

Effect of Aldosterone on Myocardial Energy Starvation

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PROPOSED RESEARCH PLAN

This proposal is intended to obtain sufficient data to allow an application to the NHLBI to further our understanding of the pathophysiology of heart failure (HF) and to evaluate the “energy starvation hypothesis” of HF in patients. We can now use metabolic imaging with positron emission tomography (PET) and anatomic-functional imaging with cardiac magnetic resonance (CMR) to study energy starvation in HF.

1. SPECIFIC AIMS:

a. To employ PET and CMR to evaluate several determinants of myocardial “energy starvation” in patients with HF due to nonischemic dilated cardiomyopathies (NIDCM):

- 1) Left ventricular (LV) volume, ejection fraction (LVEF) and wall stress (CMR).
- 2) LV hypertrophy (LVH) and fibrosis (CMR).
- 3) LV subendocardial hypoxia, using blood oxygen level derived (BOLD) imaging and adenosine/regadenoson-induced hyperemia imaging (CMR).
- 4) The rate of myocardial oxidative metabolism using [¹¹C]acetate (PET).

b. To study LV energy supply-demand relations and efficiency in patients with NIDCM using the [¹¹C]acetate decay rate, kmono, an index of energy supply, compared to indices of demand (LV wall stress and the rate-pressure product) plus an index of efficiency, the work-metabolic index (LV minute work/kmono).

c. To evaluate LV mass, volume and LVEF before and after aldosterone blockade, compared to changes in myocardial fibrosis, reactive hyperemia, BOLD estimates of hypoxia and myocardial oxidative metabolism.

d. To evaluate the relations between clinical improvement, energy starvation and LV volume, for judging the hypothesis that drugs that reduce LV fibrosis and volumes are beneficial in HF.

e. To evaluate the reproducibility of CMR measurements of myocardial perfusion.

2. BACKGROUND AND SIGNIFICANCE: (References are sometimes listed, rather than discussed in detail, due to page limits.). **Energy starvation.** Heart failure (HF) may be caused by myocyte death, myocyte dysfunction and LV remodeling, leading to ischemia and neurohormonal abnormalities, with inadequate energy production, termed “energy starvation”, with HF progression⁽¹⁾, key elements in the HF syndrome.^(2,3) **There are long term maladaptive anatomical responses related to energy starvation**, especially hypertrophy, reduced capillary density and abnormal mitochondrial architecture. **Energy-sparing compensation.** B-adrenergic downregulation is important, but is maladaptive by reducing LV performance, increasing β-myosin heavy chains and decreasing sarcoplasmic reticulum calcium pumping sites^(1,3). **Remodeling**^(4,5,6,7,8,9,10,11,12). Remodeling includes LV dilation, LVH and reduced function. There is re-expression of fetal gene programs^(9,10). Myocyte loss (via necrosis and apoptosis) leads to subendocardial cell death with replacement fibrosis and a loss of vasodilator reserve⁽¹²⁾ (all related to poorer prognosis).

Aldosterone and myocardial fibrosis. Aldosterone’s (ALDO) role in LV pathology and HF became clearer following publications showing neurohormonal profiles in HF^(13,14) and research showing the renin-angiotensin-aldosterone system was related to LVH and fibrosis^(15,16,17,18). Two HF trials showed reduced mortality in patients with HF randomized to treatment with the ALDO antagonist, spironolactone⁽¹⁹⁾, or eplerenone⁽²⁰⁾ following myocardial infarction. A substudy of RALES showed decreased B-type natriuretic peptide (BNP) in patients randomized to spironolactone⁽²¹⁾. Tsutamoto found in patients a decrease by spironolactone of the myocardial extraction of ALDO⁽²²⁾. In a randomized study of patients with NIDCM and H, 4 months’ treatment of 20 patients with spironolactone was associated with significantly reduced LV mass and volume, increased LVEF, and neurohormonal improvements, with a decrease in BNP, plus a decrease in plasma procollagen type III aminoterminal peptide (PIIINP)⁽²³⁾, an index of myocardial fibrosis. Decreased LV mass on echocardiography was correlated with decreased PIIINP. Others confirmed a slight increase in LVEF with spironolactone in HF patients^(24,25). In animals with myocardial infarctions, eplerenone increased the speed of isovolumic relaxation, increased endothelial nitric oxide synthase, and also reduced type I collagen gene expression and LVH⁽²⁶⁾. Similarly, eplerenone reduced LV hydroxyproline, improved LV filling and

