload duration (3). Left ventricle function could be preserved up to 4 mo post-aortic banding (even with 72% aortic constriction) with collagen fiber accumulation in the interstitial and perivascular space (7). Despite that, gene-deficient and knockout rodent models were globally used in heart failure research, and no individual gene-deficient and knockout models could bring a breakthrough in the treatment of heart failure, probably because of a simple reason: heart failure is not a disease induced by monogene/protein (4).

Advances in heart failure treatment have been mostly achieved in surgical progress, like coronary artery stents, bypass, heart assistant devices, or heart transplantation. However, limitations associated with angioplasty and stent have been the restenosis that can occur within 6 mo after the initial procedure. The chance of restenosis is from 25 to 40% (9). Heart failure research in pharmacological management has been largely disrupted. There have been many advances in studying myocyte contractility, but inotropic agents just could not improve cardiac dysfunction. The fibrosis inhibitors such as the angiotensin-converting enzyme inhibitor, like candesartan (15) and irbesartan, did not show a beneficial effect in a patient with CHF (13, 18). To date, there is no single drug regimen that could effectively reverse cardiac dysfunction. Despite the fact that gene therapy and stem cells therapy offer great promise for heart failure treatment, uncertainties and controversies still remain, including the high-yield transgene expression/stem cell implantation in the heart and long-term utility. In that regard, the obvious question is, What type of cells can be regenerated to strengthen cardiac performance: myocytes or endothelial cells (capillaries)? Do the regenerated cells or repaired LV part (ischemic area or remote area) play a key role in the overall progression of the heart failure and to what extent (2, 17)? This largely addresses our predicament in understanding heart failure: Which cardiac component(s) play(s) a key role in the development of heart failure: myocytes, extracellular matrix, and/or vasculature?

Coronary arterial disease is a main cause of heart failure. But most published research and techniques have been focusing on coronary arterial main branches, and only recently has microvascular dysfunction been getting more attention (6, 14, 16). Coronary microvascular dysfunction was observed in patients with hypertrophic cardiomyopathy. But its detailed role in heart failure is not very clear because accurate quantitative assessment of microvascular function and myocardial ischemia is not easily feasible in clinical practice and bench research, especially in rodents (1, 12). Microvascular obstruction, index of microcirculatory resistance, and hyperemic microvascular resistance were widely used parameters to identify microcirculation dysfunction. Invasive methods were based on principle of thermodilution or Doppler flow with guide wires (1), whereas noninvasive positron emission tomography (PET) served as a gold standard for noninvasive assay of myocardial blood flow (5, 11). However, there is no solid proof to directly correlate coronary microvascular dysfunction to ischemic heart failure in vivo in human patients and animals to date, which is probably due to the lack of proper model and the need for more advanced finer techniques.

In this current issue of the American Journal of Physiology-Heart and Circulatory Physiology, Chen and colleagues (8) reported their serial studies on coronary arterial disorder in congestive CHF in rats. The authors showed successive vascular changes of coronary arteries from main, middle, and small arterial branches to arterioles and capillaries in the CHF model. Heart failure was induced by chronic aortic constriction with ischemia-reperfusion followed by aortic debanding. Their main hypothesis is that the development of heart failure is associated with vascular disorders that occur in not only main branches of the coronary artery but also arterioles and capillaries. The capillary structural disorders found in CHF hearts were diverse to include stenosis, nonlinear arrangement, curled shape, drastic changes in diameter, proliferation, and roughened surface texture. Capillary disorder can be one of the critical contributing factors to the energy starvation that leads to the reduction of intrinsic contractile properties of the underlying myocytes. However, it is still a big challenge to simultaneously assess myocardial contractility and microvascular blood flow in rodent animals.

Future studies on the role of coronary microcirculation disorder (CMD) in CHF should involve the assessment of 1) the correlation between the degree and range of CMD and heart failure, specifically, the impact of the regional CMD on the global cardiac pumping function of the heart (contractility) by using invasive and noninvasive techniques; 2) the relationship between narrowing (atherosclerotic) of the main arteries and the impact on distal and proximal capillary disorders, which assess the importance of the global coronary blood flow reserve to the regional blood flow disorder, as well as to microvascular and endothelial dysfunction; and 3) an evaluation of the impact

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of novel therapies, such as AAV.VEGFα transgene, stem cell therapies, and antiangiina (ivabradine and ranolazine) therapies.

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