

## **Ventricular Synchrony increases Cardiac Output as a Response to Temporary Biventricular Pacing in Cardiac Surgery Patients as Analyzed by Speckle Tracking Echocardiography**

### **I. Study Purpose and Rationale**

Patients who undergo open heart surgery are at risk of acute heart failure and low cardiac output (CO). Traditional therapies include volume infusion, inotropic and vasoactive agents, diuretics and mechanical devices<sup>1</sup>. These treatments, while effective, are associated with complications that increase mortality, morbidity, length of hospital stay and cost<sup>2</sup>. Thus, additional treatments are needed to improve postoperative ventricular function, with biventricular pacing (BiVP) as a potential therapy.

Permanent BiVP, also referred to as CRT, is now a standard of care for patients with New York Heart Association Class III or IV congestive heart failure, left ventricular (LV) ejection fraction  $\leq 35\%$ , and QRS duration  $> 120$  msec complexes<sup>3,4</sup>. Three important clinical studies (InSync, MUSTIC, and MIRACLE) showed that the benefits of BiVP in dilated cardiomyopathy included improved hemodynamics, quality of life, and decreased hospital admission due to congestive heart failure<sup>5-7</sup>. Importantly, BiVP can improve systolic function without increased myocardial oxygen consumption and depletion of high energy phosphates, unlike most inotropic agents<sup>8</sup>. In spite of these benefits, however, approximately 30% of patients do not respond to BiVP for reasons including inadequate patient selection criteria, inappropriate lead positioning, and suboptimal device programming<sup>9</sup>.

There have not been, to the best of our knowledge, studies that have looked at the effects of BiVP on open heart surgery patients, a patient population particularly vulnerable to hemodynamic instability, often requiring beta agonists, afterload reducing agents, and diuretics. In the immediate postoperative period, these patients are often subject to depressed cardiac function due to ischemic injury, inflammation, myocardial edema and other factors. The BiPACs trial in the Spotnitz Lab proposes that temporary optimized BiVP in cardiac surgery patients will cause an increase in CO compared to nonpaced patients. BiVP will be optimized for atrioventricular delay (AVD) and interventricular delay (VVD) at a set paced heart rate immediately after weaning off the cardiopulmonary bypass machine. Unpublished results are thus far promising, with open heart surgery patients that are biventricularly paced exhibiting an increase in cardiac output. However, like the nonsurgical heart failure population, a proportion are not responding, the reason for which remains unknown.

Speckle tracking echocardiography (STE) is a new technology that can measure temporal changes of strain and deformation on individual sections of the ventricle<sup>10,11</sup>. It is able to

measure radial, circumferential, and longitudinal strain and synchrony and has been shown to be an accurate measure of ventricular synchrony<sup>12, 13</sup>. In previous unpublished studies from our laboratory, radial strain synchrony yields cleaner and more robust data and remains the current focus. Additionally, studies have found that a baseline level of radial strain dyssynchrony is a positive predictor for response to CRT and that radial dyssynchrony of greater than 130 ms was able to predict response to CRT with a sensitivity of 83% and a specificity of 80%<sup>13, 14</sup>. However, there is no known study that has analyzed the relationship between synchrony and cardiac output in response to temporary BiVP in open heart surgery patients.

## **II. Study Design and Statistical Analysis:**

This will be a prospective cohort study of temporary BiVP patients undergoing open heart surgery with preoperative left ventricular dysfunction and an interventricular conduction delay > 120ms. This study aims to correlate a positive response to BiVP as an increase in cardiac output with the improvement of synchrony as measured by speckle tracking echocardiography.

Since all patients will be paced with optimized BiVP, patients will be divided into a responder group and a nonresponder group. Those that exhibit an increase in cardiac output will be placed into the responder group and those that do not exhibit an increase in cardiac output will be placed in the nonresponder group. All patients will receive transesophageal echocardiography that will be analyzed with speckle tracking echocardiography software at 4 time points: before sternal opening, prior to BiVP, during a final comparison when the patient is paced with BiVP, atrial first pacing, and no pacing each for 30 seconds, and 30 minutes later at sternal closing. The primary endpoint is level of left ventricular synchrony, as defined as the standard deviation of peak radial strain between 6 ventricular segments. Change in synchrony will be the difference in standard deviation prior to BiVP and during BiVP.

