

Cardiac Resynchronization Therapy; Biventricular Pacing

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ABSTRACT

Although the estimates from limited studies vary on the proportion of patients with heart failure who also have ventricular dyssynchrony as reflected by a prolonged QRS complex, often in the form of left bundle branch block, the number of such patients is large (27% to 53%) and it is certainly in excess of the rate for the general population. Among these patients, 10% to 15% are candidates for cardiac resynchronization therapy (CRT) via biventricular pacing. Accumulated evidence from randomized controlled studies over the last few years has indicated that significant hemodynamic and clinical improvement is conferred by CRT to the class III or IV heart failure patients with idiopathic or ischemic dilated cardiomyopathy and who also have a low left ventricular ejection fraction ($\leq 35\%$) and a wide QRS complex (≥ 120 -150 ms). Newer data suggest a significant reduction in mortality and heart failure hospitalization, particularly when CRT is combined with an automatic defibrillator backup. This technique has transformed the traditional concepts associated with stimulation of the heart, and it is now being applied not only to restore an appropriate heart rate, but also to change the process of cardiac mechanical activation. Since this treatment must be integrated within a comprehensive and multidisciplinary CHF management program, CRT has altered the medical practice of heart experts in the field of cardiac pacing. Technical advances with percutaneous methods that access the tributaries of the cardiac veins have raised the success rate of implanting left ventricular leads to $>90\%$. Further confirmation from ongoing trials is eagerly awaited, and more data from the studies on this procedure's cost effectiveness are needed before CRT is considered as a prime therapy in the heart failure population. (*Korean Circulation J* 2006;36:329-336)

KEY WORDS : Heart failure, congestive ; Resynchronization ; Biventricular pacing.

Introduction

Heart failure is the fastest-growing cardiovascular diagnosis and the life time risk of incurring this malady is nearly 20%. Even though considerable progress has been made in the management of heart failure over the last decade with the use of angiotensin-converting enzyme inhibitors (or angiotensin antagonists), aldosterone antagonists, and more recently the new beta-blocking agents with vasodilating properties, the management of CHF still requires more effective therapy to modify the progressive nature of the disease.

In the early 1990s, right sided atrioventricular (AV) sequential (dual-chamber) pacing with a short AV delay was proposed as a potential therapy to relieve the symptoms of congestive heart failure in the patients with severe left ventricular dysfunction. However, markedly

discrepant responses to dual chamber pacing with great interindividual variability and no consistent benefit were demonstrated, and the need for correction of intraventricular conduction disturbances and whether this might result in clinical improvement were considered. 12 years ago, the first case report introduced the concept of cardiac resynchronization therapy (CRT)¹⁾ and this opened the way to the development of the first successful non-pharmacological treatment for congestive heart failure (CHF). From the viewpoint of being a therapeutic alternative for CHF, CRT is a milestone development that is changing the conventional concepts of CHF therapy. This newer pacing techniques have emerged as a vital therapeutic alternative for the patients who remain refractory to optimal medical therapy. The coordination of ventricular contraction (ventricular resynchronization) has emerged as an important and very promising pacing technique that goes beyond the conventional therapies that are used to treat bradycardia.

Implantation of CRT systems is now applicable to a multitude of patients as an adjunctive therapy for treat-

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ting advanced CHF.

Electro-Mechanical Dyssynchrony

Regardless of whether heart failure is due to ischemic or nonischemic structural heart disease, it is accompanied by characteristic electrical and mechanical abnormalities. A prolonged QRS duration indicates that there is slow conduction in the His-Purkinje system and/or the ventricular myocardium. This can be due to either bundle branch block or abnormally slow conduction in the myocardium (intraventricular conduction disturbance). The consequences of abnormal ventricular activation and the accompanying contractile abnormalities are referred to as electromechanical dyssynchrony.

Left ventricular dyssynchrony is a relatively common problem in heart failure patients, and particular in those patients suffering with a prolonged QRS complex duration.¹⁾ Dyssynchronous LV contraction leads to a reduced ejection volume because blood moves around the left ventricle from the early activated segments to late activated segments. This obviously leads to reduced LV contraction efficiency and it reduces the systolic function despite the same energy use. In addition, mitral valve dysfunction frequently occurs because of lack of coordination of the papillary muscle.

