Jurnal
Kardiologi Indonesia
J Kardiol Indones. 2010; 31:126-141
ISSN 0126/3773

Case Report

Hybrid implantation of Cardiac resynchronization therapy device

Alexander Edo Tondas, Yoga Yuniadi

Recent trials have proven the clinical and functional benefits of cardiac resynchronization therapy (CRT) by biventricular pacing in patients (pts) with severe heart failure and intraventricular conduction delay, principally left bundle branch block (LBBB). However, placement of the transvenous left ventricular lead of CRT device is unsuccessful in 5–10% of patients and a further 20% fail to respond. For these groups, epicardial left ventricular lead placement is one alternative
A 75-year-old male patient diagnosed as non ischemic dilated cardiomyopathy patient NYHA Class III-IV meeting the clinical initiation criteria of QRS duration > 120 msec, and low ejection fraction (≤35%), with worsening symptoms despite one year of medical therapy.A hybrid approach of LV lead implantation by mini thoracostomy and conventional implantation of the RA and RV leads were performed because the coronary sinus cannot be accessed transvenously due to small caliber even after angioplasty. The patient responded quite well to CRT and was discharged with stable hemodynamics, and NYHA Functional Class II.

(J Kardiol Indones. 2010;31:126-141)

Keywords: dilated cardiomyopathy, cardiac resynchronization therapy (CRT), hybrid approach

Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia, and National Cardiovascular Center Harapan Kita

Jurnal
Kardiologi Indonesia
J Kardiol Indones. 2010; 31:126-141
ISSN 0126/3773

Laporan Kasus

Implantasi hibrid alat terapi resinkronisasi jantung

Alexander Edo Tondas, Yoga Yuniadi

Beberapa uji klinis baru-baru ini telah membuktikan keuntungan klinis dan fungsional dari terapi resinkronisasi jantung (*cardiac resynchronization therapy, CRT)* dengan pemacuan biventrikel pada pasien-pasien dengan gagal jantung berat dan gangguan konduksi intraventrikel, terutama *left bundle branch block* (LBBB). Bagaimanapun, pemasangan lead ventrikel kiri transvena dari alat CRT mengalami kegagalan pada 5-10% pasien dan sekitar 20% gagal berespon. Untuk kelompok pasien seperti ini, pemasangan lead ventrikel kiri secara epikardial dapat merupakan salah satu alternatif.
Seorang laki-laki usia 75 tahun didiagnosis sebagai kardiomiopati dilatasi non iskemik dengan kelas fungsional NYHA III-IV yang memenuhi kriteria inisiasi : durasi QRS>120 ms, dan fraksi ejeksi rendah (≤35%) dengan gejala yang memberat walaupun telah diterapi selama 1 tahun. Dilakukan pendekatan hibrid pemasangan lead LV dengan mini torakostomi dan implantasi konvensional transvena dari lead RA dan RV karena sinus koronarius terlalu kecil sehingga tidak dapat diakses secara transvena walaupun telah dilakukan angioplasti. Pasien berespon cukup baik terhadap CRT dan dipulangkan

(J Kardiol Indones. 2010;31:126-141)

Kata kunci : *kardiomiopati dilatasi, cardiac resynchronization therapy (CRT), pendekatan hibrid*

Advances in medical therapy seem to be improving survival in patients with heart failure. Among subjects in the Framingham study cohort, the 30-day, 1-year, and 5-year age-adjusted mortality rates among men declined from 12%, 30%, and 70%, respectively, in the period 1950–69 to 11%, 28%, and 59%, respectively, in the decade 1990–99. The corresponding rates among women were 18%, 28%, and 57% for the period 1950–69 and 10%, 24% and 45% for the decade 1990–99. Overall, there was an improvement in the survival rate after the onset of heart failure of 12% per decade.

Alamat Korespondensi:
dr. Alexander Edo Tondas, Departemen Kardiologi dan Kedokteran Vaskular, Fakultas Kedokteran Universitas Indonesia. E-mail: *tondas2000@gmail.com*

Even so, the limitations of medical therapy for heart failure have generated great interest in non-pharmacological treatments. The most efficacious non-pharmacological treatment so far has been cardiac resynchronization therapy (CRT) a device-based therapy that targets electromechanical ventricular dyssynchrony.[1]

Recent trials have proven the clinical and functional benefits of cardiac resynchronization therapy (CRT) by biventricular pacing in patients (pts) with severe heart failure and intraventricular conduction delay, principally left bundle branch block (LBBB). In particular, improvements in exercise tolerance, quality of life, increased systolic heart function, reduced hospitalization and slowed progression of the disease were observed. In the

MIRACLE-trial (453 patients) [3] the combined risk of death or worsening of heart failure was significantly lower in the CRT-group compared to the control-group (12 vs. 20%). Moreover, by pooling the data of five large, prospective randomized trials (COMPANION [4], CONTAK-CD, InSync implantable-cardioverter defibrillator (ICD) [5], MIRACLE [3] and MUSTIC [6]) the all-cause mortality is now seen to be significantly reduced (odds ratio 0.74, 95% confidence interval 0.56–0.97) for the 2559 cumulative patients assigned either to CRT (1426 pts) or non-CRT (1133 pts) with a follow up duration of 6 month. To optimize CRT therapy, an additional lead needs to be placed in the right atrium to increase the preload of the failing heart by optimization of the atrioventricular delay. The most difficult part of this procedure is the implantation of the left ventricular (LV) lead: For CRT response, the LV lead has to be placed where optimal concordance is achieved between the left ventricular pacing site and the site of most delayed left ventricular mechanical activation [7].

CRT systems rely on three leads: one in the right atrium, one fixated on the right-ventricular side of the ventricular septum, and another located in the coronary sinus. However, placement of the transvenous left ventricular lead is unsuccessful in 5–10% of patients and a further 20% fail to respond. For these groups, epicardial left ventricular lead placement is one alternative.[8]

National Cardiac Center Harapan Kita (NCCHK) has performed seventeen CRT procedures from January 2005 until May 2010. Eleven of them were CRT and six others were CRT plus ICD (CRT-D). This is the second case of hybrid approach to CRT device lead implantation that ever been performed in NCCHK.

The purpose of this case report is to present a case of a hybrid approach in CRT device implantation, that is : a combination technique of epicardial left ventricle lead insertion through mini thoracotomy and conventional transvenous placement of the right atrial appendage and RV apex leads in a situation where placement of LV lead at the distal of anterolateral coronary sinus vein failed because it is too small even after percutaneous balloon angioplasty.

Case Illustration

A-75-year-old man, a regular patient of the National Cardiac Center Harapan Kita (NCCHK), labeled as advanced refractory heart failure was admitted with a plan for CRT implantation, after a discussion with cardiologist from a private hospital where he sometimes went for consultation due to shorter distance

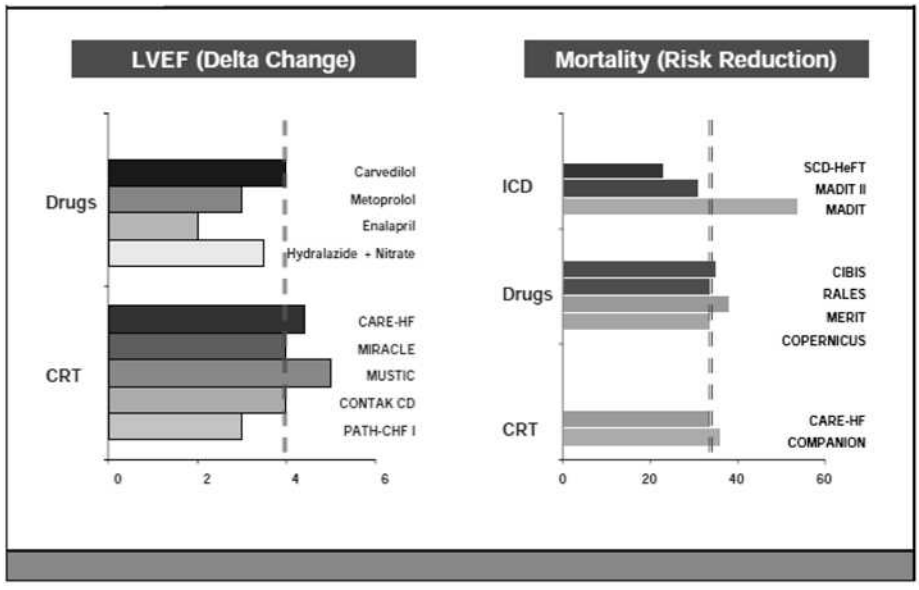


Figure 1. The effect of cardiac resynchronization therapy (CRT) on change in left ventricular ejection fraction (LVEF) and mortality (i.e. risk reduction) is shown compared with pharmacologic therapies and implantable cardioverter defibrillator (ICD) therapy only. [2]

