

# The “Missing” Link Between Acute Hemodynamic Effect and Clinical Response

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**Abstract** The hemodynamic, mechanical and electrical effects of cardiac resynchronization therapy (CRT) occur immediate and are lasting as long as CRT is delivered. Therefore, it is reasonable to assume that acute hemodynamic effects should predict long-term outcome. However, in the literature there is more evidence against than in favour of this idea. This raises the question of what factor(s) do relate to the benefit of CRT. There is increasing evidence that dyssynchrony, presumably through the resultant abnormal local mechanical behaviour, induces extensive remodelling, comprising structure, as well as electrophysiological and contractile processes. Resynchronization has been shown to reverse these processes, even in cases of limited hemodynamic improvement. These data may indicate the need for a paradigm shift in order to achieve maximal long-term CRT response.

**Keywords** Cardiac resynchronization therapy · Hemodynamics · Remodeling

## Introduction

The hemodynamic, mechanical and electrical effects of cardiac resynchronization therapy (CRT) can be seen on a beat-to-beat basis. They are immediate and last as long

as CRT is delivered. Changes in electrical conduction can be easily appreciated on surface ECG or using more sophisticated three-dimensional electroanatomical mapping techniques, whereas changes in hemodynamics can be easily monitored by systolic blood pressure, pulse pressure, stroke volume and maximum rate of rise or decay of left ventricular (LV) pressure (LV dP/dtmax or LV dP/dtmin). Finally, changes in regional contraction pattern are immediately visible by different cardiac imaging techniques, conventional echocardiography, Doppler echocardiography and advanced echocardiographic techniques (speckle tracking and tissue Doppler imaging) being most commonly used methods in clinical practice.

Given the on–off effect of CRT on different cardiac components, investigators have measured LV dP/dtmax or PV loops invasively [1–5], blood pressure [2, 6] and/or stroke volume for guiding best pacing site [6–8] and, as recommended by current clinical practice guidelines of the European Society of Cardiology, for the selection of the most optimal AV and VV delay [3, 6, 9, 10].

However, evidence in pre-clinical studies for a strong relation between acute hemodynamic response and long-term outcome is missing, and results in patients are conflicting. One study comprising 33 patients demonstrated that patients showing a large (>11%) increase in LV dP/dtmax upon CRT have a greater probability of showing reverse remodelling, defined as a significant reduction of LV volumes [8]. These results are, however, not supported by several other studies, including larger numbers of patients. In the PATH-CHF study an acute increase in LV dP/dtmax did not relate to a reduction in LV end-systolic volume [11]. A similar disagreement between acute hemodynamic response and reverse remodelling was also observed by Mullens et al., who showed that in a subset of patients deleterious cardiac enlargement may occur despite a beneficial hemodynamic

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effect of CRT [12]. More recently two large studies including a total of more than 350 patients found no relation between the acute increase in LV dP/dtmax and survival (or heart transplant; LVAD implant) [13, 14].

The puzzling absence of more positive findings, even assuming a publication bias against reporting negative data, suggests that acute hemodynamic response may only poorly relate to long-term outcome of the patient. It raises at least three major questions:

- Why is there a mismatch between acute hemodynamic response and long-term outcome?
- What is the mechanism of CRT if improved hemodynamics is *not* the main trigger of long-term benefit?
- What parameter should be considered appropriate to acutely optimize CRT, if hemodynamic measures are not reliable?

### Possible Causes of the Mismatch

A trivial answer to the potential missing link between acute hemodynamic response and long-term outcome is that heart failure is a disease with a highly variable clinical course. The latter may be considered a significant confounder to the assessment, even if a relation between acute hemodynamic effect and long-term response exists. Additional uncertainty in predicting patient outcome is due to the influence of co-morbidities or other medical conditions on the natural course of the underlying disease.

A true “missing link” is the placebo effect, or better, the psychological effect created by CRT, leading to subjective improvement of health condition even in “physiological non-responders”. In population-based studies with other implantable devices, the placebo effect has been shown to be considerable [15, 16]. Nevertheless, if hemodynamics would really play a role in long-term outcome, one would expect a clearer relation than demonstrated until now.