An unpaired T-test will be used to compare the change in synchrony between the responder group and the nonresponder group. An acceptable difference between the 2 groups is one standard deviation. In order to achieve 80% power with an alpha-error rate of 0.05, a sample size of 17 patients will be needed in each group.

## **III. Study procedures:**

For eligible patients in sinus rhythm as cardiopulmonary bypass reaches conclusion, temporary bipolar wires are sewn on the RA, anterior RV and posterior LV. An appropriately sized electromagnetic field probe will be placed around the aorta to measure cardiac output. Arterial pressure, ECG, flow velocity, cardiac output/stroke volume by EMF and PulseCO, central venous pressure and pulmonary artery pressures will be measured. DRIPS, antiarrhythmics and doses will be noted.

### *Optimizing biventricular Pacing:*

Both atrioventricular delay and interventricular delay will be optimized at heart rate of 90 beats per minute.

*AVD optimization:*

Data will be recorded at AVDs of 90, 120, 150, 180, 210, 240, and 270 msec twice in a randomized order. Data will be recorded for 10 seconds at each AVD, totaling 130 seconds. Cardiac output will be measured at each setting and the AVD setting that generates maximum CO will be kept. If maximal CO is equivalent over a range of AVDs, the median value in that range will be used. If results of AVD testing are indeterminate, a nominal value of 150 msec will be used.

*VVD optimization:*

At optimized AVD and heart rate of 90, data will be recorded at VVD of (+) 80, 60, 40, 20, 0 msec RV paced first and (-) 20, 40, 60, and 80 msec LV paced first in a randomized order. Data will be recorded for 10 seconds at each VVD. The VVD setting that generates maximum CO will be kept for final comparison.

*Final comparison:*

Testing will be done for 30 seconds at optimized BiVP, right atrial pacing, and no pacing.

*Echocardiography:*

Digital transesophageal echos will be taken prior to sternotomy, before BiVP pacing, during final comparison of BiVP versus atrial pacing versus no pacing, and 30 minutes later at sternal closure. Echos will be analyzed with speckle tracking software to determine synchrony of left ventricular contraction.

**IV. Patient eligibility:**

Inclusion criteria include preoperative CHF, LVEF < 35%, and an interventricular conduction delay of >119ms. Patients must meet all inclusion criteria. Exclusion criteria include post-cardiopulmonary bypass heart rate >120, 2<sup>nd</sup> or 3<sup>rd</sup> degree heart block, or atrial fibrillation. Consent will be obtained prior to the day of surgery. After consent, a patient can be removed from the study at any time by the surgeon based on hemodynamic instability, bleeding, or other factors. Calcification, atheromata, bleeding, or scarring of the AAO may preclude use of an AAO EMF.

**V. Equipment:**

Temporary pace maker:

This study will utilize the InSync III 8042 pacemaker (Medtronic Inc., Minnesota, MN). This is an FDA approved device fully tested and proven for sensing and pacing the atrium and ventricles as required for DDD pacing, including adjustable atrial and ventricular stimulation pulse width, rate, sensitivity, voltage, RLD, and AVD.

Flow measurement:

Median sternotomy provides access to the ascending aorta, allowing measurement of stroke volume by electromagnetic field probe from Carolina Medical. A flow probe provides instantaneous flow velocity, which can be recorded continuously, with  $CO = SV \times HR$ . While more accurate flow probe designs are available, the superior safety record of the EMF make it the preferred unit for this study. After the flowprobe has been removed an arterial pressure contour device (PulseCO) will be utilized to measure CO. This requires no further instrumentation of the patient as all patients receive an arterial line in the OR.

## **VI. Study Questionnaires**

None; questionnaires are not applicable to this study

## **VII. Study Subjects**

All patients undergoing any relevant surgery at our institution regardless of gender will be invited to participate. Children will be excluded from the proposed research. The research topic to be studied is not relevant to children.

