CLINICAL DISTRIBUTION
Pre-Implant Identification of CRT Responders
Summary by: Paul A. Levine, M.D., FACC

Reference: Pitzalis MV, Iacoviello M, Romito R, Masseri F, Rizzon B, Luzzi G, Guida P, Andriani A, Mastropasqua F, Rizzon P, Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony, J Amer Coll Cardiol 2002; 40: 1615-1622

Reference: Pitzalis MV, Iacoviello M, Romito R, Guida P, De Tommasi E, Luzzi G, Anaclerio M, Forleo C, Rizzon P, Ventricular asynchrony predicts a better outcome in patients with chronic heart failure receiving cardiac resynchronization therapy, J Amer Coll Cardiol 2005; 45: 65-69.

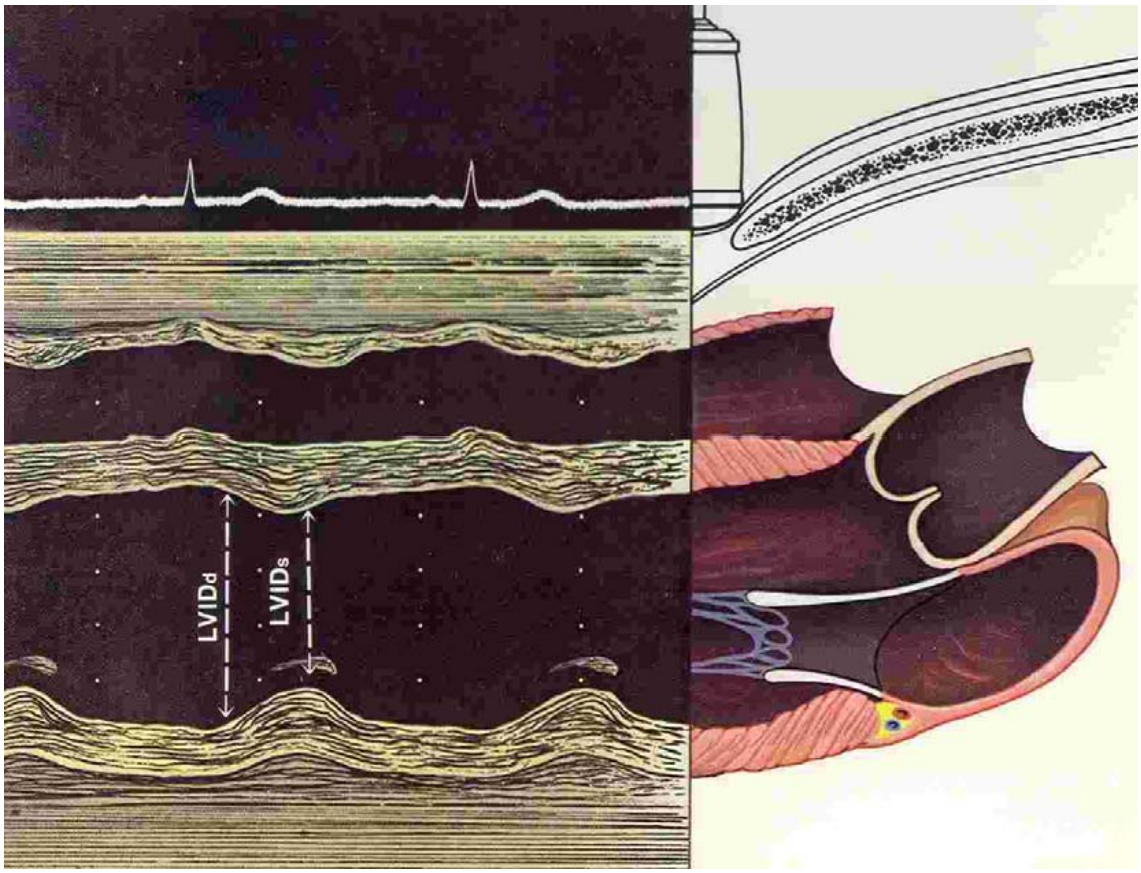
The basic criteria for cardiac resynchronization therapy (CRT) is a patient who has refractory congestive heart failure with a left ventricular ejection fraction (EF) < 30%, a markedly dilated left ventricle, left bundle branch block with a QRS duration > 130 ms and continued symptoms despite maximally tolerated pharmacologic therapy. These are complex and expensive systems to implant in a group of patients who are very ill. As such, it has been a frustration to everyone when the therapy is ineffective. Based on published studies, the incidence of non-responders is in the range of 20-30%. There is an ongoing quest to determine who is likely to respond and who will not respond to CRT prior to implantation of the system. The initial screening criterion is a very wide QRS complex (usually left bundle branch block) based on the reasoning that a disordered electrical activation sequence will result in a disordered ventricular contraction pattern. Indeed, the objective of CRT is to restore synchronous mechanical contraction of the left ventricle using stimulation therapy.

