

## Electromechanical Therapy

### A historical perspective of device therapy in the failing heart

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Introduction: Congestive heart failure is a wide spread and growing problem. We will view this disease process from an electrophysiologic and pacing perspective. Cardiac transplantation represents the “ultimate therapy” for a failing heart, however this treatment is clinically irrelevant due to the lack of resources. Medical therapy has predominated care of these patients with significant advances over the years. It is quite clear that the heart failure patient can also benefit from device therapy. To follow the evolution of device therapy would first begin with a brief discussion of conduction abnormalities seen in patients with congestive heart failure. Then we will discuss standard pacing therapies that have been attempted. We will then address the issue of sudden cardiac death in heart failure patients and the use of defibrillator technology. Lastly we will address the modality of biventricular pacing, or resynchronization therapy.

Conduction Disturbances: Disturbances in the electrical system of a failing heart are quite common. Manifestations of these disturbances are easily seen on a routine electrocardiogram as first degree heart block, axis deviation and interventricular conduction delays. It is estimated that as many as 20-50% of congestive heart failure patients may have such disturbances. In one study, 82% of patients had significant conduction delays recorded on their ECG's within 60 days before death and in 68% of these patients the disturbance was progressive. First degree heart block (a misnomer since there is only delay, not block) can occur as a result of intra-atrial, atrial ventricular nodal or infranodal conduction delays. The result in prolonged PR interval has several hemodynamic consequences. In this setting the ventricle is activated late thereby affecting the timing of ventricular systole and diastole. There is a premature closure of the mitral valve leading to diastolic regurgitation. As a result, there is a decrease in filling time which is made worse by any diastolic dysfunction, as commonly seen in CHF patients. A decrease in filling time leads to decreased preload and ultimately a reduction in stroke volume. An interesting note is that these hemodynamic abnormalities may be seen with a normal PR interval and left bundle branch block where the left ventricle is activated late resulting in a long “mechanical” AV delay.

Intraventricular conduction disturbances can also have adverse hemodynamic effects. In 50 patients with congestive heart failure and wide QRS complexes, Xiao et al, describe a positive correlation between the QRS width and the duration of mitral regurgitation, left ventricular contraction and relaxation times, and negative correlation with the peak rise in LV pressure. In addition, the prolongation of isovolemic contraction and relaxation times decreased the filling time. Of interest, is that the morphology of the QRS did not influence hemodynamic effects and left axis deviation was found to add to these abnormalities. The mechanical dyssynchrony that occurs with these electrical disturbances can also worsen systolic mitral regurgitation.

Standard Pacing: An EKG represents the first historical approach towards pacing in patients with congestive heart failure. In 1990, Hockliner et al examined patients who were all suffering from congestive heart failure in the intensive care unit. This was a small group of patients, 16 to be exact, who had congestive heart failure and other interesting abnormalities including left bundle branch block, extra systoles, history of syncope as well as the noted first degree heart block. Hockliner treated these patients with pacing with physiologic short AV delays and reported a remarkable improvement in both congestive heart failure class and left ventricular ejection fraction. The theory for the improvement was that the first degree heart block led to increased mitral regurgitation and decreased filling time and thereby shortening it improved those abnormalities. The reports from this study were that the patients improved so much that they were actually able to “walk out” of the Intensive Care Unit and this triggered much interest in the idea of pacing and congestive heart failure. Many small studies were done afterwards, however the results of Hockliner could not be duplicated. Although pacing with short AV delays in patients with congestive heart failure could not be definitively proven to help the hemodynamics, there may be some rule of this in the future, especially in exercise.

In the 1990's, another pacing procedure came to the forefront that was also noted to help patients suffering from congestive heart failure. Atrial fibrillation is a common disorder and when uncontrolled can lead to worsening LV function and congestive heart failure and the patients can be quite symptomatic. Medical therapy is not always successful and Natale et al was one of the first to perform a study that showed the impact on ventricular function and quality of life via a transcatheter ablation of the atrial ventricular junction with subsequent pacemaker implantation. Natale reported that this procedure resulted in an increase in ejection fraction and fractional shortening both at one month and twelve months later. Remarkably the patient improved quite significantly in regards to exertional dyspnea, rest dyspnea, exercise tolerance, weakness, heart failure class and a well being score. The improvement in these patients may have reflected several