coronary blood flow dynamics in the spontaneously hypertensive rat (27). Noncardiac mechanisms involve blockade of brain mineralocorticoid receptors leading to reduced sympathetic outflow and improved cardiac function in the rat following MI (28). Thus, there is substantial clinical evidence of cardiac benefit from ALDO blockade, confirmed in rat models, but relatively little evidence in patients for an actual reduction in fibrosis, or other mechanisms of benefit. **We speculate that ALDO blockade in patients with HF will reduce fibrosis and LV mass, which will likely reduce LV diastolic pressure and likely improve subendocardial perfusion, leading to less subendocardial ischemia in HF. This would improve the anatomic and physiologic substrate of “energy starvation”.**

Oxidative metabolism and cardiac efficiency in HF. Several studies have examined oxidative metabolism and LV efficiency in patients with HF, both using catheterization techniques (29) and noninvasive methods that employ PET and echocardiography (30, 31, 32). Oxidative metabolism can be estimated from the rate of clearance of [¹¹C]acetate from myocardium (kmono), which correlates closely with myocardial oxygen consumption (MVO₂) in animal models (33, 34, 35). Importantly, in NIDCM patients there is a similar, quantitative linear relation between [¹¹C]acetate decay and LV oxygen consumption (30). Efficiency may be judged by the work-metabolic index (WMI) = LV minute work/kmono. WMI has improved following metoprolol (36), **but this has not yet been related to the anatomical substrate of energy starvation or to changes in that substrate.**

Cardiac magnetic resonance imaging (CMR). CMR has become a “gold standard” method for cardiac imaging. There is a quantitative relation of CMR to LV mass, volume and performance (37, 38) and it is highly reproducible (39). CMR is likely to be superior to echocardiography in judging the work-metabolic index.

Imaging LV vasodilator reserve and hypoxia with CMR. Panting et al recently used gadolinium with adenosine/ regadenoson to image marked, inadequate subendocardial perfusion (40). **Deoxyhemoglobin** is paramagnetic (41) and can be seen on BOLD images. Several studies have employed this property to study hypoxia and ischemia (41, 42, 43, 44, 45, 46, 47, 48). There is a blunted dipyridamole-induced change in the BOLD transverse relaxation rate with LVH (p=0.0003), although in this study, none had HF (47).

It is important to note the distinction between hypoxia and ischemia. BOLD shows deoxyhemoglobin, but by itself cannot differentiate hypoxia from ischemia induced by hypoxia. Inducible LV dysfunction associated with a large BOLD signal would be confirmatory evidence, but is not likely to be proven in this study, as opposed to study of patients with coronary artery disease.

Critical evaluation of existing knowledge, gaps which this project is intended to fill, importance and relevance of the proposed research. We hope to demonstrate in patients several anatomic and physiologic abnormalities that produce myocardial “energy starvation” in HF, and that energy starvation is reduced by therapy with the ALDO antagonist, spironolactone. **Gaps in our knowledge include:** 1) Most basic information regarding ALDO has been obtained in animal models, whereas clinical reports have mostly shown cruder information such as reduced LVH and improved LVEF (cited above). 2) No clinical studies have addressed specifically the substrate of energy starvation in HF. 3) To our knowledge, there is no information about whether ALDO antagonism can reverse subendocardial hypoxia, and possibly ischemia, **and only partial information in patients about fibrosis from serum markers, such as PIIINP** 4) There is little mechanistic information to add physiologic support for the volume-remodeling hypothesis of how drugs improve outcomes in HF. 5). There are no reproducibility data regarding resting or adenosine-stimulated myocardial blood flow using CMR.

This study is likely to reduce these gaps in our knowledge of HF. By CMR and PET, we expect to show “energy starvation” in NIDCM by demonstrating LVH and fibrosis, inadequate vasodilator reserve, hypoxia and reduced metabolism vs. demand. Treatment with spironolactone will allow study of the effects of this proven therapy on the anatomy and physiology of energy starvation. This will demonstrate the physiologic basis of the volume-remodeling hypothesis about how drugs improve outcomes in patients with HF. BOLD and [¹¹C]acetate imaging may identify patients with the worst physiologic consequences of HF. Drug therapy, and even selection for cardiac transplantation, might be improved by this work. By doing repeated studies in a subset of patients, we expect to document close reproducibility of CMR estimates of myocardial perfusion. This will allow us to judge with greater confidence the serial changes we expect following spironolactone treatment.