Although LBBB has been used as an initial screening requirement, this is the group with a 20-30% non-responder rate presuming that the LV lead can be successfully positioned. As such, investigators have been looking for another marker that will separate responders from non-responders with the eventual goal of not subjecting a patient who is unlikely to respond to the implant procedure. A variety of complex technologies have been proposed, the basic limitation to general application being that these techniques are not generally available except in unique referral centers.

Pitzalis and coworkers in an initial paper in 2002 with a follow-up study published in 2005 have shown that a specific echocardiographic measurement associated with the “standard” 2D-echocardiogram and can be readily performed in virtually

This summary and review of a published article has been created by Dr. Levine and expresses his expert medical opinion based on his years of experience as a Board Certified Cardiologist and Testamur, NASPExAM. The observations and conclusions reflect his interpretation of the published article. This summary and review does not represent an official recommendation or opinion of St. Jude Medical, Inc., its subsidiaries, officers or directors. Ref: Clinical\05081801-echo prediction of CRT responders

every cardiology department and most cardiologists' offices if they have an echo machine is a superb discriminator. One of the standard echocardiographic measurements is Left Ventricular End-Systolic and End-Diastolic diameter. These are measaured with the echo-beam aimed just below the mitral valve as shown in the picture below:



Modified based on Reichek N, Echocardiography Primer, Merck Sharpe & Dohme, 1978

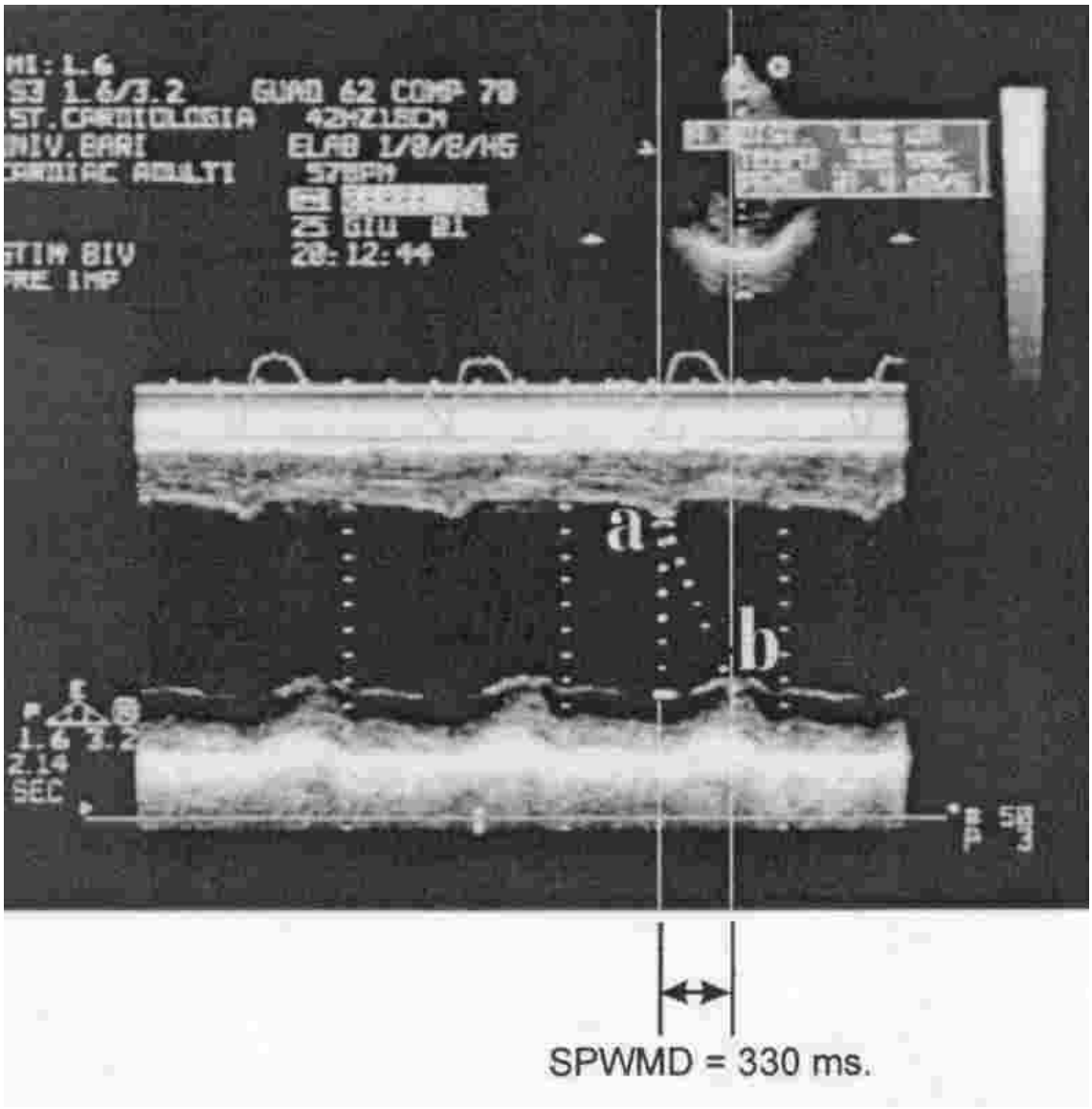
Pitzalis and coworkers looked at all standard echocardiographic measurements in addition to some that have been proposed to be specific and helplful in CRT patients. These included:

- **Left Ventricular Electrical Mechanical Delay (LVEMD)** which is the interval from the onset of the QRS complex to the opening of the aortic valve and the start of effective forward ejection
- **Interventricular delay (IVD)** which is the difference between LVEMD and a similar measurement on the right side (RVEMD) with respect to pulmonary valva opening
- **LV Septal to posterior Wall Motion Delay (SPWMD)** measuring the delay between peak septal contraction of the posterior wall of the left ventricle.

Regardlees of the pre-implant measurements, all patients recived a CRT system and then were followed with repeat testing at 6 month and correlating the results of the echocardiographic study with the 6 minute walk test, NY Heart Association Functional Classification, Quality of Life and other measurements. In the authors' initial study published in 2002, there were 21 patients of whom 17 received a CRT-P system and 4 received a CRT-D system. This first study

utilized Guidant and Medtronic devices. The second study included 72 patients of whom 65 provided data for the study because of either inability to implant the LV lead or poor echocardiographic image quality.
Of all the various measurements, the authors found that the SPWMD (septal posterior wall motion delay) proved to be highly specific and sensitive.

If th SPWMD was greater than or equal to 130 ms, there was a significant benefit of CRT and subsequent ventricular remodeling. Indeed, the wider the SPWMD, the greater the apparent benefit of CRT. If the SPWMD was less than 130 ms, there was a poor response with a very high incidence of continuing severe CHF.



The baseline QRS duration significantly correlated ONLY with SPWMD ($r = 0.62$, $p<0.01$) while LVEMD and IVD did not correlate with QRS duration. There was also a statically signicant and positive correlation between baseline QRS and SPWMD and reverse remodeling – the wider the QRS and the rider SPWMD, the greater degree of improvement with CRT. Another interesting observation was that patients with a longer PR interval (onset of the P wave to onset of the QRS duration) had a better response. In the first study involving 25