factors including a decrease or control of heart rate, a resolution of tachycardia induced cardiomyopathy and the fact that drugs with negative inotropic effects could be discontinued. However the study of Natale was not a controlled study and a more scientific approach was taken by Brignoli. Brignoli randomized patients to the modality of AV junction ablation with pacing versus adequate heart rate control via medical therapy. In all there were 66 patients randomized, 34 to drug therapy and 32 to ablation and pacemaker. Reported there was an improvement in the ablation pacemaker patients, however it was also noted that heart rate control also improved the symptoms. Of note also, was that the ejection fraction did not change significantly in either group, either at enrollment or to a month follow-up. In conclusion, ablation with pacemaker is an acceptable non-pharmacological approach to treating patients with a refractory atrial fibrillation and can improve on patient's heart failure symptoms. Whether or not there is a significant improvement in LV function via this pacing maneuver remains to be seen. There were also some other factors to consider with this procedure, specifically the risk of sudden cardiac death which was initially reported occurring after direct current or DC ablation of patients. Therefore, it is important to remember that if this procedure is performed that pacing must be kept at a rate of 90 bpm for at least six weeks post procedure. Also at this time, of note, it began to be questioned as to whether or not the right ventricular apex was the optimal site to be pacing patients.

Atrial fibrillation clearly can worsen congestive heart failure symptoms and an interesting question that can be posed is can we prevent atrial fibrillation via various modalities in order to help in the care of these patients. The hypothetical benefits of maintaining sinus rhythm compared to atrial fibrillation may be an improvement in overall cardiovascular mortality, stroke, and of course heart failure. However, this bias is based on retrospective studies and this issue needs to be examined more uniformly. These are questions for thought and are not conclusive. Additional studies are forthcoming in order to examine these questions further.

Sick sinus syndrome is a large diagnosis that includes atrial fibrillation as well as other rhythm disturbances that might affect heart patients with congestive heart failure and these include sinus bradycardia, pauses or sinus arrest, sinoatrial exit block, other atrial tachyarrhythmias and the under diagnosed chronotropic incompetence. There are pacing techniques that may help with the maintenance of sinus rhythm. There are pacing algorithms that are used such as conventional overdrive pacing which is setting the lower rate limit at a fixed number or an aggressive sensor driven rate modulation to achieve continuous atrial pacing. There is also the modality of dynamic atrial overdrive pacing which is automatic pacing rate acceleration using sensing of P-wave followed by deceleration with rates moving until a new P-wave is sensed. There is also the pacing

maneuver of post extra systolic pause suppression. Of note, the DAO or (Dynamic atrial overdrive pacing) has been noted to decrease the atrial fibrillation burden in patients. Also the pacing site can also influence atrial fibrillation. Pacing from Bachmann's bundle can result in greater activation symmetry and decrease the atrial activation time. Selective pacing from this bundle may reduce AF due to altered atrial activation. In 84 patients by Baline in PACE 1999, it was noted that there was a greater maintenance of sinus rhythm as opposed to standard right atrial appendage pacing. There have also been reports in literature in regards to dual site pacing, specifically the superior right atrium as well as pacing from the posteroseptal right atrium at the site of the os of the coronary sinus. Much of this work has been done by Dr. Seksena and there have also been reports of decrease atrial fibrillation burden. Of note, it has been studied by Papageorgiou in 1996-1997 that AF was never induced with atrial premature depolarizations delivered at either the high right atrium or coronary sinus during continuous pacing from the distal coronary sinus. Coronary sinus distal pacing may suppress the propensity of high right atrium atrial premature depolarizations to induce AF by limiting their prematurity at the posterior triangle of Koch and not allowing local conduction delay and local reentry to occur. With this in mind, bi-atrial pacing is of consideration. Reports in regards to this are starting to enter the literature with an example in November 2002, in JAC, a randomized study looking at bi-atrial pacing in atrial fibrillation patients who underwent pacing and that bi-atrial pacing causes a significant decrease in the atrial fibrillation episodes. Optimal sites were concluded to be the high right atrium and the distal coronary sinus. (Mirza et al). The importance of maintaining sinus rhythm in these patients remains a very large question. This will be answered, hopefully when the AF/CHF trial is concluded worldwide.