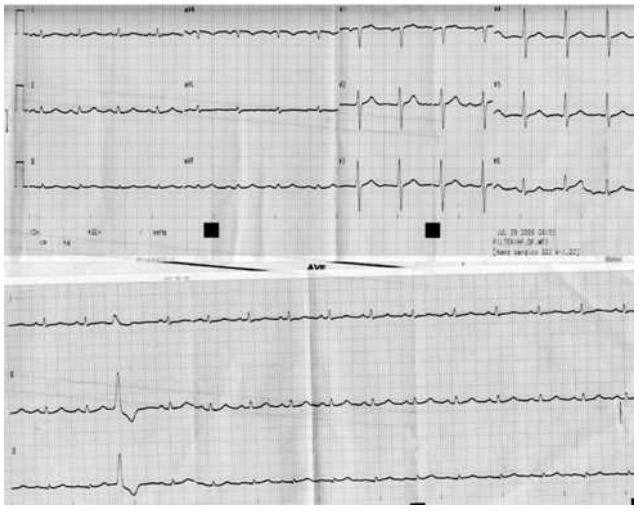


Figure 2. Prior ECG of the patient on routine outpatient checkup, eight months before admission

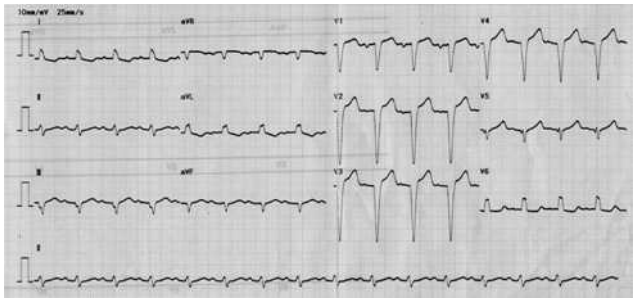


Figure 3. ECG of the patient at the emergency department, four months before admission

from his home.

Seventeen years ago, he once had a medical checkup at the National Cardiac Center. At that time the treadmill test showed negative ischemic response, fair physical fitness, functional class one and 7,23 mets of aerobic capacity. The resting blood pressure was 150/100 mmHg at rest, and 190/100 mmHg at the end of exercise test. X-rays demonstrated CTR of 50%, no buldging of pulmonary segment, an elongated aorta and normal pulmonary vascularization. However he was ignorant of his hypertension and did not seek a physician for treatment. Two years later he started to feel mild dyspnea triggered by book dust and humid air once in a while that prompted him to see a pulmonologist who diagnosed him as having asthmatic bronchitis and chronic pulmonary obstructive disease. He was treated with budesonide inhalation for a while, but due to absence of symptoms thereafter, he did not continue the medication.

The patient first noticed that he was easily fatiqued about one year ago. The 500 meter distance to his office, that he usually travelled everyday with ease, suddenly became harder to reach and he sometimes felt shortness of breath after the activity. After ten days of worsening symptoms, he then consulted a cardiologist at a private hospital. He presented with mild orthopnea and minimal rales at the base of lungs. ECG finding was normal but coronary MSCT screening exam showed severe stenosis of the left anterior descending and first diagonal. Ejection fraction from echocardiography was 28%. There was an increase in creatinin

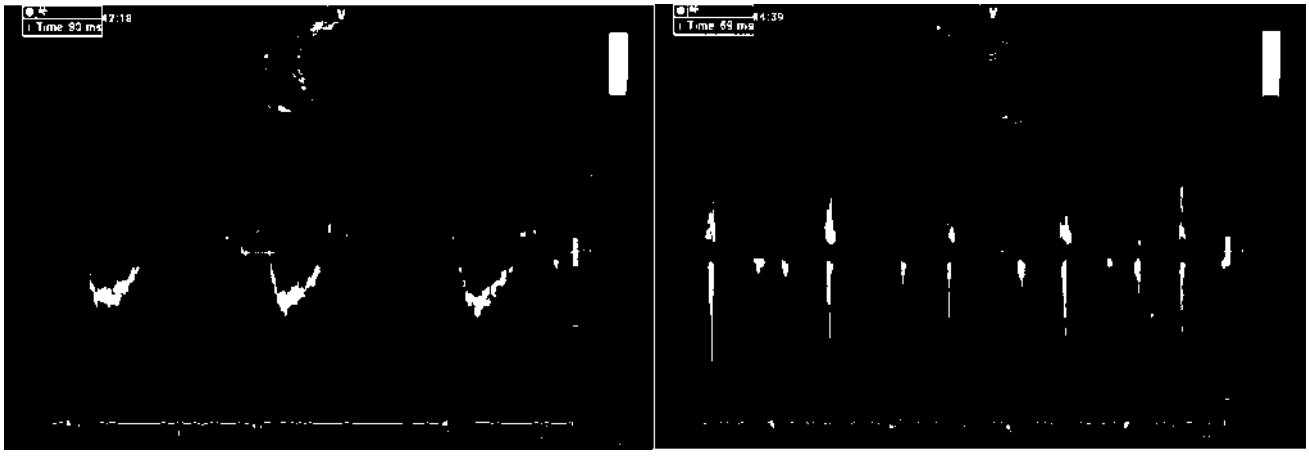


Figure 4. Pulsed wave doppler showing : right ventricular and left ventricular (LV) preejection intervals are measured from the onset of the QRS on the electrocardiogram (ECG) to the onset of pulmonary (Pulm) (RV-PEI) and aortic (Ao) (LV-PEI) outflow; IVMD is calculated by subtracting the RV-PEI from the LV-PEI.

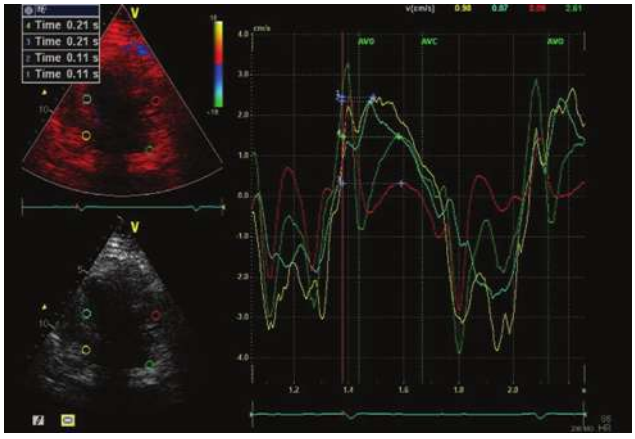


Figure 5. Offline analysis of tissue doppler imaging on segments assessed for dyssynchrony

level (1,6 mg%), and random blood sugar level was 158 mg%. Furosemide was given for decongestion and the patient was sent to NCCHK for hospitalization and coronary angiography. However, catheterization study revealed normal left main, LAD, LCX and RCA coronary arteries with no significant stenosis. He was discharged with hypertensive heart disease , chronic kidney disease stage III, dyslipidemia and hyperuricemia as working diagnoses and given the following medications : ramipril 1 x 5 mg, atorvastatin 1 x 10 mg, aspirin 1 x 100 mg and allopurinol 1 x 300 mg.

