Notes concerning the Second Annual Heart Failure Clinical Skills Development Core Retreat
Friday, October 31st, 2008
12:00 – 3:30 pm
The Shapiro Board Room

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The second annual Clinical Skills Development Core Retreat was held on October 31st in the Shapiro Board Room in the Shapiro Cardiovascular Center in the Brigham & Women's Hospital. 32 faculty, fellows, research and clinical coordinators attended from both the Brigham & Women's Hospital and the Massachusetts General Hospital.

*Faculty in attendance*

Dr. William Dec (co-chair)
Dr. Eldrin Lewis
Dr. Carolyn Ho
Dr. Lynne Warner Stevenson
Dr. Marc Semigran
Dr. Kenneth Baughman (co-chair)
Dr. Michael Givertz
Dr. Christine Seidman
Dr. Gregory Lewis
Dr. Akshay Desai

*Clinical Skill Core Fellows*

Dr. Gregory Lewis
Dr. Garrick Stewart
Dr. Neal Lakdawala
Dr. Ravi Shah

- Overview of Partners site – Dr. Lynne Warner Stevenson
  The Harvard site is one of eight U.S. and Canadian sites including Duke, Vermont, Mayo Clinic, Montreal, Baylor, Emory and Utah. The goals of the Heart Failure Network were reviewed as well as current protocols. The Network was initiated in June of 2006 and funding became available October 2006. The next award will be in 2010 and preparations must be well underway and applications submitted by 2009. Markers of success will include publications, new science, and demonstration of therapies which benefit patient populations with heart failure. The progress has been slowed somewhat by the over 180 documents necessary to be signed at each site associated with initiation of protocols. The metrics as applied to our site were reviewed including participation in current protocols, development of core facilities, and submission of additional protocols for Network consideration. Progress of the proposed MODERN trial and its subsequent delay due to funding were reviewed and counter-balanced with recently approved consideration of the xanthine oxidase inhibitor trial which has its roots at the Harvard site.

  On balance, Dr. Stevenson felt the Network was too small for certain trials requiring high enrollment to achieve adequate power. For this deficiency, additional sites need to be included to complete certain trials. Additionally, the Network is felt to be too big for detailed mechanistic trials and in this

regard small sub-trials will be important in the future. Certainly there will be opportunities for publications from data acquired as part of the ongoing participation in Network trials which can be published.

- Fellowship presentations.
  - Dr. Garrick Stewart

    Dr. Stewart is interested in viral and autoimmune causes of cardiomyopathy. This is predicated on the concern that even with full diagnostic evaluation including endomyocardial biopsy 50% of all patients with dilated cardiomyopathy do not have an etiology determined. Histologic Dallas criteria are neither sensitive nor specific for myocarditis and do not address viral persistence. The variability in recovery of viruses from different geographic sites and authors was reviewed including German contributors who identified viral pathogens in 2/3 of their biopsy samples as opposed to American investigators who find them in only 10-15% of samples. Virtually all data thus far have had pitfalls in that they represent single center experience, the phenotype evaluated is poorly described, the number of pathogens identified has varied widely, and there is no clear cut association between a viral pathogen and causality.

    The recently completed viral and autoimmune causes of cardiomyopathy trial (NIH sponsored) evaluated viral recovery, anti-cardiac immune markers, and tissue typing. Dr. Stewart concentrated on the viral portion of this study. Of 100 patients submitted to endomyocardial biopsy with new or refractory heart failure, parvovirus was found in 12%. This represents the only pathogen identified of those searched for including adenovirus, cytomegalovirus, Epstein Barr virus, parvovirus, and enterovirus. Patients with parvovirus cannot be differentiated from others based on their history, hemodynamics or histopathology. No patients had myocarditis by Dallas criteria. The limitations of this approach were reviewed. Future directions include use of DNA micorray techniques to identify any foreign DNA in endomyocardial biopsies with subsequent identification of the pathogen. This does not require selection of a pathogen to be probed for as over 20,000 probes are represented in the VIROCHIP technique. It is hope that this technique will identify pathogens of any nature in patients with cardiomyopathy. It is anticipated that this will be Harvard-wide and an application has been made to the Catalyst program. Once the reliability, sensitivity, and specificity of this technique are defined, it would appropriate for a Network project.

    Several of those in attendance forward questions.

- Dr. Gregory Lewis.
  Dr. Lewis, now a faculty member at the Massachusetts General Hospital, has been studying metabalomics and cardiopulmonary exercise stress testing. His discussion today centered on cardiopulmonary exercise stress testing techniques and establishment of the Core program for the Network.