Prophylactic Therapy: A DeDoer quote from 1935 states "fibrillation, especially atrial has become important in the clinic. Since ventricular fibrillation usually results in sudden cardiac death, it is of course of much less importance". Things have certainly changed since that quote with respect to ventricular arrhythmias. Clearly this is a rhythm disturbance that must be looked into and if a primary event, then few of us would argue that a defibrillator would be needed. We only need look to the antiarrhythmics versus implantable defibrillator or AVID trial in order to obtain secondary prevention of this rhythm disturbance. As you will recall, this was a randomized clinical trial to evaluate ICD versus class III antiarrhythmic drugs, primarily Amiodarone with the hypothesis that one group would achieve significant lower mortality than the other. These patients were ones that either suffered primary ventricular fibrillation or sustained ventricular tachycardia with syncope or sustained ventricular tachycardia with symptoms and ejection fraction of 40% or less, or ventricular tachycardia with blood pressure of less than 80mm Hg. The trial demonstrated a 39% reduction in overall mortality for the defibrillator patients.

Sudden cardiac death is the single largest cause of natural death in the United States with over 350,000 events occurring each year. The incidence in the adult population is .1-.2%. However, the fibro(five year?) mortality of the survivors of a myocardial infarction with left ventricular dysfunction after hospital discharge is greater than 20% and sudden cardiac death accounts for at least 33% of this late mortality. Of note, only 2-30% of out of hospital cardiac arrests survive. It is known from the Swedish Cardiac Arrest registry from the American Journal of Cardiology in 1999, that defibrillation early on in this event is the key to survival. In regards to sudden death in the heart failure population it is interesting to note the mortality of class II heart failure patients due to arrhythmic causes is higher, 50-80%. In contrast, arrhythmic mortality is decreased as the stages of heart failure progress in that class III arrhythmic mortality is 30-50% and class IV arrhythmic mortality is 5-30%. With all of this in mind, it has become quite clear that primary prevention of sudden cardiac death is in order. An EKG that reveals non-sustained ventricular tachycardia in a patient that has had a myocardial infarction represents the first attempt at primary prevention for sudden cardiac death via ICD therapy. Dr. Arhtur Moss called his trial MADIT or multicenter automatic defibrillator trial. The patient profile was that the patient had to have a previous myocardial infarction with documented non-sustained ventricular tachycardia with an ejection fraction less than or equal to 35%. The patient was then brought to the Electrophysiology Laboratory and ventricular tachycardia needed to be induced as well as not be suppressed by IV Procainamide. The patient was then randomized to drug therapy versus ICD therapy and it was quite clear that there was an improvement in overall mortality with ICD implantation. The total reduction was 54%. The MADIT trial had many detractors given the lack of placebo as well as the small size of the study. However, its results were verified by the MUSTT or multicenter un-sustained tachycardia trial. This looked at a similar group of patients and EPS guided therapy for the prevention of sudden cardiac death. These patients had to have coronary artery disease as well with non-sustained ventricular tachycardia and an EF of less than 41%. If inducible at EPS, the patient was randomized to no therapy versus EP guided therapy which could include drugs or defibrillator therapy. The trial demonstrated a 72% risk reduction in arrhythmic death or cardiac arrest and a 51% reduction in overall mortality with EPS guided therapy, which was due solely to the defibrillator. Of note, the patients who did the worst were the MUST patients who were treated with antiarrhythmic drug therapies. Please note that the placebo group had a better mortality than these patients treated with antiarrhythmic drug therapies. This can not be overemphasized. The MUST and MADIT patients however are probably only the tip of the iceberg and prophylactic therapy needs to be looked at from an even broader perspective. With this in mind, the MADIT II trial was performed which looked at patients with coronary artery disease and an ejection fraction of less than or equal to 30%. The randomization was quite simple in that these patients either

received an ICD or did not. The electrophysiology study was not part of this and neither was non-sustained ventricular tachycardia. There were 1232 patients randomized over 74 centers with an average follow-up of 20 months. The groups were amazingly equal in regards to those who had bypass surgery, intervention, ejection fraction and congestive heart failure class. Of note, more than 85% of these patients had their MI 6 months prior. Also of note, the beta-blocker use was greater than 70% as well as the ACE inhibitor use. The results show that there were 197 deaths in the follow-up with a 14% total mortality in the ICD arm versus a 20% mortality in the conventional arm. This yielded a 31% reduction in mortality for the ICD group, which was statistically significant.