Despite medical therapy and regular visits, the symptoms gradually worsened. Eight months ago he began to feel loss of appetite, decrease of body weight and weakness. He was advised to avoid strenuous activities : taking baths with shower, having his laptop carried by a helper and urinating using urinals. In the end, he was even unable to travel to his office by foot, restricted by the dyspnea on effort. The symptom relief provided by sublingual nitrate did not seem to work as good and sometimes he experienced paroxysmal nocturnal dyspnea. He came to the outpatient clinic once every one or a couple of months and ECG routine showed sinus rhythm, QRS rate 82x/min, normal QRS axis, normal P wave, PR interval 0,12 sec, QRS duration 0,08 sec, no ST-T wave changes, with infrequent ventricular extrasystoles.

Four months ago he was admitted to NCCHK emergency department with complaint of atypical chest discomfort that has been going on for a week, unassociated with physical activities, with less than 2 minutes duration. On physical exam no rales was heard on the lung field. Electrocardiography demonstrated a presumably new LBBB. That time, acute coronary syndrome was thought as less likely on the account of unspesific symptoms, and normal cardiac biomarkers (CKMB 10 and Troponin T <0,01). Serial cardiac enzymes CKMB and Troponin T were 12 and <0,01 respectively. The patient was hospitalized and given intravenous diuretics. Then he was discharged with sinus rhythm, persisting LBBB on ECG, with QRS rate 83 bpm, PR interval 0,152 sec and QRS duration of 0.125 sec, continuing his previous medications.

During the next few months until this last admission, the patient was hospitalized at NCCHK several times due to symptoms of acute heart failure. Throughout his disease history there was no acknowledgement of typical angina or recent flu-like symptoms accompanied by myalgia.One time he went to a cardiologist at a nearby private hospital and the idea came that the patient might be a nonischemic dilated cardiomyopathy case and a candidate for CRT, which could be facilitated by NCCHK.

Later at NCCHK's, the patient underwent echocardiograpy assessment. There was dilatation of left ventricle (EDD 60 mm and ESD 55 mm) and left atrium (LA diameter 46 mm). Diastolic IVS dan LVPW thickness were 7 mm and 7 mm, respectively. He had low LV ejection fraction of 18% with akinetic septal, anteroseptal, apical and anterior segment, while other segments were hypokinetic. Diastolic dysfunction (compliance disturbance) was present, with E/A>1 and deceleration time 134 msec. Right ventricular function was normal with TAPSE of 2 cm. Aortic cusps was a bit calcified, with normal function and AoVmax 0,6 m/s. Mild mitral regurgitation, mild pulmonary regurgitation and mild tricuspid regurgitation (TVG 30 mmHg) were shown on color doppler.

Interventricular mechanical delay was 21 msec. By offline analysis of tissue doppler imaging, septal lateral delay was 30 msec, 12 segments SD was 37 msec and maximum difference was 90 msec. In conclusion, there was no interventricular dyssynchrony but borderline intra ventricular dyssynchrony was present.

At the moment of admission he complained of productive cough and fever for the last three days. Blood pressure was 90/60 mmHg, heart rate 102x/minute and respiratory rate 24x/min. Neither murmur nor gallop was heard on cardiac exam. Rough ronchi was heard over the lower half of the lung fields. Laboratory exam values were: hemoglobin 13 g/dL, leucocyte 23.800, hematocryte 39%, thrombocyte 265.000, ureum 126, creatinine 2,4 mg/dL, BUN 58, natrium 131 mmol/L,potassium 3,8 mmol/L. Chest

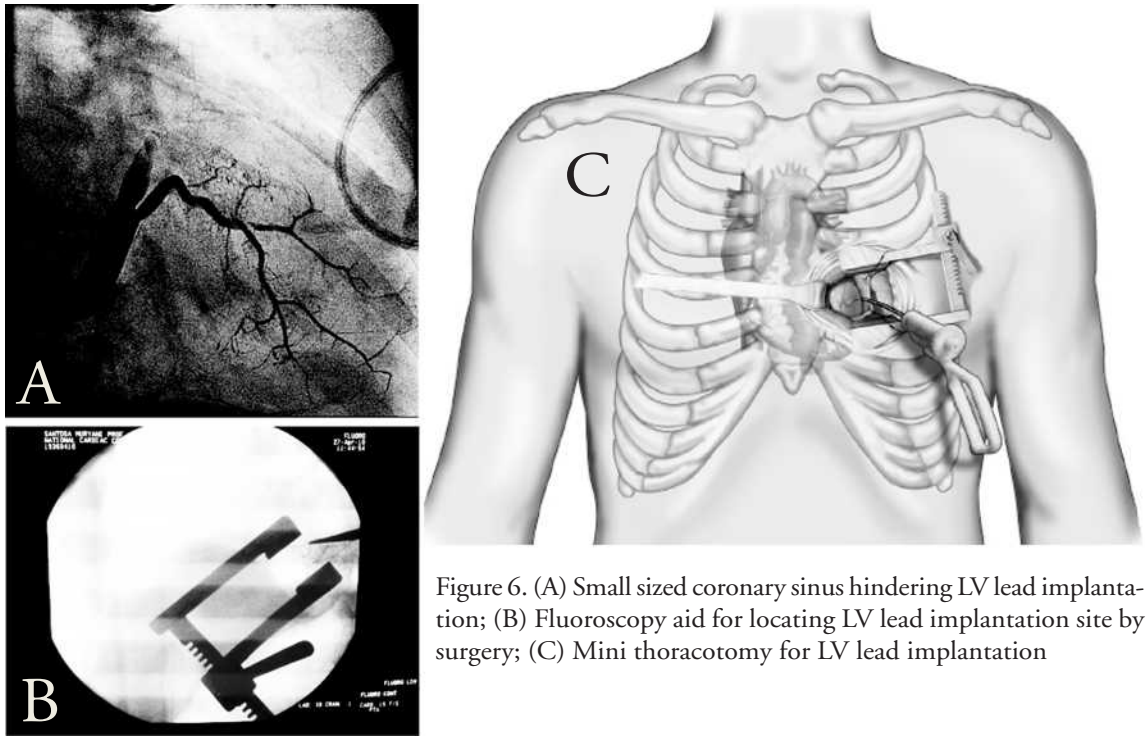


Figure 6. (A) Small sized coronary sinus hindering LV lead implantation; (B) Fluoroscopy aid for locating LV lead implantation site by surgery; (C) Mini thoracotomy for LV lead implantation

x-ray showed enlarged heart with 60% CTR, dilated aorta, normal pulmonary segment, and infiltrates over the mid and lower right lobe of the lung. Signs of congestion were not prominent.

Ultrasonography findings showed that internal organs, i.e. liver, gall bladder, spleen, pancreas and both kidneys were within normal limits with cortical calcification of the left kidney. Apparently he also had accompanying acute on chronic kidney disease and community acquired pneumonia at admission. There was no known coronary risk factor other than hypertension and dyslipidemia He was treated with antibiotics and IV diuretics for a few days, showing good clinical response. Leucocyte count reduced to 7.440 and creatinine level returned to 1,4 mg/dL baseline.

After he was stabilized, the first attempt of pacemaker implantation was done. Four centimeter incision of right deltoideo-pectoralis junction area was made after antiseptic procedure. Puncture of the right subclavian vein and insertion of peel away sheath. With the use of Rapido and guiding catheter, the posterolateral branch of coronary sinus was canulated. Placement of LV lead at the distal of anterolateral CS vein failed because the vein is too small even after POBA was done and the procedure was withheld.

A week later, the patient underwent hybrid approach for CRT device implantation. Firstly, mini thoracotomy was performed by cardiac surgeon at the left ICS VI linea axillaris anterior after antiseptic procedure. Fluoroscopy was used to aid locating epicardial CRT device implantation site. An active lead was inserted into the epicardium at left ventricle which showed : output threshold of 2.75 V, resistance of 665 ohm, R wave of 9.7 mV and then tunneling to left subclavian area. Left intra pleural drain was inserted and the incised wound was stitched.

The next steps was subsequently taken over by cardiologist who made two puncture of left subclavian vein. The right ventricle lead was inserted to RV apex. The measurement showed R wave of 6.0 mV, resistance of 588 ohm and threshold of 0.5 V. The RA lead was placed in the right atrial appendage, the measurement showed P wave of 7.2 mV, resistance of 688 ohm and threshold of 0.3 V. After fixation of lead to surrounding muscle and tissue, an appropriate size pocket was tailored subcutaneously. Ampicillin-sulbactam 1.5 gr was douched. The generator was connected to the leads and the ECG showed biventricular pacing rhythm 60-110 bpm. The incised wound was then stitched. CRT was set with St.Jude Medical Frontier™ SN, mode DDD 60-110 bpm, bipolar. Atrial output was 3.5 V, R ventricle output was 3.5 V, and L ventricle output 4.0 V.