Although the effects of dyssynchrony are noticeable, they are generally not dramatic and they have certainly not attracted much clinical attention. However, recent studies have been performed in which this pathophysiology been applied to the dilated cardiomyopathic heart, and the net effect appeared to be more substantial. This may be partly related to the enlarged size of the failing ventricle, which renders greater geographic separation between early activated and late-activated regions, and this worsens their impact on the net systolic function. In addition, factors such as slowed or weakened contraction and delayed cell-to-cell conduction in the failing heart can worsen dyssynchrony. Although the differences for the impact of dyssynchrony on the normal versus failing dilated hearts remain somewhat speculative, the clinical impact does appear more significant and so this has recently garnered far more attention.

The LBBB-type conduction delay involves initial wall motion in the septal region, which is often accompanied by reciprocal lateral wall prestretch. Much of this early septal shortening occurs prior to mitral valve closure,²⁾ and this blurs the distinction between end-diastole and early systole. The reason for this is that the early activated myocardium can not generate sufficient chamber pressure to close the valve as most of the energy is transferred to prestretching the opposing yet-to-be activated wall. The mitral valve remains open, and diastolic filling can still potentially occur as long

as the LV pressure remains below the mean left atrial pressure. Thus, from the standpoint of mitral valve closure and initiation of isovolumic contraction, diastole is prolonged and systole is initiated later by contractile dyssynchrony. The second phase of systole starts with the onset of delayed contraction in the late-activated wall (typically the lateral free wall). This wall, coupled with the already activated muscle and higher developed pressures, must contract at higher levels of regional wall stress. Yet this contraction also involves wasted effort because part of it is converted to stretching the early activated wall that is now beginning to enter its relaxation phase. The result is generally mid-to late systolic septal motion toward the right ventricle, which has traditionally been termed paradoxical motion in the sense that it behaves as if the septum were ischemic without having this underlying pathophysiology. However, the motion is not paradoxical, but it is really the consequence of systolic stress from a balance of forces. The septal myocardium is less capable of withstanding the systolic stress being developed by the late-activating LV free wall and thus, the septal myocardium is pushed away from the central LV chamber toward the right heart. Late-systolic septal stretch worsens cardiac function for several reasons. First, it effectively acts as an intracavitary sink for the blood volume that would otherwise be ejected, and so it reduces forward output. Second, the late stretch of the contracting muscle can break cross-bridges, diminish systolic force development and so result in repolarization inhomogeneity and stretch-activated channel stimulation; this can trigger arrhythmia.³⁾ Inhomogenous contraction is also a mechanism for delaying muscle relaxation and it likely contributes to diastolic dysfunction.⁴⁾

In addition to a paradoxical bowing of the septum away from the left ventricular wall during contraction, the late activation of the left ventricular free wall (in LBBB) also alters the atrioventricular (AV) timing and results in impaired diastolic filling and a lower stroke volume (intraventricular dyssynchrony).^{5,6)} Mechanical abnormalities contribute to chronic myocardial stretch and cardiac remodeling. The consequences of cardiac remodeling include changes in the left end diastolic filling pressures/volume that can shift the pressure-volume relationship and directly impact on systolic performance.⁷⁾ There are also important regional and global metabolic/energetic consequences that develop from dyssynchrony. The prematurely activated myocardium develops less overall work and consumes less energy.⁸⁾ The energy it does consume, however, is largely wasted with respect to ejection because the pressure remains low. In contrast, the late activated free wall operates under a higher load with a high higher metabolic demand. It also wastes work in stretching the more compliant early activated territory rather than

contributing to ejection, so the net effect is a reduction in chamber efficiency.⁹⁾

Iatrogenic Dyssynchrony and the Evolution of Resynchronization Therapy

There are also some clinical and experimental studies that have indicated the deleterious effect of long standing RV apical pacing.^{10,11)} The adverse effects of RV apical pacing are explained by the anomalous ventricular electrical activation process from the apex to the base. This activation may be the cause of contraction heterogeneity and asynchrony within the entirety of the ventricles, and it may also cause haemodynamically detrimental right-left interventricular delays. These mechanical delays were identified long ago by echocardiographic or phase-analysis angioscintigraphic studies.¹²⁻¹⁵⁾ Capture of the RV modified the contraction of both the RV and the LV. It is noteworthy that the considerable prolongation of the overall ventricular contraction was due to a marked difference between the two ventricles, such that LV contraction begins when contraction of the RV ends. Therefore, conventional dual chamber pacing induced interventricular asynchrony, even after programming of an AV delay that is optimized by biatrial stimulation during echocardiographic monitoring.