Resynchronization therapy: An interesting piece of information that came out of MADIT II is that CHF admissions were increased specifically in those that received a dual chambered device. This has been further verified by the recent release of the DAVID trial which looked at single versus dual chamber defibrillators and it was quite clear that dual chamber defibrillators when inappropriately programmed led to a worsening of congestive heart failure with increase admissions with this diagnosis. This has verified what many of us have thought for quite some time that conventional pacing in an abnormal heart can lead to worsening of LV function. The mechanism for this worsening was a non-synchronous ventricular activation associated with abnormal decreased filling time. This can also be viewed as electromechanical decoupling. Conventional right ventricular pacing can be thought of as a pre-activation of the right ventricle versus the left which by definition would be dyssynchrony. It is not hard to visualize that patients with left bundle branch block have the same problem. The mechanism of dysfunction due to contractile dis-coordination can be viewed in several ways including a reduced ejection volume secondary to internal sloshing from premature activated regions to late activated ones. There is also an increase in systolic volume and therefore stress. There is mechano-energetic inefficiency which leads to reduced systolic dysfunction despite maintained or increased energetic cost. There is late systolic stretch with cross bridge detachment and reduced force. Additionally delayed relaxation as well as after contractions may be proarrhythmic. Mitral valve dysfunction leading to papillary muscle dis-coordination and therefore mitral regurgitation is also seen. Cardiac re-synchronization therapy in association with an optimized AV delay can improve these abnormalities and hemodynamic performance by forcing the left ventricle to complete contraction and begin relaxation earlier allowing for an increase ventricular filling time. Acute studies by Kass have shown that biventricular pacing is a more efficient way for the ventricles to work. Re-synchronization can be achieved by pacing not only the right ventricle but the left ventricle most commonly now via the coronary sinus.

Is there an energetic cost to biventricular pacing? Given the fact that therapy that enhances systolic function without reducing arterial load or heart rate typically increases myocardial

metabolic demand. Inotropes that increase metabolic demand of the heart have generally proved disappointing as effective therapies for heart failure. Anes Nilson et al, Circulation 2000, observed that biventricular pacing improved cardiac performance at a decreased cost as compared to Dobutamine, clearly showing us that biventricular pacing has tremendous promise. Why are we so interested in these patients? If we take a look at the Vesnarinone study or the VEST study, we see that patients with significant heart failure, those with the widest QRS did the worst. It was a significant and independent predictor of mortality. With this in mind, let us focus on some of the trials that have taken place on biventricular pacing. There has been the INSYNK trial, the MUSTIC trial, the Miracle trial as well as Companion. We will focus on MUSTIC, Miracle and Companion. The first trial to be discussed is MUSTIC which is multi-site stimulation and cardiomyopathy trial which was published in the New England Journal in March 2001. The rationale of this trial was that atrial? biventricular pacing (cardiac re-synchronization) improves hemodynamics in acute studies by reducing ventricular asynchrony. Based on uncontrolled french pilot studies, biventricular pacing was shown to improve and sustain the symptoms, exercise tolerance and well being. The study design was a randomized cross over single blinded trial with three months of active pacing and three months of inactive pacing. The primary end point was the distance walk in six minutes with secondary end points including the quality of life via the Minnesota LWHF questionnaire. The inclusion criteria for this study were that patients must have chronic heart failure due to ischemic or dilated cardiomyopathy with an established heart failure class of class III for at least one month. The patient must have been treated with optimized drug therapy as well as having certain echo criteria including LV ejection fraction of less than 35% with a left ventricular end diastolic volume of greater than 60mm. The QRS duration used for this study was 150msec and the six minute walk distance was less than 450 meters. Of note, the coronary sinus lead placement success rate was overall 88% in these patients which represents the experience with the first generation coronary sinus leads. The results of the study regarding the six minute walk distances were noted to show improvement specifically with pacing turned on, as shown in this graph. Also of note, the quality of life scores were improved again consistently with biventricular pacing on. The second trial looked at would be the MIRACLE or Multicenter in sync randomized clinical evaluation. This study population was very similar to that of MUSTIC and the patients had to have at least class III or IV heart failure with QRS durations of 130msec. The left ventricular ejection fraction had to be less than or equal to 35% and the left ventricular end diastolic volume was greater than or equal to 55mm. The patient had to be on optimum medical therapy for at least one month. This was a cross over double blinded trial with follow-up over six months. This again had several end points including quality of life, heart failure class and six minute walk. To confirm the results of MUSTIC, merka also showed an improvement in the six minute walk with biventricular pacing as compared

to control. Again, there was an improvement in the quality of life scores that was seen both at one month and six months out. Also of note, coronary re-synchronization therapy seemed to improve heart failure class.