There was no observed complication after CRT. The patient suffered a little pain for a while at the

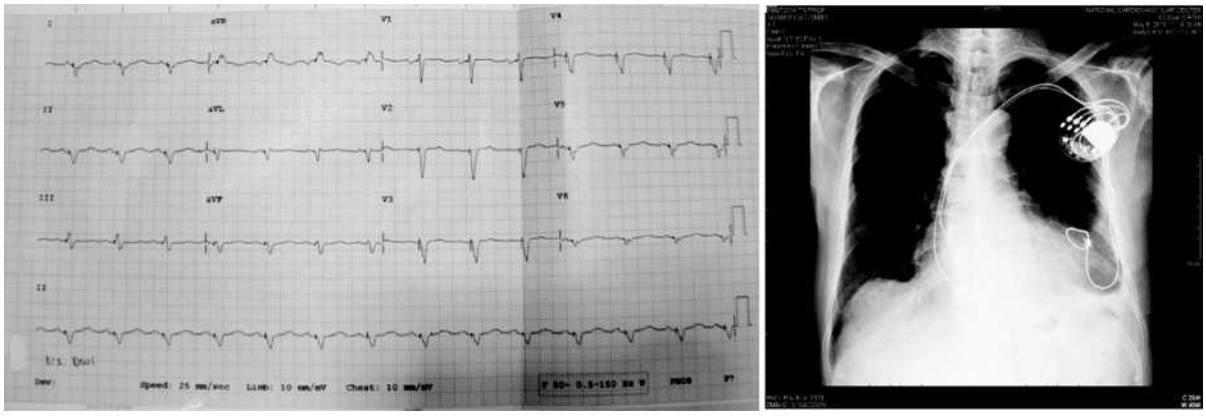


Figure 7. Post CRT electrocardiogram and chest x-ray.

thoracotomy site, which can be relieved by pain killer medication. Clinical and hemodynamic status were stable during 7 days post-procedural hospital stay and the patient was discharged with the following medications : ramipril 1 x 5 mg, carvedilol 2 x 3.125mg, furosemide 1 x 40 mg tablet, spironolactone 1 x 25 mg, aspirin 1 x 80 mg. Pre-discharge ECG indicated pacing rhythm with QRS rate 83 bpm, PR interval 0,152 sec and QRS duration of 0,12 sec. Blood pressure at discharge was 100/70 mmHg.

Literature Review

Dyssynchrony and Heart Failure : Epidemiology

Cardiac dyssynchrony has now taken its place as an important independent predictor of poor outcome in patients with CHF. In addition to well-established predictors of mortality – age, degree of systolic impairment, ejection fraction, New York Heart Association (NYHA) function class – data now show QRS prolongation and/or evidence of mechanical contractile dysynchrony to be independent predictors as well. The mortality risk increased by 45% in the CHF-STAT cohort of 669 dilated cardiomyopathy patients if their QRS duration exceeded 120 ms.12 The larger Italian Network on CHF Registry (5500 subjects) found that the presence of a LBBB (which occurred in 25% of the cohort) was an independent predictor of both annual overall mortality and mortality from sudden cardiac death. Furthermore, having an LBBB chronically increases risk. In a case–control study of more than 17 000 subjects (from 1958 to 2002), Imanishi et al[9] found LBBB occurring in less than 1%, typically older subjects, but that it raised their risk of dying from heart failure. Patients receiving pacemakers and developing de novo LV mechanical dyssynchrony are at risk as well. In a study of 11.656 patients without known heart failure, Freudenberger et al[10] showed 20% of paced patients suffered a new hospitalization for heart failure, compared with 12.5% of controls, and deaths from heart failure were 53% higher in the paced group. In addition to surface electrocardiography, mechanical dysynchrony has also been assessed using newer tissue Doppler imaging methods. This has been shown to be a predictor of worsened outcome in heart failure patients, independent of QRS duration and other conventional factors.

Electromechanical Delay (Mechanical Dyssynchrony)

In the failing heart, myocardial contractility is severely reduced and highly dependent on preload and afterload. Further impairment of left ventricular (LV) performance and energy consumption is seen with the development of an electrical conduction delay, most frequently presenting with a prolonged PQ interval and a prolonged QRS complex of left bundle branch block (LBBB)-type morphology. The left ventricle is activated slowly through the septum from the right side and the LV endocardial activation time may exceed 100 ms. LV pre-ejection pressure is lower than in the right ventricle and septal motion is abnormal. This results in an uncoordinated contraction sequence and delays LV ejection at the expense of diastolic filling. The electrical conduction disturbance in patients with advanced heart failure may involve the complete conduction

system from the sinus node to the Purkinje fibers.

Thus, atrioventricular (AV) and ventricular conduction can be similarly affected and three different levels of dyssynchrony can be distinguished by echocardiography as proposed by Cazeau *et al*. [12]:

• Atrioventricular dyssynchrony: delayed ventricular activation in relation to the atria owing to prolongation of the PR interval (applies only to patients in sinus rhythm).

• Interventricular dyssynchrony: delayed onset and end of LV systole due to delayed LV electrical activation in comparison to the right ventricle.

• Intraventricular dyssynchrony: delayed activation of some LV segments with prolonged contraction after aortic valve closure.

Recent data have demonstrated that mechanical dyssynchrony is not necessarily related to electrical dyssynchrony, and that the presence of substantial left ventricular (LV) dyssynchrony is a major predictor of response to CRT. Indeed, some patients with a wide QRS complex do not exhibit LV dyssynchrony, whereas some patients with a narrow QRS complex may demonstrate LV dyssynchrony. These considerations suggest that the surface electrocardiogram may not be the optimal marker to select candidates for CRT.[13]

Hemodynamic Consequences of Dyssynchrony

The dyscoordinate contraction patterns caused by abnormal ventricular activation, especially during RV apex pacing and LBBB, induce a wealth of systolic and diastolic hemodynamic perturbations, which are summarized in the figure below. An abnormality usually limited to ventricular pacing is uncoupling or improper timing of atrial and ventricular contraction, leading to impaired filling and mitral regurgitation.

The asynchronous activation of the ventricles usually leads to inter- and intraventricular asynchrony. During RV pacing and LBBB, interventricular asynchrony leads to delayed LV activation and consequently to an altered trans-septal pressure gradient that then leads to abrupt pre-ejection posterior interventricular wall motion. This may result in displacement of the posterior papillary muscle towards the mitral annulus, causing early systolic regurgitation. The increased intraventricular asynchrony gives rise to prolonged isovolumic contraction and relaxation phases without an increase in the total duration of systole. Consequently,

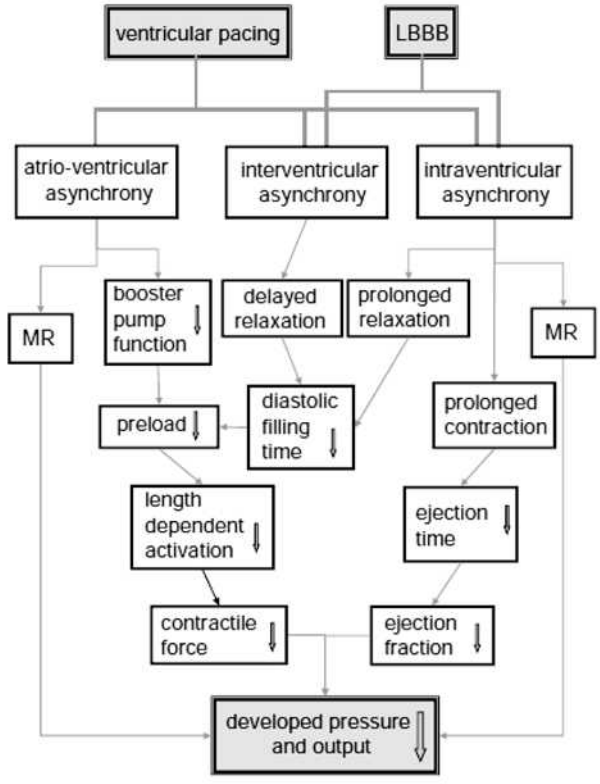


Figure 8. Schematic relationship between the various consequences of asynchronous activation of the ventricles, from ventricular pacing or conduction disturbances, and the deterioration of pump function over time.14

the duration and the extent of ejection are reduced.

