Assessment of dyssynchrony in patients with severe heart failure by nuclear imaging: paradise lost and regained or lost and gone forever?

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Cardiac resynchronization therapy, based on biventricular and/or left ventricular preexcitation, is a recently introduced therapeutic option for patients with severe heart failure and intraventricular conduction disturbances. The invasive nature and expense of resynchronization therapy has highlighted the need to prospectively identify optimal candidates, because of the poor correlation of QRS duration with patient response.

Scintigraphy and positron emission tomography made it possible the research investigation of the pathophysiological consequences of cardiac conduction disturbances on myocardial contraction, metabolism, and perfusion.

Increasing evidence shows that nuclear imaging techniques allow a comprehensive evaluation of the candidates to resynchronization. In fact, phase analysis of equilibrium radionuclide angiography enables a simple, quick and reliable measurement of both of inter- and intraventricular mechanical dyssynchrony, affording an optimal predictive accuracy of the response. In addition, being scintigraphic data highly reproducible, they are suitable for sequential longitudinal follow-up of the ventricular performance and mechanical dyssynchrony in patients implanted with devices.

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Introduction

Despite major advances in medical therapy with beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, digoxin, diuretics and aldosterone antagonists, the prognosis of patients with severe heart failure remains poor, both in terms of quality of life and life expectancy.

Clinical data from numerous studies and trials have suggested the beneficial role of cardiac resynchronization therapy (CRT) on symptoms, functional capacity and functional parameters of the left ventricle, thus an increasing number of patients is treated with this modality.

The serial functional assessment of electromechanical dyssynchrony and of its consequences on systolic performance, and the evaluation of the pathophysiological consequences of cardiac conduction disturbances on myocardial perfusion and metabolism, is an interesting new application for cardiac nuclear imaging because of the effectiveness and reliability of these techniques.

Prevalence of QRS prolongation and clinical-prognostic significance

QRS prolongation in patients with chronic heart failure is commonly due to a disruption of myocardial collagen matrix and is frequently associated with an impairment of mechanical efficiency[1].

Left bundle branch block (LBBB) is a marker of disease progression in cardiomyopathy. Its prevalence increases in accordance with the degree of left ventricular (LV) systolic dysfunction, reaching almost 40% in individuals with moderate to severe degree of dysfunction[2,3]. LBBB is also an independent predictor of an adverse outcome[4].

The unfavorable prognostic effect of a wide QRS probably ensues from the consequent reduced ventricular performance: septal-minor and long-axis contraction are delayed, time to maximum rate of rise of ventricular pressure is prolonged, functional mitral regurgitation can appear, the duration of isovolumic periods of a preceding mitral regurgitation and the ventricular volume are increased; the pulse pressure, LV

ejection fraction (LVEF), cardiac output and diastolic filling time are reduced. However, the occurrence of electrical dyssynchrony has a limited reliability in identifying the presence of mechanical dyssynchrony. Fauchier et al.[5] evaluated 103 patients with idiopathic dilated cardiomyopathy using equilibrium radionuclide angiography (ERNA) and phase analysis. They found that intra- LV dyssynchrony was lacking in 54 and 8% of the patients with complete LBBB on the normal and left axis, respectively. However, dyssynchrony was also present in 41% of the patients with "normal" QRS. Garrigue et al.[6] obtained analogous findings using tissue Doppler imaging, when examined 104 patients with LBBB or right bundle branch block: inter- and intraventricular dyssynchrony were lacking in 35 and 20% of the patients with electrical dyssynchrony, respectively.

Cardiac resynchronization therapy

The American College of Cardiology/American Heart Association/North American Society of Pacing and Electrophysiology 2002 guideline update for implantation of pacemakers and antiarrhythmic devices classifies CRT with the level of evidence IIA, for patients with idiopathic dilated or ischemic cardiomyopathy, severe heart failure NYHA functional class III to IV despite optimized medical therapy, LVEF ≤ 35%, QRS duration ≥ 130, and LV end-diastolic diameter ≥ 55 mm[7].

However, despite the use of these classic criteria, a substantial proportion of patients (approximately one third) does not experience a clinical benefit from CRT, showing no improvement in clinical functional class and quality-of-life score after biventricular or LV pacing. These patients do not have any subjective and/or objective advantage from pacing, except perhaps that evoked as a placebo response. In addition, the cost of the device, as well as the risk of implant-related complications, and their associated expenses should be taken into account.

Interestingly, the proportion of non-responders does not appear to be related to the baseline QRS duration, being present fairly uniformly across the whole range of QRS width[8]. This finding is consistent with the existence of only a modest correlation between the enhancement in isovolumic systolic function (percent dP/dt max) assessed acutely after VDD pacing and baseline QRS duration ($r = 0.55$, $p = 0.012$) in patients with dilated cardiomyopathy and LBBB[9].

There are numerous possible reasons at the basis of a failure to respond to CRT, including:
• lack of understanding of the underlying abnormality (electrical vs mechanical dyssynchrony) and therefore inappropriate targeting of the therapeutic goal;
• poor reproducibility of the clinical and non-invasive parameters used to assess the benefit;
• treatment with the device when the primary pathologic process has progressed in the natural history beyond the point of "no return";
• off-beam indication (e.g. atrial fibrillation, permanent pacemaker, etc.);
• inability to match the identified area presenting delayed electrical/mechanical activity with pacing site, because of constrains dictated by coronary venous anatomy that hinders lead placement, high pacing thresholds in scarred areas, etc.;
• inappropriate programming or loss of capture of the device.