  Dr. Lewis reviewed current metrics of cardiopulmonary exercise including the standard $VO_2$ maximum, $VE/VCO_2$ and oxygen pulse. The effect of respiratory efficiency in the recently completed Sildenafil study were reviewed. The potential to enhance pulmonary efficiency by targeting pulmonary vascular resistance and right ventricular function were reviewed and felt to serve as a paradigm for future studies. Dr Lewis has also been evaluation the ERGO reflex based on products accumulating with exercise which are altered in various states of cardiac and peripheral decompensation. The investigators are evaluating in the ERGO reflex in association with exercise and Magnetic Resonance Imaging determination of large muscle group Ph and phosphocreatine recovery.

  Dr. Lewis and Dr. Semigran have established a Core Laboratory for the NIH Clinical Research Network. This has included development of standardization of protocols, establishing equivalency between bicycle and treadmill exercise stress testing, assessing all Network protocols to standardize the stress test performance techniques and metrics, and certifying Network sites as capable of performing Network-related protocols.

  A number of questions by those in attendance were directed to Dr. Lewis, particularly relative to the application of these techniques to the subsequently proposed xanthine oxidase trial.

- Dr. Neal Lakdawala.
  Dr. Lakdawala's interest is in the genetic causes of dilated cardiomyopathy. Dr. Lakdawala's mentors have previously demonstrated that dilated cardiomyopathy can be caused by sarcomere gene abnormalities, similar to hypertrophic cardiomyopathy. Dr. Lakdawala is particularly interested in whether patients with genetic mutations but without clinical evidence of disease have functional abnormalities of their myocardium as single myocyte studies have suggested that this may be the case. Dr. Lakdawala, Dr. Ho, and Dr. Seidman are whether patients with genetic abnormalities predisposing to dilated cardiomyopathy have abnormal contractile function before heart failure presentation and

whether or not these abnormalities are similarly or different from those with hypertrophic cardiomyopathy.

From six probands with dilated cardiomyopathy of a genetic nature, 70 family members have been fully evaluated phenotypically at the Brigham & Women's Hospital. In addition to standard echocardiographic techniques, strain and tissue velocity are being evaluated. These results are compared with similar analyses from a group of previously identified patients with genetic mutations predisposing to hypertrophic cardiomyopathy before they develop disease. It appears that patients with hypertrophic cardiomyopathy have increases tissue velocity and decrease strain while those with dilated cardiomyopathy predisposition have decreased velocity and increased strain.

The second project that Dr. Lakdawala is involved with relates to molecular epidemiology of patients with new onset dilated cardiomyopathy. Those that are termed idiopathic may be familial in origin in up to 40% of cases. Better phenotypic analysis of these patients is critical and expansion of the sarcomeric and non-sarcomeric etiologies is needed.

A number of questions came from the audience including:

- Consideration that the work of Dr. Stewart and Dr. Lakdawala could significantly impact on our understanding of what remains as idiopathic cardiomyopathy.

- Protocol presentations – Dr. Marc Semigran.
  Dr. Semigran presented the RELAX protocol and the SMART protocol. The RELAX protocol is evaluating the use of the PDE5 inhibitor in patients with diastolic heart failure. The protocol and challenges to enrollment were reviewed, particularly those relating to the required metabolic exercise stress test criteria. The SMART protocol is also challenging and mandates 60 patients in each arm of a surgical intervention versus standard medical therapy for patients with idiopathic cardiomyopathy and mitral regurgitation.

  Dr. Michael Givertz reviewed DOSE and CARESS protocols, both associated with the cardiorenal syndrome. Patients undergoing inhopsital diuresis for CHF with an increase of creatinine of greater than 0.3 mg/dl or an increase in serum-creatnine by 25% have a worse prognosis. The DOSE trial evaluates high and low dose diuretic therapy and bolus versus continues intravenous diuretics n a 2x2 factorial design. Recruitment has been brisk for this protocol. CARESS is a trial of ultrafiltration versus standard diuretic management for patients with Lyme overload and renal insufficiency.

*Additional protocols.*
Dr. Givertz reviewed the consideration for a xanthine oxidase inhibitor sub-protocol hoping to identify the importance of oxygen radicals in the progression of heart disease. Dr. Gregory Lewis reviewed studies of the RELAX protocol related to ventilatory efficiency (ventilatory oscillation) in the ERGO reflex analysis.

The Retreat was ended by Drs. Dec and Baughman expressing their appreciation to those who attended and calling for recommendations to improve the program in upcoming years. Drs. Givertz, Semigran, and Dr. Stevenson, thanked specifically the research coordinators who have worked diligently to enroll populations of patients thus far participating.