Dyscoordination between the two LV papillary muscles can also create mitral valve regurgitation. This combination of factors may lead to LV dilatation and increased pulmonary wedge pressure. During RV pacing and LBBB, the increased interventricular asynchrony may also lead to an increased interval between left atrial and LV contraction, potentially leading to suboptimal LV filling and a reduction in preload. The effects of asynchronous electrical activation on LV pump function are independent of changes in preload and afterload. The pump function-reducing effect of dyssynchronous activation, induced by ventricular pacing or resulting from conduction disorders, has been observed not only under resting conditions, but also during various loading conditions and exercise. Impairments in regional and global cardiac pump function have been observed in patients and animals with LBBB, even if LBBB was not accompanied by other

cardiovascular diseases. Therefore, it seems that dyssynchrony is an important independent determinant of cardiac pump function.

The combination of all these changes following asynchronous activation may lead to a lower cardiac output and systolic arterial and LV pressure.In general, stroke volume is affected more than systolic LV pressure, presumably because baroreflex regulation partly compensates for decreases in blood pressure. This idea is supported by increased catecholamine levels and increased systemic vascular resistance during ventricular pacing.[14]

Specifications and Effects of CRT

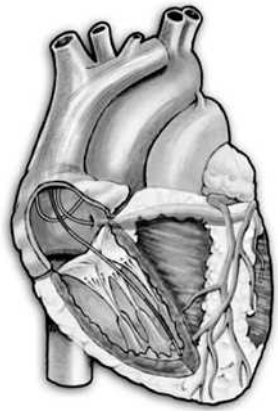
Cardiac resynchronization therapy (CRT) is a low voltage stimulation therapy. In terms of the stimulating pulses generated by the device, CRT systems use the same kind of output pulse as a conventional pacemaker. These output pulses are generally about 1–3 V at about 0.4 ms duration. In fact, most CRT systems, like most conventional pacemakers, have a maximum output of about 7.5–10 V. [15]

Cardiac resynchronization therapy (CRT) devices typically rely on three leads to deliver therapy. There is one lead in the right atrium for atrial pacing, another lead affixed at or near the septum within the right ventricle and a third lead placed in one of the coronary veins in such a way that it can stimulate the left ventricle. Although technically not in the left ventricle, this third lead is often called the LV lead. If the device is a CRT-D system, the lead in the right ventricle is the one that delivers defibrillation energy. All three leads have certain things in common: configuration, insulation and fundamental structure. Each lead also has certain special characteristics for its particular objective.

The effects of CRT can be divided into acute and chronic effects. Studies in the acute setting have demonstrated that CRT abruptly enhances LV systolic function. In both experimental and clinical studies, this is manifest by a modest (6 mm Hg) rise in systolic pressure, increase in stroke volume (10% to 30%), reduction in the LV end-systolic volume and, thus, LV end-systolic stress, and a more rapid rise of LV pressure (dP/dtmax, between 15% to 35%). There is also improved cardiac work at similar or lower oxygen consumption (34) so that chamber energetic efficiency is improved. Many of these changes can be observed within a single beat upon activating CRT, and are sustained in the short-term studies until CRT is abruptly terminated where they are rapidly reversed. The impact of CRT on diastolic function remains somewhat less clear.

Chronic CRT triggers similar changes in a number of hemodynamic parameters, but also results in reversal of LV dilation. Echocardiographic studies have shown >10% declines

in LV end-systolic and end-diastolic volumes, associated with an increase in LVEF. The immediate reduction in MR severity can be attributed to an improved coordination of ventricular contraction, including resynchronized papillary muscle activation, which results in improved systolic function and reduced mitral leaflet tethering forces. This effect can be observed in patients with ischemic and non-ischemic cardiomyopathy. Effective CRT immediately reduced the transmitral regurgitant volume at rest by about 30% to 40% on average. A further 10% to 20% improvement can be observed after some months of CRT and is probably related to the LV reverse remodeling.[16]



Acute Changes	Chronic Changes
↑ Systolic pressure	↑ Systolic pressure
↑ Stroke volume	↓ End-systolic volume
↓ End-systolic volume	↓ End-diastolic volume
↑ Cardiac energetic efficiency	↑ Ejection fraction
↑ Arterial pulse pressure	↑ Arterial pulse pressure
↑ dP/dt_{max}	↑ dP/dt_{max}
↓ or ↔ Relaxation time	↔ Relaxation time
↔ Diastolic compliance	Reverse remodeling

CRT = cardiac resynchronization therapy; dP/dt_{max} = change in left ventricular pressure over time.

Figure 9. Left : Three-lead system. Right : Acute and chronic effects of CRT [15,16]

Transvenous Left Ventricular Lead Placement

The question of where to place LV leads is intricately related to the issue of how to perform the implantation procedure. Historically, CRT involved direct surgical LV lead placement with transvenous insertion of the right atrial and RV leads. This approach required

general anaesthesia and lateral thoracotomy in advanced heart failure patients and, in the early days, was associated with considerable morbidity. With advances in techniques for retrograde coronary sinus cannulation, delivery systems, and dedicated LV lead technology, a fully transvenous approach has become the usual technique for CRT, although implanting the LV lead in a major cardiac vein may still be demanding and difficult in some patients. [17]

Left ventricular lead placement is usually performed by a transvenous approach using the tributaries of the coronary sinus. Intubation of the coronary sinus with a dedicated guiding

catheter facilitates LV lead implantation by providing support for advancing the pacing leads and allowing exchange of the angiography catheter and different pacing leads in difficult cases. Optimal projection for identifying the ostium is the left anterior oblique projection, but the right anterior oblique view may aid in defining the angulation of sidebranch take-offs. A "conventional" stylet-guided pacing lead or an "over-the-wire" approach may be used. For the latter, a guidewire is first advanced into the desired branch then followed by the lead that has a central lumen. The "over-the-wire" technique is preferred for small tortuous veins, whereas conventional leads may provide superior stability in large veins with a relatively straight course; fixation is usually passive (anchors or pre-shaped curves).

The feasibility of transvenous lead positioning is determined by anatomical and technical factors including venous anatomy, accessibility of the vein, pacing threshold, lead stability, and absence of phrenic nerve stimulation. Venous anatomy can be evaluated during the procedure by retrograde venography but is also possible with non-invasive imaging using multislice computed tomography. [16]

The precise incidence of suitable veins for CRT is not known and may differ between patients with ischemic and non-ischemic cardiomyopathy. Still, Meisel et al.[18] have shown that 55% of patients have suitable posterior veins, whereas 99% have posterior or left marginal veins. Implant failures are more often due to enlargement of the right atrium and the accompanying distortion of the coronary sinus ostium leading to inability to cannulate the ostium (up to 4%) or insufficient support by the guiding catheter. Overall, implant success rates >90% can be achieved in experienced centers.