## **VII. Recruitment**

With consent of the attending surgeon, patients undergoing relevant procedures at NYPH will be recruited by the Study Coordinator. Patients will be asked to participate voluntarily and will be fully informed of relevant risks and potential benefits. They will be notified of their right to withdraw from the study at any time. Consent will be documented by signature on an IRB approved consent form, which discusses the nature of the study and the patient's rights in detail; the patient will be given a copy of the form.

## **VIII. Confidentiality of Data**

A database has been established that links all data/electronic documents for a given patient to an anonymous study identification number, allowing patients data to remain confidential. Any information obtained during this study and identified will remain confidential and within the standards set by HIPAA. All patients will be notified of their rights through a HIPAA compliant form on use and disclosure of information.

## **IX. Level of Risk:**

The level of risk for this study is considered low. Potential risks likely to be attributable to the study are limited to those of inserting and removing the pacing wires, multielectrode pacing array, and flow probe. Extended length of cardiopulmonary bypass is expected to be minimal.

## **X. Potential Benefits**

The subject population involves patients who have preoperative CHF. If patients are responders to temporary BiVP, they could potentially experience improved ventricular function at no cost in

terms of myocardial oxygen demand. They may also potentially experience reduced morbidity, length of stay, and need for inotropic support.

1. Quinn TA, Cabreriza SE, Richmond ME, Weinberg AD, Holmes JW, Spotnitz HM. Simultaneous variation of ventricular pacing site and timing with biventricular pacing in acute ventricular failure improves function by interventricular assist. *Am J Physiol Heart Circ Physiol* 2009;297:H2220-6.
2. Ferraris VA, Ferraris SP, Singh A. Operative outcome and hospital cost. *J Thorac Cardiovasc Surg* 1998;115:593-602; discussion -3.
3. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;51:e1-62.
4. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Oto A, Sutton R, Trusz-Gluza M. Guidelines for cardiac pacing and cardiac resynchronization therapy. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Europace* 2007;9:959-98.
5. Gras D, Leclercq C, Tang AS, Bucknall C, Lutikhuis HO, Kirstein-Pedersen A. Cardiac resynchronization therapy in advanced heart failure the multicenter InSync clinical study. *Eur J Heart Fail* 2002;4:311-20.
6. Linde C, Braunschweig F, Gadler F, Bailleul C, Daubert JC. Long-term improvements in quality of life by biventricular pacing in patients with chronic heart failure: results from the Multisite Stimulation in Cardiomyopathy study (MUSTIC). *Am J Cardiol* 2003;91:1090-5.
7. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-53.
8. Nelson GS, Berger RD, Fetis BJ, Talbot M, Spinelli JC, Hare JM, Kass DA. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation* 2000;102:3053-9.
9. Burri H, Sunthorn H, Shah D, Lerch R. Optimization of device programming for cardiac resynchronization therapy. *Pacing Clin Electrophysiol* 2006;29:1416-25.
10. Teske AJ, De Boeck BW, Melman PG, Sieswerda GT, Doevendans PA, Cramer MJ. Echocardiographic quantification of myocardial function using tissue deformation imaging, a guide to image acquisition and analysis using tissue Doppler and speckle tracking. *Cardiovasc Ultrasound* 2007;5:27.

11. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J, 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation* 2006;113:960-8.
12. Tanaka H, Hara H, Saba S, Gorcsan J, 3rd. Usefulness of three-dimensional speckle tracking strain to quantify dyssynchrony and the site of latest mechanical activation. *Am J Cardiol* 2009;105:235-42.
13. Delgado V, Ypenburg C, van Bommel RJ, Tops LF, Mollema SA, Marsan NA, Bleeker GB, Schalij MJ, Bax JJ. Assessment of left ventricular dyssynchrony by speckle tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. *J Am Coll Cardiol* 2008;51:1944-52.
14. Tanaka H, Nesser HJ, Buck T, Oyenuga O, Janosi RA, Winter S, Saba S, Gorcsan J, 3rd. Dyssynchrony by speckle-tracking echocardiography and response to cardiac resynchronization therapy: results of the Speckle Tracking and Resynchronization (STAR) study. *Eur Heart J* 2010;31:1690-700.