3. PRELIMINARY STUDIES BY APPLICANT: The PI has studied HF in several formats (^{49, 50, 51, 52, 53}) and recently completed a study of LV oxidative metabolism using PET, RPP and echocardiography in patients with NIDCM (figs 1-4) (⁵⁴). Data for calculating kmono in NIDCM are shown in fig. 1. Compared to normal subjects, the LV supply/demand relation (kmono/RPP) was depressed in patients with NIDCM (fig 2). Normal subjects had a linear, significant relation between kmono and RPP, but patients with NIDCM did not (fig 3). Three of 7 patients had results similar to 7 normal subjects, but 4 did not. The literature demonstrates normally linear relations between LV wall stress and MVO2 (^{55, 56}). But, in the present study, there was no significant relationship in NIDCM between kmono and LV wall stress, as another index of oxygen demand (fig.4).

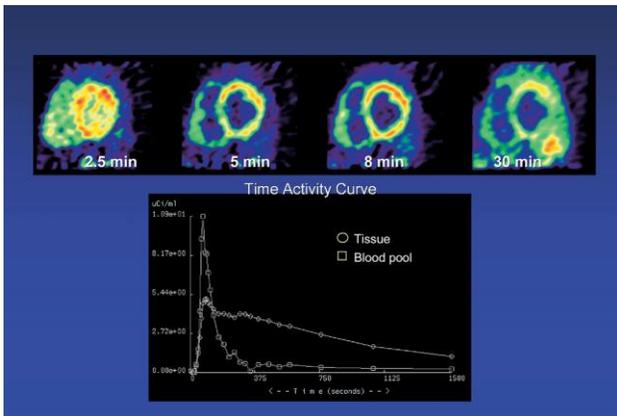


Fig. 1.

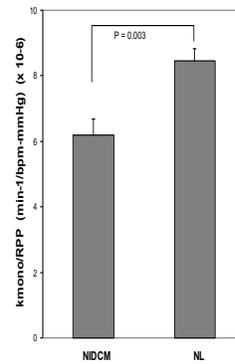


Fig. 2.

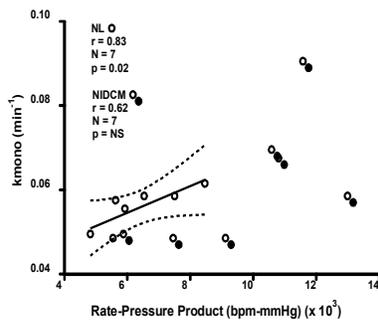


Fig. 3.

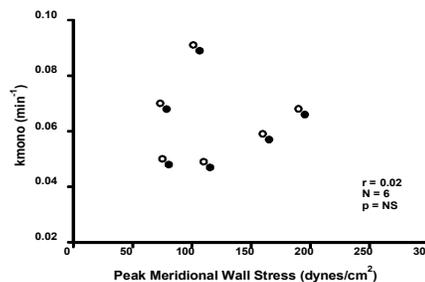


Fig. 4.

Such lack of correlation supports the hypothesis of "energy starvation" in HF. The PI has studied LV remodeling as part of the Radionuclide Substudy of SOLVD which was among the first to establish that the angiotensin converting-enzyme inhibitor, enalapril, reduced LV volume, while placebo-treated patients had progressive LV volume dilation (remodeling) (⁵¹). A meta-analysis showed that drugs that are clinically beneficial for HF reduce or have a neutral effect on LV volume (⁵⁷). The PI has continued studies of the LV volume-remodeling hypothesis (⁵⁸), used the 6 minute walk test (⁵⁹) and has significant nuclear cardiology experience (please see biosketch).

4. RESEARCH DESIGN AND METHODS:

Patient inclusion criteria. We plan to study 10 patients with NIDCM in each of two years (n based on budget). Most patients will have hypertensive or idiopathic dilated cardiomyopathy. The limited literature suggests that with 20 patients we will see a significant improvement in LV ejection fraction(²³).