In an effort to optimize LV function via stimulation from alternate ventricular sites, Victor et al.¹⁶⁾ have reported the results of a randomized, double-blind comparison of RV apical versus RV outflow tract in 16 patients who were in chronic AF and complete AV block. No difference was observed in the LV ejection fraction (EF) and functional capacity at the end of 3 months of stimulation from either site. Likewise, in a population of patients undergoing coronary artery bypass surgery, among the several short-term single- or dual-site configurations that were tested including the RV and LV epicardial apex, and the RV septal and RV outflow tract, none was found to be haemodynamically superior.¹⁷⁾ These observations suggest that electro-mechanical abnormalities cannot be corrected by merely optimizing a single or dual RV stimulation site.

In 1995, Foster et al.¹⁸⁾ reported an increase in cardiac output by atrio-biventricular stimulation via temporary epicardial electrodes after the withdrawal of cardio-pulmonary bypass in the patients undergoing coronary artery bypass surgery. Over the following years, Cazeau et al.¹⁹⁾ have published the data on the first series of patients who received the CRT systems. Prior to the implantation of a permanent pacing system, they identify responders by temporary stimulation, which confirmed that all the biventricular configurations were superior to the conventional dual chamber configuration, and this was regardless of the RV lead position. The study included angioscintigraphic im-

aging after the implantation of the permanent CRT system, and this confirmed a decrease in the heterogeneity and duration of ventricular contraction by multisite stimulation. These observations have been amply confirmed by others researchers²⁰⁾ whose further contributions include an emphasis on the importance of optimal lead placement in the LV, and particularly on the lateral wall.²¹⁻²³⁾

Cardiac Resynchronization Therapy (CRT)

Cardiac resynchronization is usually achieved through atrial-based, biventricular pacing (unless the patient has permanent atrial fibrillation). In addition to placing a lead in the right atrium and the right ventricle, a third lead is placed in the cardiac venous system to stimulate the left ventricle. The left ventricular lead is positioned in the epicardial venous system overlying the left ventricle. The ideal location for the cardiac resynchronization is typically over the lateral wall of the left ventricle. Unlike traditional cardiac pacing and defibrillation on the right side of the heart, the left ventricular lead is not in direct contact with the endocardial surface of the heart. Instead, transvenous left ventricular stimulation via the coronary venous system is done through the venous wall and epicardial fat pad, and it is delivered to the epicardial surface of the left ventricle. The greater distance between the site of stimulation and the area to be stimulated may require a greater amplitude of electrical stimulus to pace the left ventricle. As a result, resynchronization, which is also known as biventricular pacing, synchronizes electrical conduction by pacing both the right and the left ventricles simultaneously. In addition to interventricular (left ventricle and right ventricle) synchrony, resynchronization therapy impacts on heart failure by the restoration of intraventricular synchrony (the septum and lateral wall of the left ventricle) and the optimization of left A/V timing; this ultimately results in measurable improvement in the physiological indices of ventricular performance. In a sense of reestablishing the intraventricular synchrony, CRT adjusts the septal to lateral wall timing, thereby reducing the paradoxical septal wall motion and improving the left ventricular change in pressure over the change in time (LV dp/dt). This allows greater stroke volume at a lower myocardial oxygen cost, which results in more efficient and improved myocardial contractility.

Resynchronization therapy also improves cardiac performance by optimizing the timing of the left atrial and left ventricular contraction.⁷⁾ Prolonged intraventricular conduction in the setting of a left BBB results in diastolic mitral regurgitation, and this is due to the delayed left ventricular papillary muscle contraction. AV dyssynchronization that is identifiable only during

sinus rhythm is the result of abnormal timing of the end of atrial systole and the beginning of ventricular systole, and it is often facilitated by prolonged AV conduction. AV dyssynchronization is characterized by an abbreviated filling period and it is sometimes accompanied by the summation of early passive (E wave) and late active (A wave) atrial emptying; it can be normalized with a conventional dual chamber pacing system by optimizing the AV delay during Doppler echocardiographic imaging.²⁴⁾²⁵⁾ By reestablishing the optimal left atrial to ventricular timing, the diastolic filling time is optimized and diastolic mitral regurgitation is reduced. The optimal AV delay correlates with the closure of the mitral valve at the end of atrial systole. If the AV delay is too long, there is reduced time for passive filling, left atrial contraction occurs too early and the mitral valve may allow late diastolic mitral regurgitation. The opposite occurs if the AV delay is too short. The mitral valve closes before the conclusion of atrial contraction and active ventricular diastolic filling is compromised.²⁶⁾²⁷⁾

Clinical Trials

Efficacy of CRT

Biventricular pacing has shown promise for symptomatic heart failure in recent trials. Heart failure symptoms were seen to diminish and the objective measures of functional status improved with biventricular pacing.