The LV lead, like other leads, requires perioperative testing to confirm proper placement. Testing should be performed before the delivery system or sheath is removed, in case repositioning is required. A stimulus delivered from the pacing system analyzer (PSA) through the LV lead should cause a cardiac contraction. Low thresholds are ideal (a pacing threshold < 1 V should be considered outstanding), but LV stimulation typically requires more energy than RV pacing. In fact, it is not unusual for an implanting physician to accept a relatively high pacing threshold from the LV lead, such as 3 V and 0.5 ms. Lower thresholds are clearly preferable, but the limited opportunities of LV lead placement may cause the implanting physician to accept higher thresholds [15]

Coronary Sinus Angioplasty

Difficulties result often from anatomical venous bed pattern, such as atypical, tortuous CS ostium anatomy,

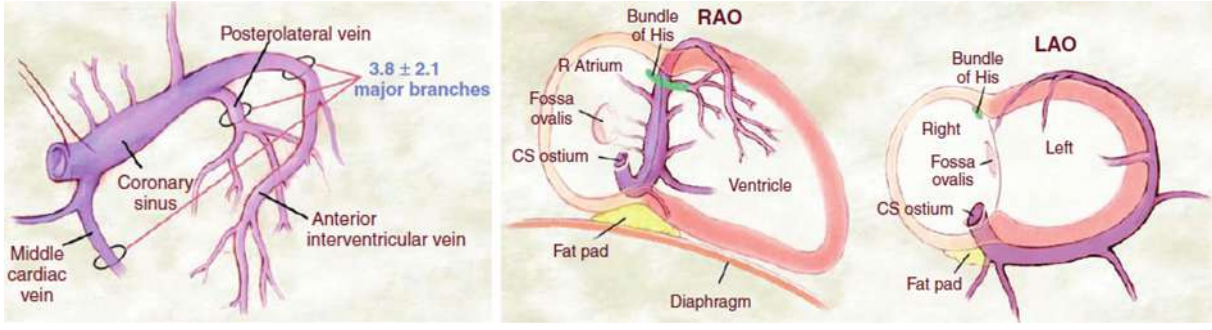


Figure 10. Coronary sinus anatomy and its landmarks 1

presence of venous valve, thrombi, or stenosis, postoperative deformation, functional constriction, narrowing and tortuosity of potential target vein, and finally, absence of vessels in the desired location. LV-lead placement via the transvenous approach can be challenging in the case of low phrenic nerve stimulation thresholds and/or inability to reach adequate coronary sinus (CS) branches. [19]

Although coronary vein stenoses are rare, as noted by Hansky et al (4 [1.83%] of 218 patients),previous coronary artery bypass graft procedures, scarring after myocardial infarction and previous implantation of a CS lead are all possible etiologies for this entity. In one center's experience, 10% of patients who underwent BVP implantation had asymptomatic coronary venous stenosis. Symptomatic coronary vein stenosis has not been reported, which is likely due to the presence of abundant collateral circulation. Various methods adapted from interventional cardiology are used to resolve these problems.[20]

Data on the usage of coronary sinus angioplasty were limited, mostly in form of case reports. Stenoses and small-caliber veins, as reported by Makaryus et al, can be successfully dilated with standard coronary angioplasty catheters and stented, if necessary, for the optimal placement of LV BVP leads.[20] An observational study by Oskar et al analyzed eight consecutive patients with the indications for CRT, who needed additional procedures within CS to overcome technical problems during left ventricular (LV) electrode implantation. The analyzed group consisted of three subgroups: patients in whom percutaneous balloon angioplasty within CS was needed (n = 4); patients with acute instability of the lead, requiring stenting of the vein to fix the electrode (n = 2); and patients with the stenting of CS due to late dislocation of the lead (n = 2). Success rate, procedure duration, fluoroscopy, complications, and electrical parameters of leads were analyzed. Success rate of the procedures was 87.5%; additional interventions increased overall efficacy of CRT implantation at our center from 88% to 98% ($P < 0.05$). Procedure duration (155.0 minute) and fluoroscopy time (42.5 minute) remained acceptable for the patient and operator; however, both were higher than in the procedures performed routinely in our hospital. Electrical properties of the LV leads were stable and within normal ranges during the observation period. We noted two local dissections of CS during the procedure, which remained clinically silent.[21]

Patients who undergo coronary venous stent implantation are usually not initiated or maintained on antiplatelet therapy. As with any new technique, however, caution is advised with this novel procedure. It should only be performed in centers with extensive experience in the combined techniques of transvenous LV leads and PTCA. Potential complications include venous rupture, resulting in cardiac tamponade and interference with lead threshold. The question of the limits of balloon inflation needs further investigation in order to minimize the risk of venous rupture. Other complications include access site complications due to inadequate length of the delivery catheter, and infection through the open-wound access site in the chest wall. Another complication involves thrombosis of the coronary sinus. This, however, has not been reported to result in significant complications. Further study also needs to be undertaken with respect to the long-term effects of stent implantation in the coronary venous system. A multidisciplinary team consisting of an interventional cardiologist and electrophysiologist is advised, with cardiac surgical backup available.[20]

Caveats in Coronary Sinus Lead Implantation

In an early reported, 6 year experience of biventricular pacing the overall procedural success rate in 116 patients was 88%,49 although there was a high rate of re-intervention due to LV lead dislodgement, increase in LV pacing threshold, phrenic nerve stimulation, and infection. A learning curve and technological developments enabled the reported procedural success to rise from 69% in the first year to 98% in the final year of this early study. In the MIRACLE study, transvenous CRT implants failed in 8% of patients; coronary sinus or coronary vein dissection/perforation occurred in 6% of implants; combined complete heart block, haemopericardium, and cardiac arrest were observed in 1.2%; and two patients died as a result of complications related to the implantation within a month after the procedure.[3]

Lead technology and technical success has improved, and in a more recent report on the procedural characteristics of over 450 CRT implants in the landmark CARE-HF7 study, the overall implant success rate was 95.9%. Early complications (<24 h) were seen in 10% of patients largely due to lead dislodgement and coronary sinus dissection or perforation and late complications (between 24 h and 30 days) were reported in a further 5.5% of implants and attributed largely to lead displacement.

Institutional and individual experience, together with improved equipment, will ensure the success rate of CRT remains high. To date, the overall CRT implant experience suggests that transvenous implantation of LV pacing leads provides an effective, well-tolerated approach to biventricular pacing. Procedural success is over 90% with a 30-day all-cause mortality of 1.5% and a ≈10% risk of a second procedure for LV lead dislodgement, extracardiac stimulation, or infection after an initial successful implant.

Even though the ability to secure LV leads in a major cardiac vein through coronary sinus cannulation is increasingly feasible, procedural success does not appear to herald a major shift in the clinical and echocardiographic response rate of CRT. The particular coronary vein used for the LV lead may be important and is of course dependent on individual coronary venous anatomy. [17,18]

In one series, placement of the LV lead tip in the intended target area (namely lateral, anterolateral, or posterolateral tributaries of the coronary sinus) was achieved in only 70% of cases. A variety of coronary veins are employed for the LV lead: Alonso et al reported that 36% of LV leads were placed in the anterior and middle cardiac veins; in the Easytrak Registry (2001), 67% of LV leads were placed in lateral or posterior coronary veins; and Molhoek et al. reported that 35% were placed in posterior veins and 28% in lateral veins. When coronary lead position is reviewed in the context of area of latest LV myocardial activation, LV lead tip concordance to, or in the vicinity of, the region with maximal delay was seen in only 64.8% (35 of 54) and 55.2% (32 of 58) patients, respectively.

Therefore, although a feasible implant technique, the coronary venous anatomy may limit placement of the LV lead and the ability to pace a defined region of the LV for CRT via the transvenous route. Direct surgical epicardial LV lead placement may overcome these limitations and provide the potential to pace the optimal target site. [17,18]

Discussion

Candidate for Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is a well-accepted, device-based intervention for patients with dilated cardiomyopathy and heart failure symptoms. The efficacy of CRT in improving morbidity and mortality in such patients has been explored through scores of large and small trials. Accordingly, the most recent recommendations from some of the major cardiac societies have been to strongly endorse CRT in a selected population. A high level of evidence supports CRT in patients with systolic dysfunction, for example, an LVEF ≤35%, a QRS complex duration >120 ms, in sinus rhythm, and who remain symptomatic (as in New York Heart Association (NYHA) functional class III or IV)despite *optimal* or *maximal medical therapy*.

Unfortunately, there are no additional clues in any of the guidelines as to what constitutes optimal medical therapy before CRT should be considered. Clinicians must make reasonable judgments not only about the kind of medications on which their individual patients should be maintained, but also for how long the patients should be observed on medical therapy alone. Furthermore, it is not clear what criteria should be used to determine failed medical therapy.

