The role of coronary microvascular disorder in congestive heart failure.

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Running Title: microvasculature in CHF

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Abstract

This editorial focus highlights the importance of the recent work published by Chen et. al. on the significant role of the cardiac microvasculature in the development of congestive heart failure. Many animal models have been proposed and used to decipher the basis for the cardiac dysfunction without much attention to the alterations occurring in the microvasculature and focusing mainly on the main coronary arteries. New insight has emerged from this article to show that diverse and significant changes occur at the microvasculature level as well in conjunction with CHF. Thus the need to explore further their role and correlation to the severity and range of the heart failure and to develop treatment-driven research strategies that takes the microvascular alterations into consideration.
Common causes of heart failure are: (a) coronary heart disease (coronary artery atherosclerosis), (b) hypertension, (c) cardiomyopathy, (d) heart valve disease (4). Accordingly, the most common models of heart failure are: (I) coronary arterial temporally (partly) or permanently (completely) occlusion, (II) aortic constriction or high salt feeding, (III) gene deficient and knockout, (IV) 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 MI model, distal myocardial tissue to the occlusion site was almost normal, especially in rodent animals even couple of months post-occlusion (7). Aortic constriction offers a good model for myocyte hypertrophy in mice, rats, swine and dogs. However, the occurrence of congestive heart failure post-aortic constriction depends upon the degree of aortic stenosis and the overload duration (3). Left ventricle function could be preserved up to 4 months post-aortic banding (even with 72% aortic constriction) with collagen fiber accumulation in the interstitial and perivascular space (7). In spite of that, gene deficient and knockout rodent models were globally used in heart failure research, none of any individual gene deficient and knockout models could bring a breakthrough in the treatment of heart failure, probably just due to a simple reason: heart failure is not a disease induced by mono gene/protein (4).

Advances in heart failure treatment have been achieved mostly in surgical progress, like coronary artery stents, bypass, heart assistant devices or heart transplantation. However, limitations associated with angioplasty and stent has been the restenosis which can occur within 6 months after the initial procedure. The chance of restenosis is from 25% to 40% (9). Heart failure research in pharmacological management has being
largely dispirited. There has 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 (ACEI), like candesartan (15) and
Irbesartan, did not shown beneficial effect in congestive heart failure patient (13, 18).
To date, there are 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 cells 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 (CAD) is a main cause of heart failure. But most published
research and techniques have been focusing on coronary arterial main branches, and
only recently that microvascular dysfunction is 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 rodent animals (1, 12).
Microvascular obstruction (MVO), index of microcirculatory resistance (IMR) or
hyperaemic microvascular resistance (HMR) were widely used parameters to identify microcirculation dysfunction. Invasive methods were based on principle of thermodilution or Doppler-flow with guide-wires (1), while non-invasive positron emission tomography (PET) served as a gold standard for non-invasive 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 current issue of *Am J Physiol. Heart Circ. Physiol. (8)*, Dr. Chen and colleagues reported their serial studies on coronary arterial disorder in congestive heart failure (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 de-banding. Their main hypothesis is that the development of heart failure is associated with vascular disorders that occur not only in main branches of the coronary artery, but also in arterioles and capillaries. The capillary structural disorders found in CHF hearts were diverse to include stenosis, non-linear 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 which 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 congestive heart failure should involve the assessment of (1) the correlation between the degree and range of CMD and HF; specifically, the impact of the regional CMD on the global cardiac pumping function of the heart (contractility) by utilizing invasive and non-invasive techniques; (2) the relationship between narrowing (atherosclerotic) of the main arteries and the impact on distal and proximal capillary disorders, which assesses the importance of the global coronary blood flow reserve to the regional blood flow disorder, as well as to microvascular and endothelial dysfunction; (3) to evaluate the impact of novel therapies, such as AAV.VEGFa transgene, stem cells therapies and anti-angina (ivabradine and ranolazine) therapies.

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