A pathophysiological clue to the acute–chronic mismatch is that CRT gives rise to an acute effect, which is, especially in good “responders”, followed by a further increase in long-term benefit. This has been observed in experimental LBBB [17] and in patients [18]. The improvement appears to continue even over a period of years as consistently shown in both observational and controlled trials [19]. These observations are interesting and relevant, because treatment with drugs frequently shows a saturation effect, causing a levelling off of the beneficial effect, which requires additional therapy or a higher dose of the same drug. Thinking along these lines, if the acute hemodynamic response to CRT were the only

or the predominant effect, it would be expected to have a saturating effect rather than to elicit a continuing improvement. Thus, the fact that continuing improvement is observed implies that other mechanisms are likely involved. Also, in some hemodynamic non-responders molecular remodelling has been observed.

It is also important to note that in order to have a good prediction between acute hemodynamic effect and chronic response to CRT, the accuracy of measurement during the acute phase should be high enough and the spontaneous variability of the parameter should be limited. As recently pointed out, there is significant difficulty in clinical practice to collect data accurate enough [20].

Finally, a good example to demonstrate the mismatch between acute and chronic effect of CRT is given by the reversal of maladaptive remodelling process which is a very complex process including profound effect at molecular, cellular and structural level. During the last decade a number of studies have elucidated processes involved in such cellular and molecular remodelling in dyssynchronous hearts, predominantly in experimental models (see the next section). Note that in clinical practice “reverse remodelling” usually refers to a decrease in LV volume(s) given the inability to routinely assess *in vivo* the effect of reverse remodelling on other parameters.

Remodelling processes are initiated by triggers, frequently more than one. For example, in hypertension the high blood pressure is a clear trigger, but also the elevated plasma levels of hormones like angiotensin play a role in changes at the cellular and molecular level [21, 22].

Based on the above reasoning the inability to find a link between acute hemodynamic effect and clinical response to CRT is not unexpected, and given the complex interplay of electrical, hemodynamic, mechanical and structural factors, no single parameter will likely predict chronic outcome after CRT. Nevertheless, understanding of processes related to remodelling in the dyssynchronous heart and reverse remodelling in CRT may give us insights on how we may better predict outcome in CRT patients and potentially identify those patients who will have impressive volume changes after CRT (so-called “super-responders”) and those who will not show meaningful changes in volume or in ventricular function (so-called “non-responders”).

### Remodelling in Dyssynchronous Hearts

When a heart switches from normal, synchronous activation to abnormal, asynchronous activation, the first event to occur is that the initially uniform contraction becomes heterogeneous, leading to reduction in pump function. As a consequence, similar to what happens after the onset of

infarction, compensatory mechanisms such as neurohormonal system become activated in an attempt to stabilize the hemodynamic situation. A recent study showed that the baroreflex alters activity within 5 s after changing the activation sequence [23]. Sympathetic activation is probably maintained during long-term asynchronous activation, because elevated levels of catecholamines have been measured in dogs during chronic ventricular pacing [24] and greater systemic vascular resistance in patients during ventricular pacing [25].

It has been shown that during ventricular pacing the LV pressure–volume relations show a rightward shift, indicating that the heart operates at a larger volume, thus leading to global stretching of the muscle fibers, a known stimulus for subsequent remodelling processes. These aforementioned processes appear similar to what happens after myocardial infarction; therefore, also remodelling processes originating from these derangements may be similar to those observed in hearts after myocardial infarction. However, the heterogeneous contraction patterns have unique characteristics that may relate to remodelling processes that appear to be highly specific for dyssynchronous hearts. During dyssynchrony contraction in the various regions is not only out of phase, but also workload within the ventricular wall becomes heterogeneously distributed, low values being present in early-activated regions and high values in late-activated regions [26–28]. The latter changes are also reflected by changes in regional blood flow and oxygen consumption [29, 30]. In the long run, this redistribution of mechanical load within the ventricular wall leads to asymmetric hypertrophy, as demonstrated in dogs during LV pacing [31] and with LBBB [17] as well as in patients with LBBB [32]. This asymmetric hypertrophy is characterized by an overall increase of LV muscle mass that is most pronounced in the latest-activated regions (the LV lateral wall in case of LBBB).

Over the last 5 years a series of studies in the canine model of LBBB, alone or in combination with tachypacing-induced heart failure, as well as in the mouse heart after chronic RV pacing [33] have been published that shed some light into the changes at the cellular level in asynchronous hearts. These changes are very complex, more or less mimicking the asymmetry of the macroscopic hypertrophy in dyssynchronous hearts. Expression of some genes and proteins is depressed uniformly, while others show regional differences in expression. Examples of uniformly depressed genes and proteins are virtually all potassium channels, several calcium channels and beta-adrenergic receptors [34, 35]. The fetal gene program and apoptosis related genes are activated uniformly in dyssynchronous failing hearts.