Therefore, the clinical challenge is not in identifying patients with delayed electrical activation QRS prolongation fulfilling the currently accepted criteria for implantation, but identifying specific and reliable markers that predict improvement in functional capacity and/or volumes in the individual patient.

Definition - types of dyssynchrony

Four different forms of electromechanical abnormalities that may lead to dyssynchrony have been currently identified: 1) atrioventricular, 2) interventricular, 3) intraventricular, and the most recently described 4) intramural. Although the effects of CRT on the intramural delay have not been thoroughly investigated, the effects on interventricular delay probably play a secondary role after the correction of both atrioventricular and intraventricular delay[10].

Assessment and quantification of dyssynchrony with imaging techniques

It has currently been postulated that, in addition to utilizing standard inclusion criteria, the mechanical evaluation of LV contraction should be taken into consideration for the appropriate selection of responders to CRT.

Magnetic resonance imaging. Three-dimensional dyssynchrony assessed by magnetic resonance-tagged imaging was first shown to best correlate with acute mechanical benefit[9]. This imaging modality has superior spatial and temporal resolution, but cannot be applied in the presence of pacemakers.

Echocardiography. M-mode, two-dimensional, tissue Doppler imaging, strain, strain rate, tissue tracking and three-dimensional echocardiography may permit the assessment of the first three forms of dyssynchrony[11]. It has the advantage that, at least the more conventional modalities, are widely available to cardiologists and new patient selection criteria based on additional echocardiographic imaging technique have been recently adopted in clinical trials on CRT[12].

However, these methods are limited at the present time by the use of a single-plane imaging, suboptimal signal-to-noise ratio and, most of all, operator dependency, which restricts reproducibility of the measurements obtained. Real-time three-dimensional echo has a better spatial resolution, which overcomes the single-plane imaging limitation restricting the other echocardiographic techniques, and thus has an improved ability of assessing the extent of dyssynchrony, but it is currently constrained by the limited time resolution[13].

Systolic velocity-based parameters are difficult to apply to the thin walls of the enlarged, dilated ventricles, which are the expected target of CRT yet. In addition, these indices are not only related to local contractile function, but are affected by the overall heart motion and by tethering effects as well, which in the end may influence the results.

Equilibrium radionuclide angiography. Phase analysis is a well-established application of ERNA. However, despite the widespread distribution of the equipment, the technique is currently underutilized.

ERNA is performed by *in vivo* red cell labeling by intravenous injection of stanneous ion followed by injection of 800 MBq ^{99}Tc-pertechnetate. Acquisition is made at rest in the antero-posterior, lateral and best left anterior oblique projections with caudal tilt, with ECG-gating and using 24 or 32 frames per cardiac cycle. Scintigraphic data from successive beats are accumulated, until the cardiac image contains a predetermined number of counts (at least 5 million counts).

The use of radioactive materials causes radiation exposure to both occupational and non-laboratory personnel. The effective radiation absorbed dose by the whole body of the patients for an ERNA study is 3.6 mSV[14].

Applying a mathematical function, the fast Fourier transform, the time-activity curve of each pixel in the region of interest can be obtained, which resembles the time-activity curve of the whole ventricle. The activity in each pixel can be characterized in terms of amplitude (a function of stroke volume) and phase (time in emptying).

The representative R-R cardiac cycle is divided into degrees, ranging from 0 to 360°, so that the time of contraction of the pixels can be expressed as a "phase angle" and is assigned a particular color from a continuous color scale, so that all pixels that contract at the same phase have the same color. The temporal resolution varies according to the heart rate, so it changes between 36 and 18 ms when the heart rate fluctuates between 50 and 100 b/min. The accurate detection of clinically relevant abnormalities in the timing of regional ventricular mechanical events requires the use of the highest possible frame rate values.

To assess the pattern of phase distribution and sequential phase changes over both the right ventricular and LV regions of interest, a color-coded phase image and corresponding histograms (indicating the number of pixels on the image with a given phase) are generated.

The following parameters can be computed (Fig. 1):
• mean phase angles for the right and left ventricles, as the arithmetic mean of the phase angle for all pixels in the ventricular region of interest relates to the mean time of ventricular contraction onset;
• interventricular contractile synchrony measured as the absolute difference in right ventricular and LV mean phase angles;
• intraventricular contractile synchrony measured as the standard deviation of the mean phase angle for the right and left ventricles.

The values of intraventricular dyssynchrony for the left ventricle and interventricular dyssynchrony in normal healthy subjects were reported 22 ± 12 ms (or 8.9 ± 2.8°) and 15 ± 13 ms, respectively[15,16].

The method has demonstrated the advantages of optimization of the atrioventricular synchrony in paced rhythms in improving the ventricular performance[17].