The **inclusion criteria** are :

- 1) 18-80 years old, of either sex and any race;
- 2) diagnosis of NIDCM based on clinical criteria;
- 3) New York Heart Association Functional Class (NYHA FC) II-IV;
- 4) an ECG showing no prior myocardial infarction;

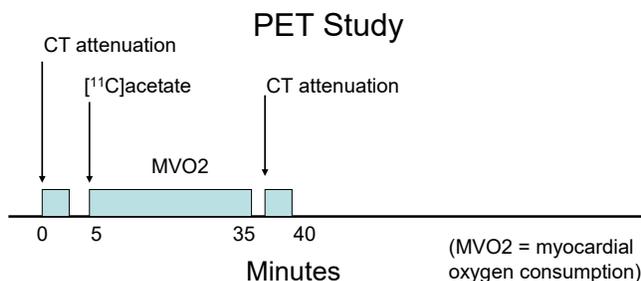
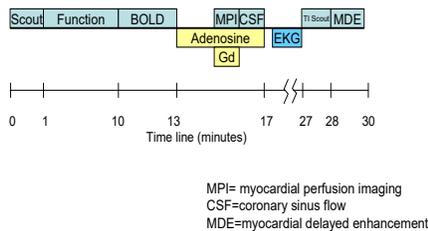
- 5) LV ejection fraction of 35% or less;
- 6) able to lie supine for PET and MRI studies.
- 7) standard medical therapy for heart failure, including an angiotensin converting enzyme inhibitor or an angiotensin receptor blocking drug; beta-adrenergic blocking drugs, and possibly digitalis and potassium, if needed; a no added salt diet; fluid restriction if needed. Patients will be stable on the above anit-failure therapy for 3 months.
- 8) Serum potassium less than 5.0 and serum creatinine 2.5 or less.

Exclusion criteria will include 1) need for an internal cardioverter-defibrillator (ICD) based on ventricular tachyarrhythmias (we cannot perform CMR in patients with ICD's); 2) other severe, concomitant illness; 3) prior stroke or orthopedic problems that limit exercise capacity. 4) Abnormal renal function as defined above;

Cautious exclusion: For patients with chronic moderate obstructive pulmonary disease (COPD) of severity that requires chronic, daily inhaler therapy the physician may consider Regadenoson for the diagnostic portions of the MRI. This will be based on the physicians medical opinion. If the patient has severe COPD he/she will be excluded from the study.

Recruitment Plan. Patients with newly identified HF due to NIDCM will be recruited from Vanderbilt University Medical Center, the Nashville VA Medical Center and Meharry Medical College. After stabilization with the above treatments, we will request their participation in this study. Informed consent will be obtained using forms approved by our IRB.

CMR Timeline



The above figures demonstrate the **protocol for the CMR and PET studies**. For **CMR**, patients will be studied while fasting to reduce chances of nausea during adenosine/regadenoson infusion. The HR and BP by sphygmomanometer will be recorded every minute during the adenosine/regadenoson infusion, and at least 5

times during the PET study. These results will be averaged. **For PET**, after an attenuation CT scan, kmono will be assessed with serial imaging after bolus injection of [¹¹C]acetate. The CMR and PET studies will be performed on the same day to reduce variability in BP, HR and medications between studies. Following PET, the patients will perform a 6-minute walk test 3 times for reproducibility within 10% of each other, with results on a standard form.

Spironolactone therapy. The initial dose will be 12.5 mg daily, and will be increased to 50 mg daily based on serum potassium and side effects, which will be monitored on days 3,7, 30 and then monthly. The BP, HR, body weight, cardiac physical examination, electrolytes and NYHA FC will be recorded at each visit on a standard form. If there is symptomatic gynecomastia with spironolactone, eplerenone, 25 or 50 mg as tolerated, will be used instead. (20). **Follow-up tests.** After 6 months' treatment, all the above tests will be repeated.

The following chart shows the protocol in table format.