In contrast, the L-type calcium channel and the transient outward potassium current (I<sub>to</sub>) show, in addition to overall

downregulation, most pronounced downregulation in the late-activated regions [34]. In addition, in the late-activated LV lateral wall, stress response kinases as well as TNF $\alpha$  were upregulated [36], and the gap junction protein connexin 43 showed lateralization, the latter being associated with slowing down of conduction velocity [37]. Finally, in dyssynchronous failing hearts, myocardial catecholamine levels rose in both anteroseptal and lateral walls (slightly more in the lateral walls) [34, 35].

Altogether, these global and regional changes lead to a complicated “molecular fingerprint” of remodelling in the dyssynchronous heart. Importantly, some abnormalities were not observed in synchronous heart failure (rapid atrial pacing), thus highlighting the importance of the discoordinate contraction in the pathophysiology of heart failure.

To date, the exact triggers for the locally different remodelling processes are incompletely understood. In general, abnormal stretch (a surrogate for mechanical load) can change expression of genes and proteins in isolated cultured myocytes and can induce a hypertrophic response (e.g. mass or volume increase, BNP expression) [22, 38]. There is conflicting evidence as to whether this cellular response depends on local myocardial angiotensin production. Data from some investigators indicated that angiotensin II plays a critical role as an autocrine or paracrine factor in stretch-induced hypertrophy of cardiomyocytes [22, 39], whereas another study showed that stretch-induced hypertrophy was not blocked by the angiotensin receptor blocker irbesartan [38].

A potentially confounding factor is the presence of fibroblasts in the myocyte culture. Blaauw et al. took special care that their culture was almost free from fibroblasts. More recently they found that stretched fibroblasts produce factors that, added to unstretched myocytes, can stimulate myocyte growth. Because myocardial stretch will influence both myocytes and fibroblasts, these data suggest that stretch-induced hypertrophy is a concerted action of the various cell types in the myocardium, partly mediated by paracrine neurohumoral factors (Blaauw et al., personal communication).

An important question in this respect is as to whether drugs, like beta-blockers, ACE inhibitors and angiotensin receptor blockers, that inhibit the neurohumoral response at the global level also do so at the local level. This is an important question, because virtually all CRT candidates are treated with these drugs. Be that as it is, molecular abnormalities have been observed in myocardial samples taken from ventricles of CRT candidates [40, 41]. Some of these abnormalities, like downregulation of SERCA, alpha-MHC and upregulation of BNP, are partly normalized within 4 months in CRT responders [40, 41]. In contrast, CRT non-responders appear to have a distinctive

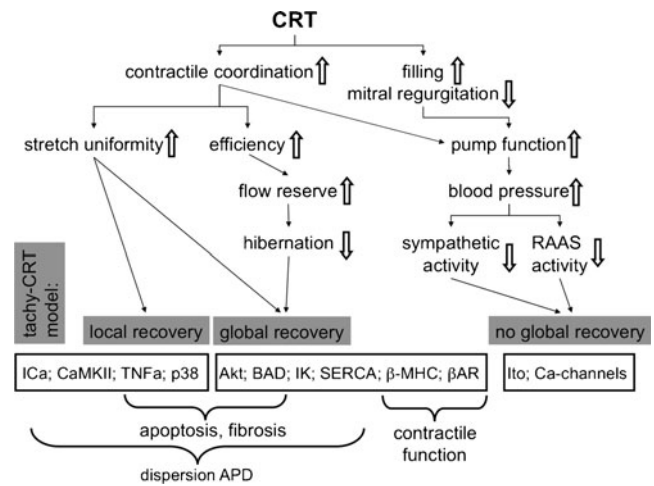
molecular pattern that may indicate that these patients are genotypically different. A recent study in CRT patients showed that among the three most common polymorphisms of the beta-1 and the beta-2 adrenergic receptors, only beta-2 adrenoceptor Gln27Glu gene polymorphism has a significant association with the LV response to CRT, with Glu27 carriers showing a better response to CRT [42]. Although the study does not allow to infer mechanisms for these gene related differences, it is interesting to note that a greater improvement in LV function in Glu27 carriers has been described also after beta-blocker therapy [42].