MUSTIC,²⁸⁾ a clinical trial that compared, in a single-blind, 3 × 3 months crossover design, active versus inactive biventricular stimulation in a group of patients suffering with sinus rhythm and another group of patients suffering with atrial fibrillation (AF).²⁹⁾ The patients were then underwent long-term follow-up with the stimulation mode being programmed according to each patient's preference. The patients in sinus rhythm and who were in stable New York Heart Association (NYHA) CHF functional class III during optimal medical management, they had no conventional pacing indications. A QRS duration >150 ms was arbitrarily chosen as a marker of ventricular dyssynchrony. All the patients received an atrio-biventricular pulse generator that was interfaced with the right atrial, RV and LV leads. The primary study endpoint was the evolution of functional capacity as measured by a 6-minute hall walk. Secondary endpoints included the quality of life as ascertained by the Minnesota questionnaire, the peak oxygen consumption, the number of hospitalizations for the management of CHF, the patient's preference of stimulation mode at the end of the crossover phase and the overall survival. The CRT system implantation success rate was 92%; at the end of the crossover phase, 88% of the LV leads were correctly functioning. The

effects of CRT were confirmed by a 25 ms decrease in the QRS width.

Both phases of the trial were completed by 48 patients, and a 23% increase was seen between the active and inactive modes in the distance walked in 6 minutes ($p < 0.001$), and in the peak oxygen consumption ($p < 0.03$). The number of hospitalizations for the management of CHF was decreased by two thirds ($p < 0.05$), and 85% of the patients preferred the atrio-biventricular over the inactive stimulation mode ($p < 0.001$). These results, which proved the existence of a treatment effect for CRT in the patients suffering with CHF and inter- and intraventricular conduction abnormalities, were amply confirmed by the MIRACLE trial that with its parallel design, yielded similar results.³⁰⁾

However, not all patients respond favorably to CRT. Failure to achieve consistent pacing, suboptimal AV timing and the location of the left ventricular lead can all impair a favorable response.

Effect on survival

The COMPANION trial has demonstrated that CRT with an ICD junction may improve survival in the CHF patients having a prolonged QRS.³¹⁾ The patients were randomly assigned to the optimal medical therapy group versus the CRT group, versus the CRT+ an implantable cardioverter defibrillator (ICD) group. The 30-day mortality, including operative deaths, was 1.0% in the medically treated group, 1.8% in the CRT group and 1.2% in the CRT+ICD group. At 1 year, the corresponding combined rates of deaths or hospitalizations for the different modes of CHF management were 45%, 31% and 29%, respectively. Unfortunately the 35% relative risk rate and the high rate of adverse events in the medically treated group forced the early interruption of the trial and so complicated interpretation of its results. The CARE-HF trial was recently published in which 813 patients were enrolled and followed up for a mean of 29.4 months; it reported 82 deaths in the cardiac resynchronization group as compared with 120 in the medical-therapy group (20% vs. 30%, respectively; hazard ratio: 0.64; 95 percent confidence interval: 0.48 to 0.85; $p < 0.02$).³²⁾

A recent meta-analysis of CRT³³⁾ demonstrated a survival benefit of a 20% reduction of all cause mortality and a 35% reduction in heart failure hospitalization; this appeared to be largely driven by reductions in deaths from progressive heart failure and this become apparent by 3 months after implantation. Although the peri-implantation mortality rates were low, it is not surprising that the benefits were thought to be mediated through morphometric remodeling of the left ventricle rather than the acute changes in the neuro-hormonal systems.

Eligible Patients and Other Issues for CRT Application

A key issue for CRT is identifying the eligible patients who are most likely to respond and receive the most benefit. Responders are more likely to have idiopathic dilated cardiomyopathy³⁴⁾ and no history of myocardial infarction. In contrast, prior myocardial infarction, no significant degree of mitral regurgitation and ischemic cardiomyopathy have all been suggested as independent predictive factors for identifying non-responders prior to pacemaker implantation.

The most widely used marker to identify patients with cardiac dyssynchrony has been a widened QRS complex on the surface electrocardiogram. To date, all the clinical trials have enrolled subjects on the basis of systolic dysfunction with dilated cardiomyopathy and a widened QRS duration. A duration of 150 ms was initially chosen both arbitrarily and intuitively as a cut-off value in the MUSTIC study and it was shortened to 120 ms in the MIRACLE study.