At this time, I would like to relay my personal experience with the first patient to receive a biventricular pacemaker. This patient was an 80 year old gentleman who was sent to us for second opinion regarding cardiomyopathy and mitral regurgitation. It was initially suggested that the patient have a mitral valve replacement, however given his ejection fraction of 10% and cardiac cachexia, we decided against this option and instead enrolled him into a biventricular pacemaker protocol. His CPX testing revealed that his first walk lasted 3.4 minutes and after biventricular pacer implant, he was able to walk 12.9 minutes. Of note, the patient's symptoms improved and he was able to restore much of his muscle mass over the next several months. The patient did well for exactly 18 months, however the patient passed away while hunting. Interrogation of the device revealed that the patient had died of a rapid ventricular rhythm. This brings home the point that perhaps there is more to do than to just improve symptoms with this biventricular modality. As has been set up during this entire talk, pacing may be important but we can not overlook the risk of sudden cardiac death and prophylactic use of defibrillators. This was perhaps first seen in the Contact CD trial, a trial not mentioned as of yet, in which there was a non-statistically significant reduction in sudden cardiac death with biventricular pacing. This I am sure led to the Companion trial or Comparison of medical therapy in pacing and defibrillation in heart failure. By far to date, this is the most important trial in regards to the care of congestive heart failure patients. The study purpose was to determine whether re-synchronization therapy with optimal pharmacological therapy alone or with a back-up defibrillator when compared to optimal pharmacological therapy alone can reduce all cause hospitalization and mortality, reduce cardiac morbidity, increase total survival and improve exercise performance. This trial was to answer the mortality question that was lacking in the other heart failure trials. The inclusion criteria for Companion was a New York Heart Association class III or IV patient. The patient had to be in sinus rhythm with a QRS of greater to or equal to 120msec with a PR interval of greater than 150msec. Left ventricular ejection fraction had to be less than or equal to 35% with a left ventricular end diastolic volume being greater than 60mm. The patient had to have optimal pharmacological therapy including a beta-blocker for at least 3 months, a diuretic, and ACE inhibitor or ARB and Spironolactone for at least one month. This could have occurred with or without Digoxin use. The patient had to have a history of heart failure with a hospitalization over the last 12 months, but not within one month of enrollment. The study design led to a baseline testing and randomization occurred in a 1:2:2 ratio with optimal pharmacological therapy alone being 1, the re-synchronization therapy being 2 and the re-synchronization plus defibrillator being the other 2. The primary end point was time to death



or hospitalization, both all cause. Definition of hospitalization all cause except elective admission for cardiac re-synchronization therapy which would include the treatment of decompensated heart failure with active drugs for a period greater than 4 hours in an urgent care setting. Secondary end points was all cause mortality, cardiac morbidity and maximal exercise which was a sub-study and the tertiary end point was sub-maximal exercise, quality of life and others. There were over 1600 patients enrolled in this study and in December 2002, the DSMB recommended that the trial be stopped given the clear benefit of device therapy. There was a clear improvement in death or any hospitalization with cardiac re-synchronization therapy. Reduction in hospitalization by cardiac re-synchronization was 18.6% and increased to 19.3% with defibrillator backup. All cause mortality revealed a stepwise improvement with device therapy, namely cardiac re-synchronization therapy improved all cause mortality by 23.9%, but with the defibrillator added increased that to 43.4%. In a sub-group hazard ratio in comparison of CRT-D versus optimal medical therapy, all sub-groups benefited from the device including those of any age greater or less than 65, of any gender, of any ideology in the cardiomyopathy, of any heart failure class, of any ejection fraction either greater than or less than 20% and of any left ventricular end diastolic volume either greater than or less than 67mm. The major outcomes therefore of the Companion study reveal a reduction in the combined end points of death and all cause mortality. CRT was associated with a trend for reduction in mortality. The addition of an ICD to the CRT increased mortality reduction resulting in a highly significant decrease in mortality. There was no obvious mortality benefit of CRT in ischemics or non-ischemics. Complications were acceptable. Of note, 45% of the patients enrolled in Companion were non-ischemics. The Companion trial had many firsts to it. It was the first trial of cardiac re-synchronization therapy to use mortality and morbidity as primary end points. It was the first trial to measure the affects of cardiac re-synchronization therapy versus cardiac re-synchronization therapy with a defibrillator. It was the first trial to measure the efficacy from time of randomization. It was the first heart failure trial to use total hospitalizations as its primary end point. It was the first heart failure trial to be conducted on the background of three drugs, namely ACE inhibitors, beta-blockers and Spironolactone. It was the first trial to use historical heart failure hospitalization as an inclusion of criteria. In essence, the results of the Companion trial are quite outstanding in that it is one of the first studies in quite some time to show an added morbidity and mortality benefit to current medical therapy of heart failure.