Patients with a favourable response to CRT also show changes in myocardial gene expression, including an increase in mRNA levels of alpha-myosin heavy chain (MHC), sarcoplasmic reticulum calcium ATPase (SERCA), a decrease in BNP mRNA levels and an increase in the ratio of alpha-MHC/beta-MHC [40, 41], which recapitulate those previously shown with beta-blocker therapy.

### Reversal of Dyssynchrony-Induced Remodelling

In experimental LBBB where heart rate is maintained in the physiological range, application of CRT could almost completely recovers the normal geometry and asymmetric hypertrophy, as determined by standard echocardiography [9]. In studies in the tachycardia-induced heart failure, resynchronization was applied by changing RV pacing to BiV pacing, while keeping the heart rate high (>200 bpm). This mode of resynchronization created only a minor improvement in overall pump function. Yet, considerable molecular changes were observed. First of all, CRT normalized the abnormal distribution of expression of L-type calcium channel, CaM Kinase II, TNFalpha and p38 [34]; this normalization process fits with the idea that the local contraction pattern is a determinant of local gene expression. However, even without a major increase in pump function, uniformly depressed genes and proteins recovered, such as Akt, BAD, Ik, SERCA and beta-MHC [34, 43]. Moreover, CRT reduced myocardial catecholamine levels, accompanied by increased expression of beta1-adrenergic receptor expression [35]. Still, high heart rate CRT did not result in complete normalization of molecular factors, because Ito and several calcium channels (all uniformly depressed during DHF) did not show any recovery [34]. One could speculate that complete reversal also requires complete hemodynamic recovery.

These data do show that the more uniform contraction patterns during rapid BiV pacing can create significant reverse molecular remodelling. In Fig. 1 the various effects of CRT are depicted, and based on the data from the tachy-CRT model, it is supposed that the normalization



**Fig. 1** Schematic representation of the various effects of cardiac resynchronization therapy (CRT). Below the grey text blocks molecular effects are mentioned, as observed in the animal model of tachy-biventricular pacing, a model where the switch from tachy-RV pacing to tachy-biventricular pacing resulted in only minor hemodynamic changes. In the text it is argued in more detail that the observed changes in this model are primarily triggered by restoration of uniform contraction and stretch at the local level rather than hemodynamic improvement

of strain (stretch) results in both recovery of the locally disturbed proteins and the global ones that do recover by tachy-CRT as compared to tachy-LBBB or tachy-RV pacing. Along the same lines, it could be supposed that factors that do not recover from tachy-CRT may recover with the clinically applied CRT, where a larger benefit of pump function is achieved, either acutely or after longer lasting CRT.

For the role of the various proteins involved in recovery by experimental biventricular pacing at a high heart rate (>200 bpm), it appears that these changes might improve underlying myocyte contractile function (e.g. recovery of calcium handling proteins and beta-adrenergic receptors), fibrosis and apoptosis (TNFalpha and BAD) and may reduce risk of cardiac arrhythmia (e.g. potassium and calcium channels, involved in dispersion of APD). A remarkable finding was that CRT upregulated RGS proteins, suppressing inhibitory G-protein activity. This upregulation was shown to be a unique feature of recovery from dyssynchronous heart failure [40]. Therefore, the aforementioned remodelling processes relate to functions that are highly relevant to the cure and survival of patients.

Some of the aforementioned animal data are supported by observations in patients obtained by myocardial biopsies or by circulating blood sample. D’Ascia et al. showed significant reduction in collagen deposition and TNFalpha immunoreaction at the cellular level and that cellular apoptotic activity as detected by a nuclei marked with



DAB by hairpin probe and immunoreaction for activated caspase-3 were substantially reduced after CRT [41]. Moreover, patients with effective CRT more frequently display chronic enhancement of circulating apelin, a secreted hormone that can block adverse remodelling and has positive inotropic effects [44]. Circulating biomarkers of extracellular matrix remodelling also accompany successful CRT therapy, including decreases in tenascin-C and metalloproteinases [45]. Chronic CRT also has anti-inflammatory effects, reducing monocyte chemoattractant protein-1, interleukin-8 and interleukin-6 [46].