Potential inaccuracies. There are a few potential sources of inaccuracy associated with the method, including:
• absolute phase angle values are influenced by the timing of gating with reference to the ECG and by the cardiac cycle duration;
• the gating trigger must sense the maximal ECG slope, so the choice of an appropriate lead is key in gating;
• studying patients only during regular rhythm minimizes the effect of the heart rate on the diastolic length and thus on the symmetry of the time-radioactivity curve;
• although phase data obtained in the anterior or right anterior oblique projection are useful to triangulate the location of the latest phase angle, the absolute values in these projections must be used with caution since they can be less than reliable because of significant structural overlap.

Pathophysiologic consequences of cardiac conduction disturbances

Research exploring with scintigraphy the pathophysiological consequences of cardiac conduction disturbances on metabolism and perfusion has yielded interesting results.

Animal studies have convincingly demonstrated that LBBB can be associated with an actual reduction in blood flow in the septum, in the absence of cardiac pathology[18,19]. However, the differential blood flow caused by LBBB is not associated with any demonstrable evidence of ischemia by either abnormal lactate metabolism or increased ^{18}fluorine-labeled 2-fluoro-2-deoxy-D-glucose extraction[19].

Glucose metabolism is reduced more than perfusion in the septal wall as compared with LV lateral wall in

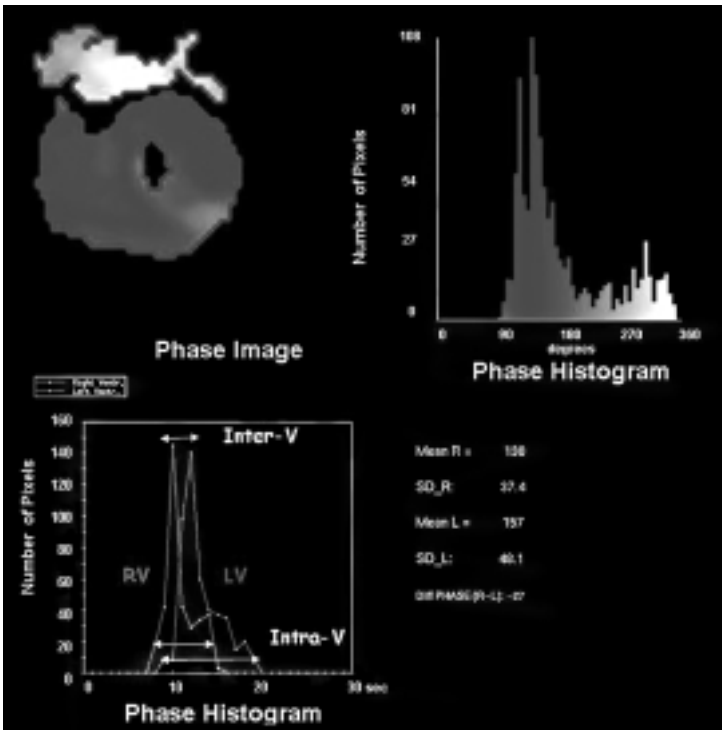

Figure 1. *Phase image and histograms, illustrating intra- and interventricular dyssynchrony in a patient with ischemic cardiomyopathy.* Upper left: *phase image of the heart in the "best septal" left anterior oblique view (atria on the* top*, ventricles at the* bottom*) showing the contraction sequence ("phase") for each pixel overlaying the equilibrium blood pool and gated to the ECG R-wave. Phase progression, from early to late: navy, azure, violet, orange, yellow, white.* Upper right: *quantitative phase histogram of atria and ventricles, plotting the phase angle over a range of 360° (X axis), and the number of pixels on the image with a given phase (Y axis).* Lower left: *quantitative phase histogram illustrating the dispersion of phase angles during ventricular ejection for the right ventricle (RV) and the left ventricle (LV), separately.* Lower right: *actual values of the arithmetic mean and standard deviation of the phase angles, computed for blood pools of the RV and LV.*

patients with dilated cardiomyopathy and LBBB[20]. CRT was found to produce an improvement and a homogenization of the LV delay activation-associated reduction in perfusion and glucose metabolism in the septum.

In addition, despite an improvement in LV function, CRT appears to homogenize but not increase resting LV myocardial blood flow in patients with either ischemic or non-ischemic heart failure, while myocardial blood flow reserve is enhanced by multisite pacing[21]. This implies that the beneficial effects of CRT do not require additional oxygen demand or regional reallocation of oxidative metabolism.

Right ventricular performance has a prognostic value in patients with congestive heart failure, and the interaction between the left and right ventricle may play an important role in CRT response. CRT appears to enhance right ventricular oxidative metabolism and metabolic reserve during stress, while responders to CRT show a lower right ventricular oxidative metabolism at rest[22].

Hearts with LBBB delays display profound basal mechanical dyssynchrony, whose extent can be adequately demonstrated with ERNA imaging. The septal region contracts briefly in early systole, then contraction slowly spreads to the lateral wall as the septum develops positive strains in late systole.

The introduction of cardiac gating in myocardial perfusion imaging has helped our ability to assess patients with LBBB and clarify the conundrum intertwined to it. Kasai et al.[23] have shown that, while a decreased septal thickening is present uniformly in patients with LBBB and a low probability of coronary artery disease, a paradoxical septal wall motion is evident only in patients with a significant deterioration in LV volume and LVEF. This makes it seem that septal dyssynchrony, *per se*, is only a minor manifestation of a major change in cardiac size and function (Fig. 2).