Anyway, this patient had met the criteria for CRT initiation, namely : low LV ejection fraction (18%), NYHA functional class III-IV, QRS duration of 125 msec (>120 msec) , sinus rhythm. He had been treated with ACE inhibitors and loop diuretics for approximately one year without significant improvement. The addition of an evidence-based beta blocker to an ACE inhibitor might results in a 35% reduction in annual mortality related to heart failure. Beta blockers have now been evaluated in over 20.000 heart failure patients and have been shown to possess a remarkable capacity for improving LV function and survival in patients with mild to severe symptoms, of both genders, and all age ranges. Following 4–6 months of treatment with an evidence-based beta blocker, one will expect an improvement in LVEF by at least 5–10% associated with an improvement in symptoms and functional capacity. Not infrequently, one may see a dramatic improvement in LV function and symptoms, particularly in those patients with hypertensive or dilated cardiomyopathy. The primary action of beta blockers is to counteract the harmful effects of the sympathetic nervous system activated during heart failure.[22]

Currently, there are three beta blockers that have been approved for heart failure management based upon results from large clinical trials. These drugs are the selective beta-1 antagonists metoprolol succinate and bisoprolol, and an agent with beta-1, beta-2, and alpha-1 blocking properties, carvedilol. ISDN/H,

ACC/AHA 2005: Guidelines for the Diagnosis and Management of Chronic Heart Failure in the Adult[1]
Patients with LVEF ≤35%, sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration >0.12 ms, should receive cardiac resynchronization therapy unless contraindicated (level of evidence A)

HFSA 2006: Comprehensive Heart Failure Practice Guideline[3]
Biventricular pacing therapy should be considered for patients with sinus rhythm, a widened QRS interval (≥120 ms) and severe LV systolic dysfunction (LVEF ≤35% with LV dilation >5.5 cm) who have persistent, moderate to severe heart failure (NYHA class III) despite optimal medical therapy. (strength of evidence A)

ESC 2005: Guidelines for the Diagnosis and Treatment of Chronic Heart Failure[5]
Resynchronization therapy using biventricular pacing can be considered in patients with reduced ejection fraction and ventricular dyssynchrony (QRS width >120 ms), who remain symptomatic (NYHA class III–IV) despite optimal medical therapy to improve symptoms (class of recommendation I, level of evidence A), hospitalizations (class of recommendation I, level of evidence A), and mortality (class of recommendation I, level of evidence B)

Figure 11. Guidelines for resynchronization therapy in heart failure [23]

digoxin, and ARBs may be added to ACE inhibitor, beta blocker, and diuretic therapy for those with persistent heart failure symptoms. Use of an aldosterone antagonist with an ACE inhibitor and ARB should be used with caution because of the risk of life-threatening hyperkalemia, especially in cases of renal insufficiency just like this patient.

Echo Assessment of Dyssynchrony

The measurement of QRS duration by the ECG – an electrical phenomenon which provides only a crude estimation on myocardial activation – is poorly correlated with the presence of mechanical dyssynchrony. In contrast, transthoracic echocardiography allows the severity of mechanical dyssynchrony and its impact on cardiac hemodynamics to be assessed immediately online and in a quantitative manner.

Echocardiography therefore seems a more reliable tool for correctly identifying suitable CRT candidates, thus reducing the number of clinical nonresponders. Despite the obvious advantages of this widely available bedside imaging technique, at present QRS duration still remains the main selection criterion for diagnosing the presence of mechanical dyssynchrony in clinical practice and in the currently available guidelines. This is mainly because the large prospective, randomized trials solely relied on the QRS width as the only marker for dyssynchrony. [11]

Interventricular dyssynchrony can be evaluated by assessing the extent of interventricular mechanical delay (IVMD), defined as the time difference between left and right ventricular pre-ejection intervals. An IVMD ≥40 ms is considered indicative of interventricular dyssynchrony.

M-mode echocardiography may be useful for assessing intraventricular dyssynchrony . Using an M-mode recording from the parasternal short-axis view (at the papillary muscle level), the septal-to-posterior wall motion delay (SPWMD) can be obtained and a cut-off value ≥130 ms was proposed as a marker of intraventricular dyssynchrony. However, frequently the SPWMD cannot be obtained, either because the septum is akinetic after extensive anterior infarction or because the maximal posterior motion is ill-defined. In addition, it is often not possible to obtain perpendicular M-mode sections of the proximal LV.[13]

Therefore, newer echocardiographic techniques had been used to overcome these limitations. The majority of studies have used color-coded tissue doppler to assess LV dyssynchrony and predict outcome, and it is the consensus by the ASE (American Society of Echocardiography) writing group that this is currently the preferred approach.

The simplest TD approach to identify intraventricular dyssynchrony by color-coded TD uses the basal segments of the apical 4-chamber view to measure the septal-to-lateral delay, known as the two-site method. Subsequently, a 4-segment model was applied that included 4 basal segments (septal, lateral, inferior, and anterior). An opposing wall delay greater than or equal to 65 milliseconds allowed prediction of both clinical response to CRT (defined by an improvement in NYHA class and 6-minute walking distance) and reverse remodeling (defined as a ≥15% reduction in LV end-systolic volume). In addition, patients with LV dyssynchrony greater than or equal to 65 milliseconds had a favorable prognosis after CRT.

Yu et al. used TDI to assess intraventricular dyssynchrony in 88 normal individuals, 67 patients with

heart failure and a narrow QRS complex (≤120 ms), and 45 with a wide QRS complex (>120 ms).In this study, 12 sample volumes were placed in the myocardium, and for each sample the time from onset of QRS complex to peak systolic velocity was measured. From these data, two parameters indicating intraventricular dyssynchrony were derived: the maximal difference between peak systolic velocities of any 2 of the 12 segments (intraventricular dyssynchrony defined as a difference >100 ms); and the SD of all 12 time intervals measuring time to peak systolic velocity (intraventricular dyssynchrony defined as a standard deviation of 33 ms, also referred to as dyssynchrony index).[23]

This patient do not meet echocardiographic criteria for interventricular dyssynchrony (IVMD ≤ 40 ms), and only borderline intraventricular dyssynchrony criteria, but CRT was initiated using ECG criteria according to guidelines. However, with current echocardiographic techniques, including TDI and tissue synchronization imaging, it is possible to precisely locate (before device implantation) the site of latest activation that will allow determination of the feasibility of a transvenous approach. When the site of latest activation is not in the region of suitable veins, surgical LV lead positioning may be considered, using limited left-lateral thoracotomy with direct epicardial lead placement.[23]

Which is Better : Transvenous or Surgical LV lead implantation ?

Navia and colleagues reported on 41 patients undergoing minimally invasive lead placement following failed CS lead insertion. Twenty-three of these patients underwent mini-thoracotomy, and 18 underwent an endoscopic approach (14 thoracoscopic and 4 robotic-posterior approach). The patient population described was quite ill, with 46% of the patients in hospital with a heart failure exacerbation. Of note, a preoperative LV mapping protocol of tissue Doppler imaging (TDI) was used to target the optimal site of LV pacing.

Similarly, postoperative echocardiography-guided optimization of LV pacing was performed on postoperative day 2. All patients had two LV leads successfully placed and there were no endoscopic conversions. Seventy-eight per cent of patients were extubated in the operating room. Two patients had prolonged respiratory failure. Mean ICU stay was 1.5 days and hospital stay was 4 days. There was no difference between minithoracotomy patients and endoscopic patients in terms of length of stay or extubation time. Over a 6-month follow-up there were 6 deaths and 34 clinical responders for an overall response rate of 73%. Interestingly, both responders and non-responders had documentation of resynchronization via TDI. Despite resynchronization, it is postulated that other factors, including severe ventricular systolic and diastolic dysfunction, can impact heavily on clinical outcome.

Koos *et al.* compared transvenous lead placement vs. lateral thoracotomy in 81 patients undergoing CRT. Patients who underwent surgical lead implantation had a much lower rate of re-intervention but increased length of hospital admission, reduced improvement in functional capacity, and a tendency to less reverse remodeling and higher mortality at 1-year follow-up.. The crucial feature of this study is that many of the LV leads in the surgical group were positioned *anteriorly* (44%) as compared to the transvenous group (4.5%). This study signifies the importance of posteriorly-positioned epicardial leads as a key component in improved clinical and physiologic outcomes. [24]

Furthermore, using mapping techniques involving intra-operative electrophysiological and haemodynamic measures to optimize lead position, the leads were placed laterally in the area of the obtuse marginal branch of the circumflex artery in all 16 surgical patients studied, suggesting that a wider area of the LV could be targeted. The authors concluded that epicardial LV lead placement is a safe reliable method for CRT and has advantages regarding lead-related complications and the necessity for reoperation.