Despite the dramatic results of Companion, there are still questions regarding a synchronized patient and I would like to take some time to discuss those. First and foremost, can we predict responders to biventricular pacing? ie: what parameters are best to predict clinical outcome? Which parameter is the best measure to show improvement? What is the influence of the QRS

duration and change with pacing. We know from Sorgard that the extent of dyssynchrony predicts functional improvement, where there is a correlation between the amount of dyssynchrony and improvement of ejection fraction. As a predictor the QRS complex has been used, however this only broadly correlates with acute response and is a poor predictor of the chronic response to biventricular pacing. Also of note, the change in the QRS duration does not correlate with any improvement as reported by Caderisian et al, in PACE and Nelson et al in Circulation. What is more likely needed is a measurement of mechanical dyssynchrony via either Echo, Nuclear, or other studies (ie. MRI). Image analysis via strained rate tissue doppler or perhaps a gated spect thallium would be of interest in this area. There are other measurements that can be made including interventricular delays with QRS onset, pulmonary flow onset minus the QRS onset, aortic apical onset being equal to or greater than 25msec or a measurement of an intraventricular conduction delay with QRS onset and lateral wall contraction being greater than 290msec or looking at the QRS onset and lateral wall contraction being greater than the QRS onset of mitral E-wave onset. Another predictor of response might be basal dysfunction with low contractile state and severe PR delay being additional features of people who would respond to biventricular pacing.

What is the optimal pacing site? Either in the ventricle or perhaps in the atrium in future studies as has been discussed previously. From Butar et al in Circulation, 2001, it is quite clear that the lateral free wall appears to be the preferred site in biventricular pacing and that the anterior position is not only not as good, but also may be harmful specifically leading to problems with hypertension.

Another question that arises is timing and how much does this matter? Timing may be made in several areas, the atrium to the ventricle, the atrium to specific ventricles, specifically A-LV or A-RV. There is also the interventricular timing. There is also the question of what is the optimal AV optimization method. Remember that the optimum AV delay is the shortest AV delay that does not interrupt atrial filling. The end of the diastolic filling matches the start of the systole resulting in a separation of E and A waves maximizing the time of diastolic filling of the LV which would maximize CRT. As noted previously, we will try to avoid prolonged AV delays that may lead to limited filling periods and mitral regurgitation. It appears that via Oriki et al, 1999, the AV delay optimization is generally less critical than obtaining the proper pacing site in the left ventricle. Typically AV delays in the range of 100-120msec most likely are adequate. In regards to interventricular timing, Sogard reports that there is a slight favoring of left ventricular pre-activation in the range of 0-20msec.

What is the role if any of non-excitatory cardiac contractility currents? Cardiac contractility modulation is currently under scientific investigation and would offer an extremely beneficial pacing modality in that dyssynchrony would not be needed to obtain improvement in left ventricular function as it is affecting the calcium current and overall muscle strength. The concern that I have always had is, are we missing something in regards to this theory? ie: Is there something about pacing the left ventricle that is improving factors that we are not recognizing at this time? I say this because we have seen that there is improvement in patients who pace from the left ventricle only which does not correlate with the dyssynchrony therapy. As well, there is improvement in patients with right bundle branch block which again does not correlate with the dyssynchrony therapy, again posing the question, is there something about pacing the left ventricle that is improving something that we have not recognized at this time.

In conclusion to the questions, we know that the responders currently are averaging in the range of 70% in patients who receive biventricular pacing. The acute mechanical response may be predictive, however it is quite clear that the QRS complex should only be used as a starting point in that other definitive measures of dyssynchrony should be used at this time. For people who do not respond, clearly the most important point is not to make it an iatrogenic cause. ie: Make sure that you obtain adequate lead placement with the left free wall being targeted as well as not creating too short of an AV delay via inappropriate programming. In conclusion, device therapy can be quite beneficial to the patients who have confirmed congestive heart failure from many different perspectives. Remembering that patients with congestive heart failure suffer from sick sinus syndrome and heart rate support may be beneficial in that regard as well as the possibilities of the treatment of atrial fibrillation or the possible prevention of atrial fibrillation. Remember always that these heart failure patients are most likely at risk for sudden cardiac death and that prophylactic ICD as shown by Companion can be quite beneficial in their survival. Lastly, biventricular pacing is clearly a modality that is beneficial at this time and when used on the correct patient can be a great addition into the medical therapy already established.