Scintigraphic evaluation of benefit derived from cardiac resynchronization therapy

The scintigraphic approach is a valuable qualitative and quantitative analytic tool for the initial assessment of the baseline functional parameters of the candidates to CRT. Most importantly, being scintigraphic data highly reproducible, they are suitable for sequential longitudinal follow-up of the patients implanted with devices. This allows for an accurate detection and quantification of the progression or regression of systolic dysfunction and ventricular dilation with ERNA or with gated-single-photon

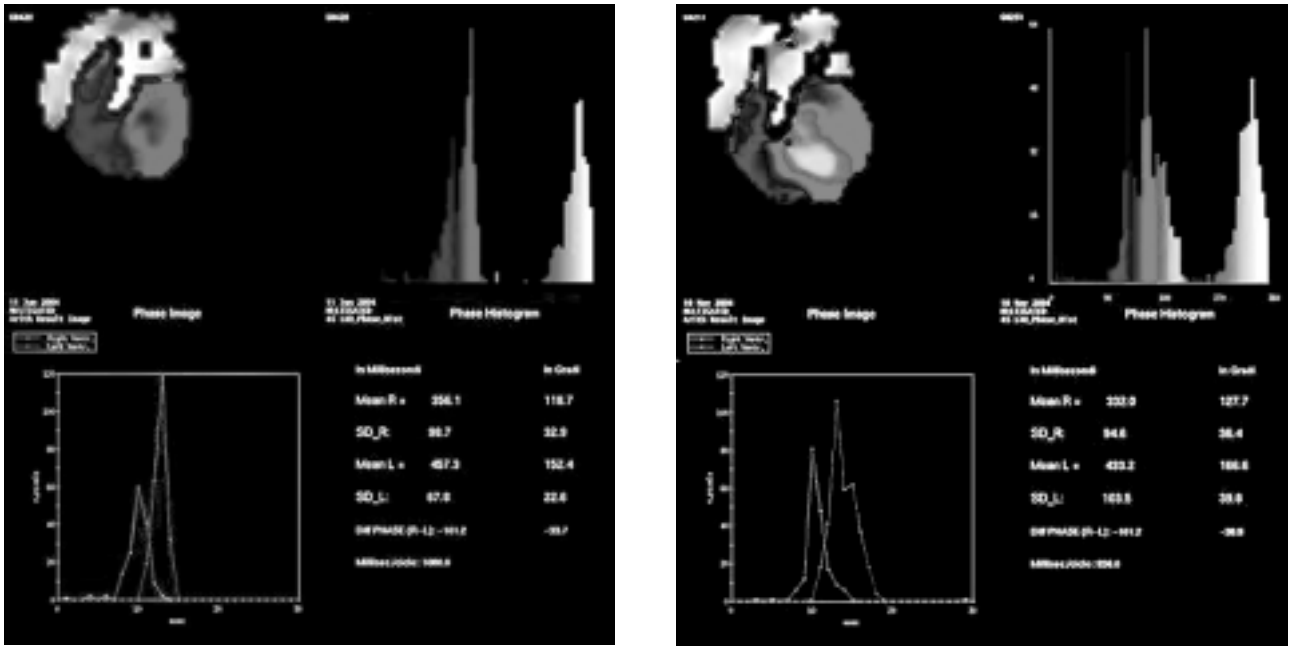

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Figure 2. *Examples of phase image analysis acquired in two patients with left bundle branch block.* A: *a patient with left bundle branch block, mild degree of intra- and interventricular dyssynchrony and preserved left ventricular volumes and ejection fraction.* B: *a patient with left bundle branch block and dilated cardiomyopathy more marked intra- and interventricular dyssynchrony associated with left ventricular dilation and depressed ejection fraction.*

emission computed tomography of perfusion images[24,25], and of the changes in mechanical dyssynchrony with phase analysis of ERNA[26].

Image acquisition and analysis are simple to perform, easy to interpret, are not time-consuming, are not commonly subject to artifacts, and, most importantly, data obtained are reproducible.

Various studies have demonstrated a decrease in intra- and interventricular dyssynchrony after CRT (Fig. 3); a consequent sufficiently large recovery in