Although no prospective, randomized comparison has yet been performed between surgical epicardial LV lead placement and CS lead placement, Mair *et al.* have reported results on a retrospective comparison. The study group included 79 patients undergoing CS lead insertion and 16 patients undergoing LV epicardial lead placement through a limited left lateral thoracotomy. The patients undergoing surgically placed LV leads included nine patients with failed CS leads and seven patients undergoing primary implant. All patients undergoing surgical placement of the epicardial LV lead achieved posterolateral lead placement as opposed to only 70% in the transvenous CS group. Length of stay was not statistically different between the two groups. Over a mean follow-up of 16 months, CS lead thresholds were significantly higher than surgically placed epicardial leads, with seven CS leads having a pacing threshold of > 4 V/0.5 ms vs. no epicardial leads

with a pacing threshold > 1.8 V/0.5 ms. In follow-up, 25 CS lead-related complications occurred, compared with one in the surgical group.[24]

In a newer prospective longitudinal study by Patwala et al, twenty-three subjects with unsuccessful transvenous coronary sinus lead placement underwent epicardial implantation. The subjects underwent clinical evaluation, cardiopulmonary exercise testing, and echocardiography before 3 and 6 months after. The results were compared with a control group (n = 35) who had received transvenous CRT. In both groups, there were significant improvements in all measures at 3 and 6 months. The improvement in peak VO_2 was delayed in the epicardial group compared with the transvenous group. At 6 months, the improvements seen in all variables showed no difference between the groups. The authors concluded that epicardial lead placement is a viable option for patients with unsuccessful coronary sinus lead placement. The improvements in most variables were of a similar magnitude and over a similar time scale compared with transvenous placement. Improvements in peak VO_2 were delayed in the epicardial group, probably as a result of a prolonged recovery time. [8]

An alternative method of transseptal endocardial LV pacing has been proposed and, in a small cohort of 10 patients, appears to be feasible. In a single case report, transapical endocardial LV lead placement to the lateral free wall has been described and appears to be feasible particularly in patients where epicardial LV lead placement may be complicated by extensive pericardial adhesions from previous cardiac surgery.Clearly safety and efficacy data for both of these techniques at present are lacking but these approaches may offer an alternative to surgical lead placement.[24]

Summary

We have presented a case of CRT in a 75-year-old male patient diagnosed as non ischemic dilated cardiomyopathy patient NYHA Class III-IV meeting the initiation criteria of QRS duration > 120 msec, and low ejection fraction (≤35%), with worsening symptoms despite one year of medical therapy. Echocardiographic assessment showed no interventricular dyssynchrony and borderline intraventricular dyssynchrony. A hybrid approach of LV lead implantation by mini thoracostomy and conventional implantation of the RA and RV leads were performed because the coronary sinus cannot be accessed transvenously due to small size even after angioplasty.

References

1. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure: incidence and survival in a community based population. JAMA 2004;292:344–50.
2. Hayes DL, Abraham WT. Clinical trials supporting current indications for CRT. In : Yu CM, Hayes DL, Auricchio A, editors. Cardiac Resynchronization Therapy. Massachusetts : Blackwell publishing , 2008.p.266
3. 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. MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002; 346:1845–53.
4. Salukhe TV, Francis DP, Sutton R. Comparison of medical therapy, pacing and defibrillation in heart failure (COMPANION) trial terminated early; combined biventricular pacemaker-defibrillators reduce all-cause mortality and hospitalization. Int J Cardiol 2003;87:119–20.
5. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, Loh E, Kocovic DZ, Fisher WG, Ellestad M, Messenger J, Kruger K, Hilpisch KE, Hill MR. Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 2003;107:1985–90.
6. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert J-C. The multisite stimulation in cardiomyopathies (MUSTIC) Study Investigators. Effects of Multisite Biventricular Pacing in Patients with Heart Failure and Intraventricular Conduction Delay. N Engl J Med 2001;344:873–80.
7. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M. Biventricular pacing in heart failure: back to basics in the pathophysiology of left bundle branch block to reduce the number of nonresponders. Am J Cardiol 2003;91:55F–661.
8. Patwala A, et al. A prospective longitudinal evaluation of the benefits of epicardial lead placement for cardiac resynchronization therapy. *Europace* 2009; 11(10): 1323-1329. doi: 10.1093/europace/eup251
9. Imanishi R, Seto S, Ichimaru S, et al. Prognostic significance of incident complete left bundle branch block observed over a 40-year period. Am J Cardiol 2006;98:644–8.
10. Freudenberger RS, Wilson AC, Lawrence-Nelson J, Hare JM, Kostis JB. Permanent pacing is a risk factor for the development

of heart failure. Am J Cardiol 2005;95:671–4

11. Breithardt, OA. Assessment of electrical and mechanical dyssynchrony:conventional echocardiography. In : Yu CM, Hayes DL, Auricchio A, editors. Cardiac Resynchronization Therapy. Massachusetts : Blackwell publishing , 2008.p.77
12. Cazeau S, Bordachar P, Jauvert G et al. Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation: a prospective study. Pacing Clin Electrophysiol 2003; 26: 137–143.
13. Bax JJ et al. Echocardiographic Evaluation of Cardiac Resynchronization Therapy: Ready for Routine Clinical Use?A Critical Appraisal. J Am Coll Cardiol 2004;44(1):1-9
14. Delhaas T. Prinzen FW. Myocardial mechano-energetics. . In : Yu CM, Hayes DL, Auricchio A, editors. Cardiac Resynchronization Therapy. Massachusetts : Blackwell publishing , 2008. pp.60-62
15. Kenny T. The Nuts and Bolts of Cardiac Resynchronization Therapy. Massachusetts : Blackwell publishing , 2007.pp.70-75
16. Bax JJ et al. Cardiac Resynchronization Therapy: Part 2—Issues During and After Device Implantation and Unresolved Questions. J Am Coll Cardiol 2005;46:2168-2182.
17. Khan FZ, Virdee MS, Fynn SP, Dutka DP. Left ventricular lead placement in cardiac resynchronization therapy: where and how? Europace 2009;11:554–561.
18. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.
19. Kowalski O, Lenarczyk R, Prokopczuk J, Pruszkowska-Skrzep P, Zielin´ska T, Sredniawa B et al. Effect of percutaneous interventions within the coronarysinus on the success rate of the implantations of resynchronization pacemakers. Pacing Clin Electrophysiol 2006;29:1075–80.
20. Makaryus AN et al. Coronary Venous Angioplasty and Stenting for Biventricular Pacemaker Left Ventricular Lead Implantation. Invasive Cardiol. 2007;19(5)E128-E130.
21. Oskar K et al. Effect of Percutaneous Interventions within the Coronary Sinus on the Success Rate of the Implantations of Resynchronization Pacemakers. PACE 2006; 29:1075-1080
22. Haas GJ. Abraham WT. Comprehensive pharmacologic management strategies for heart failure. In : Yu CM, Hayes DL, Auricchio A, editors. Cardiac Resynchronization Therapy. Massachusetts : Blackwell publishing,2008.p.30-32
23. Gorcsan et al. ASE EXPERT CONSENSUS STATEMENT Echocardiography for Cardiac Resynchronization Therapy: Recommendations for Performance and Reporting–A Report from the American Society of Echocardiography Dyssynchrony Writing Group Endorsed by the Heart Rhythm Society. J Am Soc Echocardiogr 2008;21(3):191-213.
24. Balaram SK et al. Surgical approaches to epicardial left ventricular lead implantation for biventricular pacing . In : Yu CM, Hayes DL, Auricchio A, editors. Cardiac Resynchronization Therapy. Massachusetts : Blackwell publishing , 2008.p.242-246.