PRoF Award Abstract – Call 2015

InterSod-HF

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1. Research Outline

Acronym	InterSod-HF
Project title in English	**Pro**gnostic **Inter**stitial **Sod**ium in **H**eart **F**ailure
Pitch (1 sentence)	**Interstitial sodium is a promising new target in Heart Failure**
Executive summary (max. 10 lines)	

Heart failure (HF) is worldwide a major cause of mortality, patient morbidity and enormous health costs. Current HF management strategies cannot adequately estimate patient risk on progression of the disease and identify patients who need earlier and more intensified treatment. A new and promising potential actor in the pathophysiology of HF symptoms and disease progression is interstitial sodium bound to large biopolymers: glycosaminoglycans. Interstitial sodium influences salt and fluid homeostasis and moreover vascular function. The intersod-HF study is a complete research project from fundamental pathway to clinical implementation in current HF practice and, in the future, into early on or preventive HF strategies. Furthermore, since the interstitial and vascular systems are omnipresent in the body, new insight might have far-reaching implications for other medical domains.

2. Cause and context of the research

Background

HF is a global pandemic affecting an estimated 26 million people worldwide and resulting in more than 1 million hospitalizations annually in both the United States and Europe. Although the outcomes for ambulatory HF patients have improved with the discovery of multiple evidence-based drugs and device therapies, hospitalized HF patients continue to experience unacceptably high post-discharge mortality and readmission rates that have not changed in the last 2 decades (1) We therefore believe that new HF strategies should be developed to detect HF progression early on and treat the disease before hospitalization is necessary.

Traditionally, the primary abnormality in HF was understood to be sodium handling, whereby water movement passively follows sodium to keep osmolality in balance. Due to neurohumoral up-regulation in HF the kidneys are not capable of adjusting sodium excretion to sodium intake. The resulting imbalance leads to progressive sodium accumulation, followed by interstitial and intravascular volume retention, and, eventually, to edema and increased cardiac filling pressures (2). Recent evidence has demonstrated that a large part of total body sodium is bound to glycosaminoglycan (GAG) networks in the interstitium and vascular wall; these GAG networks function as sodium buffers and play an important role in fluid homeostasis and vascular function (3). Alterations in the concentration of sodium in these interstitial networks and structural changes emerge before HF symptoms appear and can be indicative of impending HF decompensation.

Hypothesis

Interstitial sodium and interstitial network integrity play an important role in the pathophysiology of HF. Detection of alterations in both may help to identify HF patients at risk for acute decompensation and disease progression. This can initiate HF therapy adjustments in a very early stage and have a major impact on individual patient morbidity, prognosis and on economic problems related to HF.

Methods

Fundamental research arm:

- Skin biopsies in different HF populations (healthy, stabile HF, acute decompensated HF, recompensated HF) to establish the different stages of interstitial sodium accumulation and interstitial structural changed using MALDITOF techniques. It was until recently not possible to determine quantitative and qualitative characteristics of interstitial glycosaminoglycan networks. MALDITOF (matrix assisted laser desorption/ionisation time-of-flight analyzer) or massspectrometry is a very recent technique, which ionizes tissue samples and creates ionprofiles to qualify and quantify tissue content. The advantages of this techniques are the absence of harmfull substrates for the environment during the investigation, as it s a quick, reliable and efficient method (4).
- Skin samples are further assesed for their fluid and sodium contence using different techniques (sample ashing, high sensitivity magnetic resonance imaging (MRI), flamephotometry) (5,6)
- mRNA of specific polymerization enzymes as well as specific endocrine/paracrine mediators of interstitial homeostasis will be analysed (VEGF-C, 1 A-4-N acetylgalatosaminyltransferase and 1,3 acetylgalactosaminyltransferase, xylosyltransferase, inflammation, markers for the NO pathway etc)(5)
- Biochemical analyses of simultaneous blood samples, urine samples will be performed to identify new biomarkers (e.g. syndecan, VEGF-C,sodium,…)
- Histologic characterization of the samples (edema, dense interstitium, thickness off the different skin layers) will be done

Clinically applied research arm

- HF patients in different stages of the disease will undergo MRI imaging to correlate MALDITOF and High resolution MRI of skin biopsies with in vivo sodium MRI images (7). Sodium MRI is a novel technique in medicine using magnetic fields. It is a promising, non-invasive and safe technique to follow interstitial changes in a short time period before, during and after treatment for sodium and fluid accumulation in different patient setting. It can be used to guide HF treatment and decide whether patients can be safely discharged from the hospital.

Innovative research arm: future goal

- Based on the results of the previous study arms, the ultimate goal is to develop a implantable interstitial monitor, continuously registering interstitial homeostasis and connecting to a remote telemonitoring system. This already exists for patients with pacemaker based on bioimpedance measurements. The ability to identify patients at increased risk for decompensation before symptoms emerge and the opportunity to treat HF in a very early stage could have an enormous impact of disease progression and patient moribidity/mortality.

References

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3. Innovation results achieved

Our insights were recently published as a comprehensive review in the Journal of American College of Cardiology (Nijst P, Verbrugge F, Grieten L, Dupont M, Steels P, Tang W, Mullens W. The pathophysiological role of interstitial sodium in heart failure. J Am Coll Cardiol. 2015;65(4):378-388)

4. Link to the PRoF values (*awareness, comfort, safety, privacy, loneliness, non-stigmatizing, intergenerational and flexibility*)

HF is one of the most prevalent and deadly diseases nowadays. Besides tremendously high economic costs, the individual burden for patients is hard to bare due to often rapid

decline of their health, wellbeing and self-reliance. Current management strategies cannot predict and only (temporarily) prevent in a minority of cases further progression of the disease. The interstitial sodium compartment is a promising target for guiding and optimizing current HF practice as well as starting point for new – perhaps revolutionary – treatment strategies. Since the interstitium is largely unexplored, the first step is determining interstitial structure and function on cellular level. Secondly, the interstitium is readily available for non invasive imaging modalities, already commercially available and present in most hospital infrastructures, such as sodium MRI. The visualization of changes in this compartment can be a guide for optmalization of current treatment options in HF. Furthermore, since alterations in the interstitial compartment precede patient symptoms this compartment would be ideal to monitor and prevent progression of the disease and thus prevent HF related hospitalizations, morbidity and mortality. In the near future, based on the results of fundamental and clinical research such as this, it should be possible to construct chronic implantable interstitial monitors which give meaningful new information to the doctor and the patient for HF (self)management. Finally, based on a large amount of literature, the interstitium seems a critical target in many other diseases (such as hypertension, diabetes, kidney disease, metabolic disorders, neuromuscular pathology, etc.). New findings regarding HF can influence a broad medical domain far beyond the borders of cardiovascular medicine.

5. Applicable IPR rules

None

6. Information on the partners

Ziekenhuis Oost Limburg (ZOL) and Universitair Ziekenhuis Leuven (UZLeuven), respectively a large public hospital associated with the university of Hasselt and a teriary acadamic hospital in Leuven, participate in recruiting HF patients. Skin interstitial analyses , using MALDITOF techniques and MRI analyses , will be done in BIOMED Hasselt as well as analyzes of blood and urine samples for HF related biomarkers. BIOMED is a multidisciplinary institution specialised in the development of fundamental research to economic valorised strategies. The specialised cardiac labarotories of KULeuven will help in analyzing tissue samples for other specific characteristics.

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