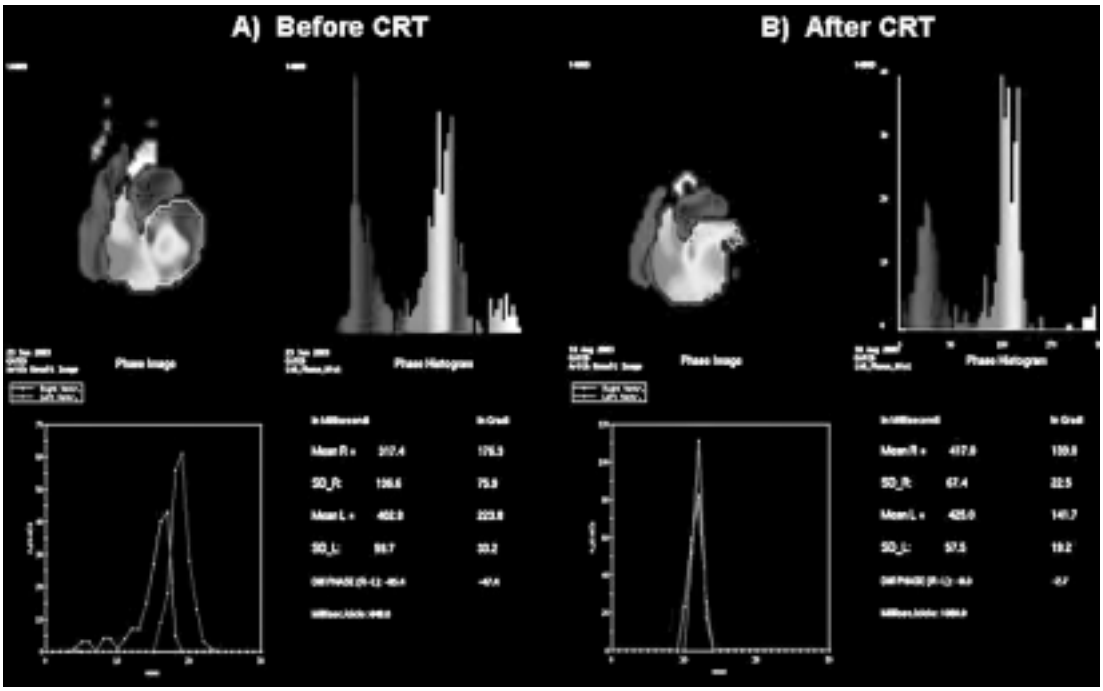


Figure 3. *A patient with dilated cardiomyopathy.* Left: *the images before cardiac resynchronization therapy (CRT) show an inhomogeneous contraction pattern in sinus rhythm, with gross dispersion of phase angles.* Right: *during biventricular stimulation there is a correction of both intra- and interventricular dyssynchrony.*

contraction synchrony can result in an improvement in LVEF, chamber dilation, symptoms, and eventually survival.

What are the cut-off values of the functional parameters that discriminate success from failure is a matter of current research.

Le Rest et al.[27], using phase analysis of ERNA studies, demonstrated the beneficial effect of LV pacing on both inter- and intraventricular delay. They investigated 17 patients with either ischemic or non-ischemic cardiomyopathy with advanced heart failure who received an LV pacemaker. Clinical improvement was observed in patients who demonstrated a reduction in inter- and/or intraventricular dyssynchrony, provided that an initial LV phase standard deviation > 50° decreased with pacing. They detected no changes in LVEF.

Other studies on non-ischemic dilated cardiomyopathy[28,29] showed that biventricular pacing reversed LV apex-to-base activation time, improved interventricular contractile synchrony with a magnitude of recovery proportional to the degree of interventricular dyssynchrony present at baseline, and increased LVEF and right ventricular ejection fraction.

Intraventricular dyssynchrony assessed with ERNA is a powerful predictor of LV reverse remodeling and is useful for the identification of the responders to CRT. In a prospective study involving 37 individuals, the criterion of standard deviation of the phase angle = 68° at baseline had a sensitivity of 77% and a specificity of 80% for the prediction of LV reverse remodeling 6 months after CRT; the area under the receiver-operating characteristic curve was 0.80 (0.63-0.91). Intra- and interobserver reproducibility of the phase angle were r = 0.95 and r = 0.93, respectively[26].

Prognosis in non-ischemic cardiomyopathy

At present, very limited data exist on the predictive value of dyssynchrony parameters in heart failure patients. Fauchier et al.[16] using phase image analysis derived from gated-ERNA evaluated the prognostic value of scintigraphic parameters. They demonstrated that left intraventricular contraction dyssynchrony was, along with pulmonary capillary wedge pressure, the only multivariate predictor of major cardiac events, cardiac death, and worsening heart failure leading to heart transplantation in 103 patients studied with idiopathic dilated cardiomyopathy.

Intraventricular contraction dyssynchrony predicted events but not interventricular dyssynchrony, QRS duration, LBBB, LVEF, peak oxygen consumption, or the findings on ambulatory ECG or signal-averaged ECG. It was interesting that right ventricular dyssynchrony was also a predictor of events on univariate but not multivariate analysis.

More recently, other investigators obtained similar results, using tissue Doppler imaging[30].

Ischemic cardiomyopathy

It is uncertain so far whether the underlying etiology of heart failure may be an important predictor of absence of response[31-35]. The basic assumption for a difference between the two is that, while in non-ischemic cardiomyopathy dyssynchrony is due to the mechanical delay between the LV septal and free walls, in ischemic cardiomyopathy dyssynchrony may occur in any region of the left ventricle, depending on the vascular territory involved.