However, the correlation between the amount of dyssynchronization and QRS duration has not been firmly established.³⁵⁻³⁷⁾ In the larger Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial,³⁰⁾ the clinical outcome showed no correlation with the basal QRS. Furthermore, despite the substantial systolic improvements with LV or biventricular pacing, the QRS duration was not consistently narrowed: many subjects showed no change or even widening of the duration. These data highlight the notion that QRS duration is at best an indirect correlate, but not a direct reflection of mechanical synchrony. While the like-lihood of a favorable haemodynamic result is greater when the QRS is >150 ms,³⁸⁻⁴⁰⁾ there are many patients who have responded to CRT in the long-term despite having a QRS <150 ms in duration; the only certainty is that a shorter QRS after system implantation rather than before system implantation carries a good prognosis.⁴¹⁾

In addition, the MIRACLE trial had identified a high percentage of non-responders or even patients whose clinical status was worsened by CRT.³⁰⁾ These undesirable responses may be due to improper patient selection or to technically deficient implantation of the system. The actual percentage of non-responders was reported to be variable, between 18% and 32%.

These limitations of the surface ECG have prompted the development of other methods that can directly quantify mechanical dyssynchrony and that are also capable of identifying the responders.

Dyssynchrony was first comprehensively examined by means of tagged MRI. However, MRI is complex and it has limitations for wide clinical use. Meanwhile echocardiography is a useful tool for quantitatively measuring the severity of dyssynchrony in patients before

and after CRT. Doppler echocardiography allows a) imaging of dyssynchronization at three separate levels, i.e., the AV, interventricular and intraventricular levels, b) the identification of potential candidates for CRT, c) the verification of proper delivery of therapy, and d) defining the mechanisms of action of CRT.⁴²⁾ A number of echocardiographic tools have been developed for such purposes, include M mode measurement of the septal-to-posterior wall delay, tissue Doppler (or velocity) imaging (TDI) for the septal-to-lateral wall delay, measurement of deviations of the peak contraction time over the 12 left ventricular segments and delayed longitudinal contraction and potentially three dimensional echocardiography.

The duration and temporal shifts of right and left ventricular systole can be measured by various methods, and shortening of these time intervals appears to predict effective resynchronization. The intraventricular conduction disturbance may be heterogeneous enough to result in the coexistence of systolic and diastolic phases of different regions of the same ventricle.

Several studies have suggested that the presence of systolic dyssynchrony at baseline suggested dyssynchrony, and the assessment of intraventricular dyssynchrony by two segmental models or by multiple segments as measured by tissue Doppler imaging may be an independent predictor for reverse remodeling, and so it is capable of identifying the responders to CRT. The septal-to-lateral delay in peak systolic velocity at baseline ≥ 60 ms⁴³⁾ or the "asynchrony index" with a Ts-SD ≥ 32.6 ms as a cut off value,⁴⁴⁾ which was measured in the 12 LV segments by calculating the standard deviation of Ts as the time to peak contraction during ejection, were reported to be useful predictors for improvement of the LV ejection fraction after CRT. The Ts-SD was confirmed to be the best predictor of LV reverse remodeling. The ECG has currently lost its diagnostic value for this type of intraventricular dyssynchronization.

Another important point to consider is the accumulation of evidence showing that not only is spontaneous left bundle branch block harmful to our patients, but iatrogenic left bundle branch block produced by right ventricular apical pacing is equally deleterious. In searching for alternate sites of ventricular stimulation, a recent pooled analysis of a clinical and experiment study indicated the possible superiority of right ventricular outflow tract pacing, but this needs further study. An upgrade of a pacing system that is capable of left ventricular pacing could be a possible option in a case of detrimental chronic RV apical pacing.

Current indications exclude the use of CRT in patients with permanent atrial fibrillation, although a small series suggested a benefit of the therapy. The role of CRT in these patients remains uncertain and it

needs further study.

Furthermore, the benefit of CRT for those patients with right bundle branch block or nonspecific conduction delay remains less clear. There remains a distinct subgroup of patients with dilated cardiomyopathy, poor left ventricular function and a normal or not so wide QRS complex for whom the preliminary data indicates that CRT may provide benefit. Tissue Doppler imaging studies indicate that mechanical dyssynchrony occurs even in the patients with a normal QRS duration. Further studies are needed to shed more light on this critical issue.