Procedures for Aldosterone Study								
	Screen and Consent		Study 1				Study 2	Study 2a
WEEK	1	1.5	2	4	5	12	24	25
History and Physical Exam	X	X		X	X	X	X	
Spironolactone Dose	25	25, CHK BMP, stop	25	50				
Review Meds	X	X	X	X	X	X	X	
Basic Metabolic Panel (blood test)	X	X	X	X	X	X	X	
Blood Sampling for Heart Failure			X				X	
6 Minute Walking Test			X				X	
Heart Failure Questionnaire			X				X	
PET			X				X	
CMR			X				X	X
STUDY 1 AND 2 = the tests shown in table by X on that day								
BMP= basic metabolic profile to check potassium and kidney function								
Spironolactone dose may be adjusted up or down as needed								
Eplerenone may substitute for spironolactone								
Weeks 1 and 5 may be done by drawing blood at other location								
Week 12 visit may be done by telephone follow up								
PET = positron emission tomography test of heart metabolism								
CMR = magnetic resonance imaging test of heart function, blood flow and scar tissue								

Data analysis. All results will be stored securely. PET and CMR data will be analyzed without reference to clinical data, and clinical results will be analyzed separately from CMR and PET data until finalized.

Specific Aims a and b: Determinants of myocardial energy starvation, LV energy supply-demand relations and efficiency. With CMR we will accurately determine LVEDV, ESV, SV, LVEF and LV mass and calculate LV systolic wall stress with standard equations (⁶⁰). Myocardial fibrosis will be graded using a visual, segmental method as outlined by McCrohon (⁶¹) in two representative short axis midventricular sections, with

results averaged. Myocardial reactive hyperemia will be estimated using gadolinium during adenosine/regadenoson infusion, according to the method of Panting (40). We will calculate percent voxels with inadequate reactive hyperemia. We will evaluate hypoxia using the BOLD imaging method suggested by Wacker (48) and will estimate the extent of myocardial hypoxia, according to the equation: $[\text{BOLD} + \text{voxels} / \text{Total voxels}] \times 100\% = \% \text{ BOLD} + \text{voxels}$. Lacking a predominantly subendocardial signal, we will employ a parametric analysis (62). Based on the findings of Panting (40), we will compare myocardial perfusion in patients with NIDCM and normals.

Specific comparisons. We will evaluate the argument that subendocardial hypoxia by BOLD imaging is related to subendocardial ischemia, and that the volume of subendocardial hypoxia is related to LVEF. For this we will study the **correlation between LVEF and the %BOLD + voxels**. We recognize that other influences on each myocyte will also affect global LVEF, but we suspect that BOLD + regions may relate to LVEF.

We will evaluate the argument that LVH is the substrate for subendocardial hypoxia by comparison of the %BOLD + voxels to LVH in gm. The relation of LVH, %BOLD + voxels and LVEF may be complex and may require a 3-dimensional display to express it satisfactorily.

We will use CMR perfusion imaging with and without adenosine to compare myocardial perfusion in patients with NIDCM to patients with structurally normal hearts. Based on CMR procedural logs, we estimate there are up to 20 patients with structurally normal hearts studied with CMR during adenosine infusion. We will review the electronic medical records of these possible normal patients to determine if they have structurally normal hearts. We will then view and quantitatively analyze, using the method of Panting (40), these normal patients' images. We will compare the myocardial perfusion indices and myocardial perfusion reserve indices of the normals to that of patients with NIDCM.

We will **compare LV mass to the percent fibrosis** and will **evaluate the relation between fibrosis and %BOLD + voxels** using standard linear correlation. We will **quantify the monoexponential [11C]acetate decay rate** using methodology we employed previously, averaging the [11C]acetate data in 4 midventricular slices.

We will compare oxidative metabolic supply as estimated by kmono to 2 indices of myocardial demand, the RPP and LV systolic wall stress. We expect this will confirm our prior, more limited observations, shown in the Preliminary Studies and will support the hypothesis of energy starvation in HF. We will **calculate the WMI and compare this to results in the literature** using the equation: $\text{WMI} = (\text{SBP} \times \text{SVI} \times \text{HR}) / \text{kmono}$, where SBP = systolic blood pressure, SVI = stroke volume index, HR = heart rate.