Despite disclosing a tendency for a shorter QRS duration in ischemic compared with non-ischemic cardiomyopathy, electroanatomic mapping systems showed a more prolonged LV activation time in the former. Moreover, coronary artery disease patients present with variable activation patterns, which reflect the location of the scar[34]. Data from the MIRACLE trial showed a lesser degree of reduction in end-diastolic and end-systolic volumes, LV mass, mitral regurgitation, and a minor increase in LVEF in ischemic versus non-ischemic cause of heart failure[35]. Similarly, Duncan et al.[36] have shown in 34 patients enrolled in a substudy of the MUSTIC trial that reverse remodeling occurs after atrio-biventricular pacing much more extensively in patients with idiopathic than in those with ischemic dilated cardiomyopathy.

There are various possible explanations for a reduced benefit when coronary artery disease is the cause of heart failure, and perfusion scintigraphy may help individuate its origin.

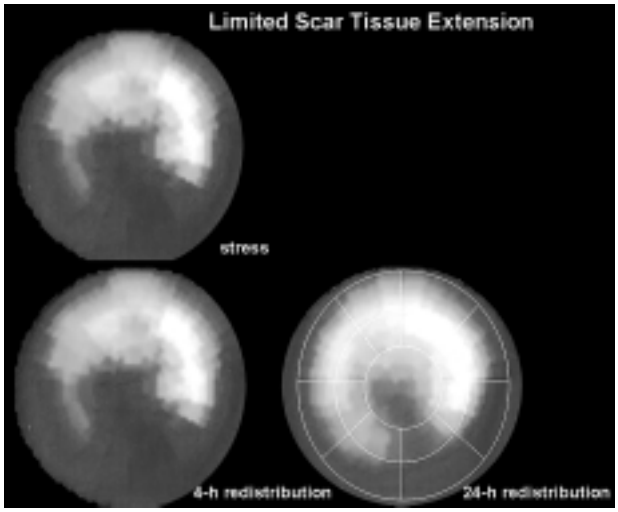
Unlike non-ischemic heart failure, ischemic cardiomyopathies have heterogeneous pathophysiological substrates. Frequently there are large areas of hibernating or scar tissue, which not uncommonly are the sites of the latest activation, and may occur in any region of the left ventricle.

As a result, lead positioning in these areas may yield disappointing results as for ventricular performance improvement, since the conventional placement of the LV lead in the lateral or postero-lateral vein of the coronary sinus may not be the most advantageous if the delay is not at the free wall region. Furthermore, pacing from such hypoperfused, late activated areas can be not only ineffective in improving dyssynchrony, given the low conduction velocity in such regions, but also potentially arrhythmogenic.

The presence of extensive areas of persistent hypoperfusion at rest, attributable to scar tissue, can limit an improvement in clinical status, in LVEF, and a reverse remodeling of the left ventricle after CRT. Conversely, patients with a limited extension of a severely abnormal perfusion defect, experience an improvement[37,38] (Figs. 4 and 5).

Thus, perfusion scintigraphy may play a role both in the optimization of LV lead positioning and in excluding from pacing patients with extensive scar tissue.

A substudy of the CHRISTMAS trial showed that treatment with carvedilol in patients with ischemic cardiomyopathy improves inter- and intraventricular con-



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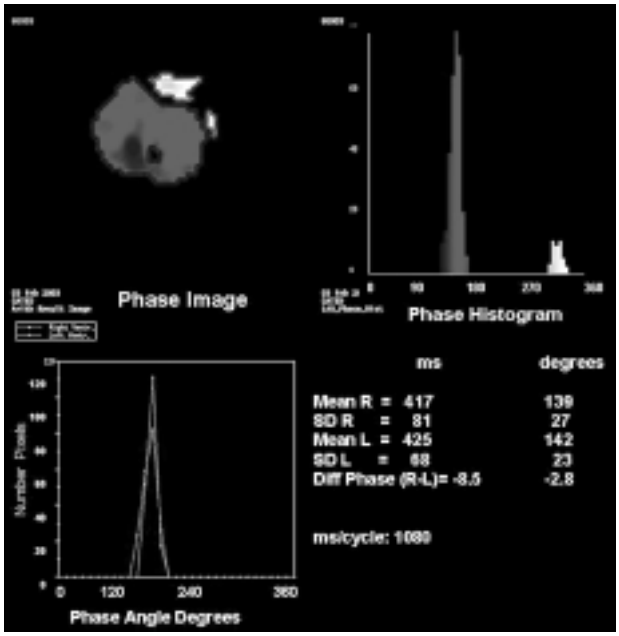

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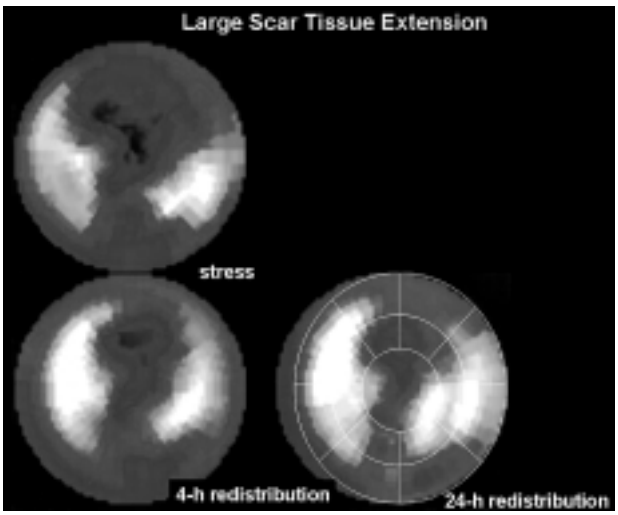
Figure 4. *Examples of polar map display of ^{201}Tl-stress redistribution perfusion scintigraphy* (A) *and phase analysis of equilibrium radionuclide angiography* (B). *This patient had ischemic cardiomyopathy, limited extension of the scar tissue, low dyssynchrony in both ventricles and no interventricular delay. Ejection fraction improved and left ventricular end-diastolic volume decreased after cardiac resynchronization therapy.*