Another important issue is the increased cost of the biventricular systems when these CRT systems should be routinely provided with ICD backup. By current definitions, most of the patients who qualify under the current indications for biventricular pacing also qualify for ICD therapy according to MADIT II criteria because these are significantly overlapping population groups. Thus, should all of these patients undergo both therapies? The answer is not clear at this point, particularly as the indications for ICD therapy continue to evolve.

Technological Considerations

Percutaneous transvenous implantation of the leads through catheterization of the coronary sinus is currently the main approach to implant LV leads. Studies have indicated that optimal resynchronization is achieved when the lateral or posterolateral left ventricular wall is paced rather than the anterior or apical region. Practically, this can be achieved by leads implanted via the coronary network through the coronary sinus or through the interventricular septum to stimulate the endocardium, though the latter approach is still experimental.

In the past 5 years, manufacturers have designed leads specifically for this purpose in an attempt to

reconcile aims that are potentially conflicting. The leads have to be both as stiff as possible to enter the CS, and as thin and maneuverable as possible to be positioned in the smaller veins of the coronary network. Kits including preshaped guiding sheaths are now widely used to catheterize the CS ostium and to perform a venogram in search of a target vein (Fig. 1). The stimulating lead itself has an inner lumen allowing the introduction of a guide wire to stiffen or curve its contour. The guide wire may be used to catheterize the target vein, while the lead is advanced over the wire to its final destination. Close contact must be achieved between stimulating electrode and the epicardium in order to obtain the lowest possible capture threshold. Leads are generally preshaped for greater stability and high-impedance to reduce the long-term battery drain of the pulse generator.

Placing the LV lead in the highly variable coronary venous system may not be possible due to the acute angulation and/or stenosis in the cardiac veins. Although few serious complications have occurred, implantation of a biventricular pacemaker (and particularly the left ventricular lead) is sometimes technically challenging even in the of an experienced hands (a 10% failure rate). Furthermore, even if the device is successfully implanted, patients with these devices require close follow-up; 7% of the devices malfunctioned and 9% of the left ventricular leads dislodged over a median follow-up period of 6 months.³³⁾ If transvenous access is not possible, an epicardial lead may be placed via surgery.

Conclusion

CRT is a recently developed therapeutic modality that is applicable a priori to patients who suffer from symptomatic LV systolic dysfunction despite optimal medical management, and these patients also present with cardiac mechanical synchronization abnormalities.

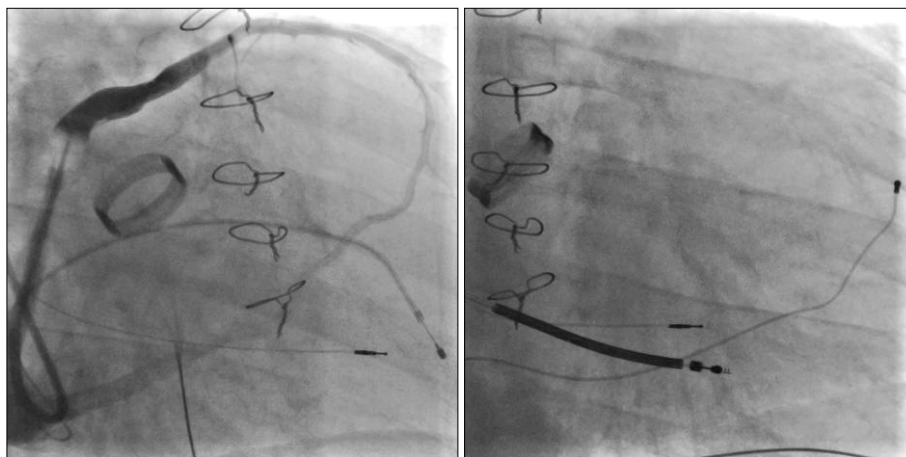


Fig. 1. Occlusive coronary sinus venography shows the large collateral channel between the posterolateral vein and the anterior interventricular vein. The LV lead was placed in the lateral wall of the left ventricle through the collateral vein.

CRT offers hemodynamic and clinical improvement to the patients with moderate to advanced heart failure, and it might significantly prolong survival in selected patients, particularly if devices with a defibrillation backup are used. At the present time, the indications for CRT are limited and they include symptomatic heart failure despite optimal medical therapy, a prolonged QRS interval and a LVEF $< \text{or} = 35\%$. However, the indications for CRT are still evolving and they may expand as further studies will identify those patients who are most likely to benefit from this treatment.

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