Specific Aim c: To evaluate relations among LV mass, volume and LVEF before and after aldosterone blockade, compared to changes in myocardial fibrosis, reactive hyperemia, BOLD estimates of hypoxia and myocardial oxidative metabolism. The improvements in clinical status, LV mass and LVEF have been shown in two studies, and we expect the same results. The goal of this Specific Aim is to **judge the parameters of energy starvation** (LVH, fibrosis, reactive hyperemia, LV hypoxia and oxidative metabolism) before and during 4 months' spironolactone treatment. Thus, we will **compare changes in LVH, % fibrosis, %BOLD+ voxels and the percent reactive hyperemia to LVEDV, LVESV, LVEF, SV, kmono/RPP and the WMI before and during spironolactone treatment.**

Specific Aim d: To evaluate the relations between clinical improvement, the energy starvation theory and LV volume, for judging the hypothesis that drugs that reduce LV volumes are beneficial in HF. We expect a spectrum of responses to aldosterone-blocking therapy. It will be useful to compare the response clinically and by LV volume analysis to myocardial supply-demand relations, BOLD imaging and reactive hyperemia. We will compare changes in LVEDV, LVESV, SV and LVEF to NYHA FC, 6-minute walk test performance to kmono/RPP, WMI, %BOLD+ voxels and reactive hyperemia. We will use paired t-tests and linear correlation. We believe these results will add evidence to support the volume-remodeling hypothesis.

Specific Aim e. To evaluate the reproducibility of CMR measurements of myocardial perfusion. We expect close reproducibility of the CMR estimates of myocardial perfusion at rest and during adenosine infusion, but since we have been unable to document this in the literature, we propose to perform this study in a subset of 8 HF patients. This is based on the advice of our biostatistical consultants. We will then have greater confidence in judging the changes that we expect to detect following spironolactone therapy.

Statistical analysis. Based on the only available actually randomized data ⁽²³⁾ 20 subjects will provide statistically significant information for our goals. Subsequent NHLBI applications will have more detailed goals. The study of patients before and during spironolactone treatment will allow us to use each patient as his/her own control. The data analysis will employ standard techniques, including paired t-tests and linear regression analysis as appropriate. Statistical significance will be judged as $p < 0.05$.

Potential difficulties and limitations. Patient recruitment. We are confident it will be possible to recruit sufficient patients with NIDCM at Vanderbilt and the adjacent Nashville VA Medical Center. **[¹¹C]acetate decay in HF.** There is a strong, quantitative relation between myocardial oxygen consumption and [¹¹C] acetate decay in HF ⁽³⁰⁾. Thus, this measurement reflects oxidative metabolism in HF. **BOLD and reactive hyperemia in HF.** There is support in the literature (see Background) for making these measurements with our equipment (1.5 T magnet). **Selection of spironolactone.** The literature supports using this drug in HF⁽¹⁹⁾ unless there are significant side effects of gynecomastia, whereupon we will change to eplerenone ⁽²⁰⁾. **Timing of repeat testing.** Based on the initial studies of spironolactone in NIDCM ⁽²³⁾ we expect to see by 4 months an improvement in LVEF and a decrease in LVEDV. **Responders and nonresponders to spironolactone.** We expect a spectrum of response to spironolactone. This should be a strength of the analysis of our data concerning the anatomic and physiologic mechanisms of energy starvation. A sample size of 20 patients ⁽²³⁾ should be adequate to demonstrate striking responses in some patients and to produce sufficient encouraging data for an application for further support

5. ETHICAL ASPECTS OF THE PROPOSED RESEARCH: We believe there are no ethical problems in the proposed research. Given the **well-documented benefits of ALDO-blocking drugs**, it is no longer ethical to conduct a placebo-controlled study of ALDO-blocking effects. Thus, we will use a before and after (during) approach. The problem of **when to implant an ICD** might be considered an issue. However, it is reasonable to institute aldo-blocking therapy, in addition to the other anti-failure therapy in newly diagnosed HF patients because this may improve LVEF such that an ICD may not be needed. **Present guidelines ⁽⁶³⁾ are moot on the duration of treatment before placing an ICD.** However, If we discover significant ventricular arrhythmias during this research that require an ICD, we will end the patient's participation in the study and promptly notify the patient's physician of these developments. **Human subjects:** Consent will be obtained using forms approved by the Vanderbilt IRB. Women and minorities will be included. The targeted enrollment will be 20 subjects of both sexes for reasons noted above. Inclusion and exclusion criteria were listed above.

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