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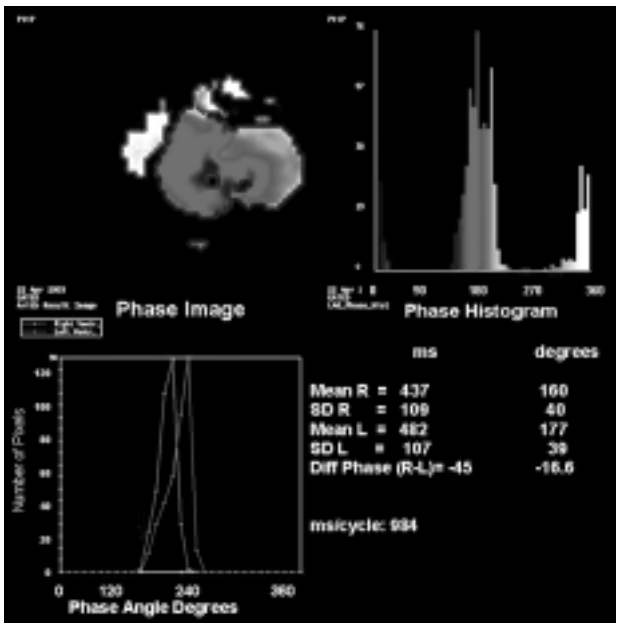

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Figure 5. *Examples of polar map display of ^{201}Tl-stress redistribution perfusion scintigraphy* (A) *and phase analysis of equilibrium radionuclide angiography* (B). *This patient with ischemic cardiomyopathy had a widespread and large extension of scar tissue, marked dyssynchrony in both ventricles and interventricular delay (ventricular activation begins at the right ventricle and at the septum, followed by the lateral wall and the apex of the left ventricle). Ejection fraction did not improve and left ventricular end-diastolic volume did not significantly change after cardiac resynchronization therapy.*

tractile synchrony. Moreover, the correction of dyssynchrony had a positive hemodynamic impact and translated into improvement of the mechanical LV function, independently of the QRS duration. Viability status, identified by resting perfusion scintigraphy with ^{99m}Tc-sestamibi, was a robust determinant of the synchronized LV contraction, and a significant improvement in intraventricular dyssynchrony in the left ventricle was observed only in patients randomized to carvedilol. This is a new finding, and may be an additional mechanism by which carvedilol exerts its beneficial effects in these patients[39] (Figs. 6 and 7).