patients all of whom had ¨standard¨ implant indications, 12 were responders and these 12 had the longer PR interval and SPWMD. All of the responders had a baseline SPWMD ≥ 130 ms, a QRS duration ≥ 150 ms and PR interval ≥ 180 ms. Using these cut-off values, the specificity of SPWMD was 63% with a positive predictive value of 80% and an accuracy of 85%. The specificity of both the QRS duration and PR interval was 13% with a positive predictive value of 63% and an accuracy of 65%. In the follow-up study published in 2005, effectively involving 65 patients, the mean follow-up was 14 months during which 4 patients died of progressive CHF and 12 were hospitalized. At the 6 month post-implant measurements, improvement in EF was evident in 22 of 28 patients with SPWMD ≥ 130 ms and in only 2 of 23 patients with a SPWMD ≤ 130 ms ($p < 0.0001$). There was also a significant linear correlation between SPWMD and EF improvement ($r = 0.69$, $p < 0.001$). NYHA functional class improved at least 1 grade in 22 of the 28 patients with SPWMD ≥ 130 ms and in only 9 of 23 patients with SPWMD ≤ 130 ms.
Septal to posterior Wall Motion Delay is an easy measurement to obtain. It only requires a standard 2D echo obtained in a standard view that can be effectively performed by virtually any echo lab. As valuable as this measurement appears Septal to Posterior Wall Motion Delay correlated better than any other measurement including QRS duration with respect to which patient will not only respond to CRT therapy but have the best response to this very complex therapy.

Comment:
Septal to Posterior Wall Motion Delay is an easy measurament to obtain. IT only requires a standard 2 D echo obtained in a standard view that can be effectively performed by virtually any echo lab. As valuable as this measurement appears to be, there were clearly responders among patients with the SPWMD < 130 ms and non-responders in the group with SPWMD ≥ 130 ms. The major criticism of this and similar studies is that the echo study identifies two focal points within the heart and compares the relative contraction between these two points. Perhaps there may be a significant delay between two different portions of the LV wall and if those respective sites could be stimulated, either intentionally or inadvertently, there will be a good response; even though this specific measurement (SPWMD) would predict a lack of response. By the same token, with respect to the non-responders in those who had a SPWMD ≥ 130 ms, the authors did not attempt to correlate actual lead location with these results. Not all of the leads could be placed on the posterior or lateral wall. A practical reality of CRT therapy is that one does not have total control over where the lead will be placed – this depends on venous anatomy as well as LV and phrenic nerve capture thresholds. The LV sensing threshold, while important, is not a practical issue with many systems where sensing is limited to the RV signal. An inability to pace from a particular location or induction of phrenic nerve stimulation means that the lead cannot be left in that position and must be moved. Adjustments in V-V timing, based on other studies, suggests that this might be able to compensate for the LV lead not being located at the site of latest LV contraction but its impact on the response to CRT has not been correlated with the SPWMD measurement. In this particular series of studies, the V-V interval was effectively simultaneous. Initially, this was a limitation of the available devices while in the second studies, devices were utilized that allowed V-V

timing but to maintain consistency, this parameter was kept as simultaneous. It is not known whether these investigators are looking at the impact of V-V timing on the responders (to further improve the results) or non-responders and its impact on SPWMD. Perhaps this will be reported in a future paper.

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long-term improvement in post-CRT clinical outcomes in patients with severe HF and LBBB" and they have "proposed (this) as a method of screening candidate patients," it is not perfect. There are patients with a short SPWMD who respond and those with a long SPWMD who do not respond. Given that CRT is only indicated (based on current criteria) for patients with pharmacologically refractory CHF with continued symptomatic (NYHA Functional Class III, IV) with a marked LBBB and a dilated LV (left ventricular end-diastolic diameter of 55 mm), there are not a lot of options for these patients. Hence, while each of these patients will have had an echocardiogram and one can specifically look at SPWMD, I would use this data in a manner that was not proposed by the authors. IF this measurement shows a significant delay (> 130 ms), attempts should be made to place the CS lead on the posterior or postero-lateral wall. If that attempt is NOT successful, either abandon the approach and proceed with placement of an epicardial lead via thoracotomy (this may mean that the full implant procedure will be need to be completed at a second procedure) or use another imaging technique, perhaps radionuclide studies that can provide a more global view of the heart, to identify the area of latest contraction. Then, based on that other study, attempt to place the transvenous LV epicardial (coronary sinus) lead in the area of latest contraction. By the same token, the RV lead should not necessarily be placed in the RV apex (this was the standard RV lead position in the two studies by Pitzalis and colleagues) but in the area of the RV septum with the earliest contraction with respect to the LV site with the latest contraction.

Indexing Terms:
Cardiac Resynchronization Terapy
Echocardiography
Septal to Posterior
CRT responders