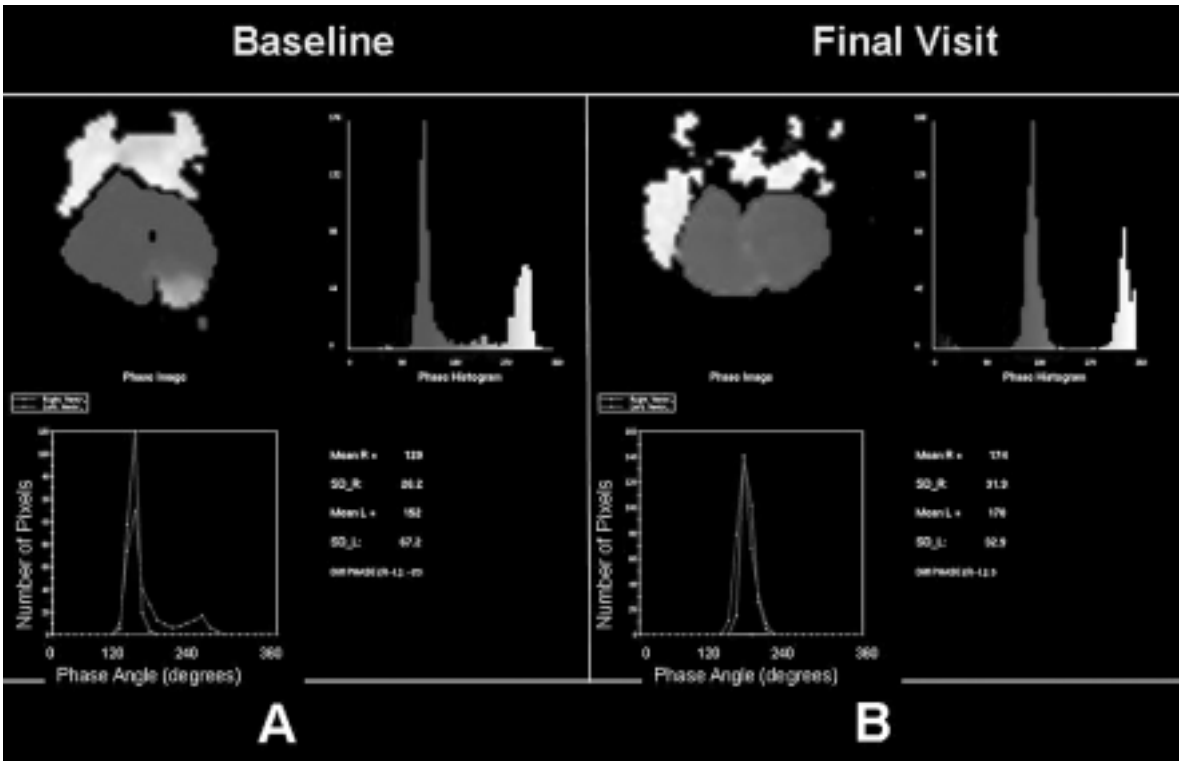

Figure 6. *Resynchronizing effect of carvedilol.* A: *baseline. An area of dyssynchrony is visible on the apex of the left ventricle of a patient with ischemic cardiomyopathy. The histogram illustrates bimodal distribution of phase angles for the left ventricle.* B: *final visit. The regression of the area of dyssynchrony on the left ventricular apex and of the delayed hump on the left ventricular histogram with achievement of a symmetric, bell-shaped pattern is evident, after 4 months of treatment with carvedilol.*

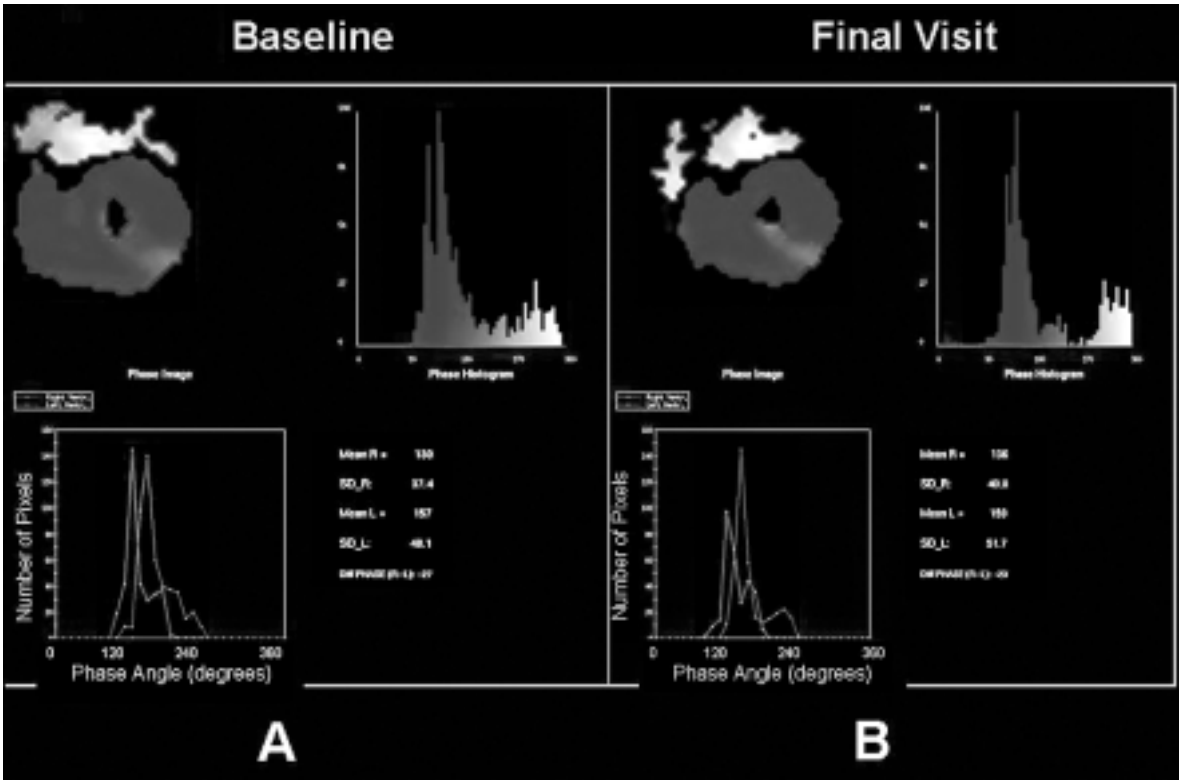

Figure 7. *Persistence of dyssynchrony in a patient assigned to placebo.* A: *baseline. Dyssynchronous contraction of the septum and of the left ventricular apex. Histograms illustrate the abnormal dispersion of the phase angles in both ventricles and a difference between the means of 27°.* B: *final visit. Images show the persistence of the abnormalities, after 4 months.*

Conclusions

Regardless of which imaging modality proves most useful, the demonstration of dyssynchrony in heart failure patients is likely to be a key in identifying those who can benefit the most from CRT and in aiding optimal pacemaker placement.

The major advantages offered by scintigraphy, in particular its feasibility and reliability, justify an expanded use of these techniques in the clinical arena of heart failure syndrome for a proper management of these patients. It should be included in the evaluation of potential CRT candidates, assessment of the extent and actual location of the delay, appraisal of optimal lead positioning and functional response.

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