### Improvements in Myocardial Oxygenation

An additional factor potentially modifying cardiac function on the long run may be the oxygen supply–demand status of the heart. In many patients the myocardial oxygen supply is not optimal. Dyssynchrony may drive the heart of such patients to the limit of the coronary dilatory reserve or even into hibernation. The latter could occur globally or locally. The entire heart may encounter lower perfusion reserve, because the dyssynchronous heart has reduced efficiency in converting metabolic energy into mechanical energy. At the local level, especially regions with the highest mechanical load, the late-activated regions, it may operate at elevated demand levels. Moreover, several studies indicate that the prolonged systolic phase and shorter diastole may hamper coronary perfusion that, after all, predominantly occurs during diastole. This effect may especially be relevant at higher heart rates [47].

Resynchronization on its turn has been shown to increase overall mechano-energetic balance of the heart [48]. Similarly, Mills et al. showed, for pacing at various sites, that the most uniform contraction coincided with highest mechano-energetic efficiency. In addition, resynchronization may reduce mechanical overload in late-activated regions [49]. Finally, resynchronization prolongs the diastole period, not only improving ventricular filling but also allowing longer coronary perfusion.

All these effects may lead to an increase of myocardial perfusion reserve, as demonstrated in patients [50]. While sudden improvement in oxygen supply/demand may cause an immediate improvement of contraction, in the case of hibernation a slow recovery is expected. Moreover, lower oxygen consumption may also lead to less formation of oxygen radicals that can produce or promote myocardial damage. These oxygenation related recovery processes may not be considered as “reverse remodelling” processes, but will certainly assist in recovery of the myocardium upon CRT and might explain (in part) the continuing improvement of cardiac function, even years after the start of CRT.

### Lessons from Other Therapies

In this regard it is also important to note that other therapies also enhance beta-adrenergic signaling, increase SERCA expression and downregulate NCX [51–53]. Such therapies, like angiotensin converting enzyme inhibition, beta-blockade and ventricular assist devices, usually antagonize deleterious neurohormonal pathways and/or reduce hemodynamic load. The fact that, except for LVAD therapy, these therapies do not improve cardiac pump function directly, while improving patient longevity, also supports the notion that the remodelling, rather than an increase in pump function, is most relevant for the long-term outcome of patients. Notably, these treatments also improve oxygenation or reduce oxygen demand. In contrast, positive inotropic agents, though improving pump function, significantly increase mortality, again stressing the mismatch between acute hemodynamic effect and long-term outcome in heart failure [4–6, 54, 55]. Inotropes typically stimulate an already inefficient and failing heart to further increase its energy expenditure [56, 57], likely contributing to the adverse impact of these drugs.

Therefore, while initially paradoxical, the mismatch between acute hemodynamic response and long-term outcome in patients is in agreement with experiences in other therapies.

### Does Non-Uniformity Relate to Long-Term Outcome?

In the literature mechanical dyssynchrony is defined in various ways. Most commonly used are indices that use time to onset or time to peak shortening in the various wall segments. While various studies suggested a good relation with CRT response (usually reverse remodelling after 6 months), other studies, including a few randomized multicentre studies, were not able to reproduce these results [58].

Alternatively, several groups have developed indices that relate to differences in amplitude of shortening between regions (“discoordination indices”). Several of the latter studies showed that CRT response is quite well predicted by a strong mechanical discoordination [59, 60, 27]. However, these studies did not compare the hemodynamic response with long-term outcome or whether optimal pump function is indeed achieved during optimal mechanical recoordination.

### Unsolved Questions

While an important role for reverse remodelling processes at the molecular and cellular level may well be linked to

long-term outcome of patients, several questions remain to be answered. First of all, if hemodynamic response does not relate to long-term outcome and mechanical recoordination does, this may imply that optimal hemodynamic function is not achieved at optimal recoordination. This has, to the best of our knowledge, not been studied nor is it well understood.

Furthermore, if recoordination of contraction is the main trigger for reverse remodelling and survival, this would imply that strain (or related) measurements should play a more important role in application of CRT, both in selection of patients and in selecting the best pacing sites and optimal AV and VV intervals. While strain measurements are becoming more feasible due to the introduction of speckle tracking, this technique can only provide data by off-line analysis. Therefore, while theoretically potentially quite valuable, in daily practice the above ideas may be challenging to apply. Clearly, more research and further development of technology may be required.

## Conclusions

Evidence is increasing that asynchrony can lead to major and distinctive types of remodelling within the ventricular wall, involving processes that might affect long-term outcome. This remodelling is more closely associated with the abnormal contraction pattern rather than to global hemodynamics. Theoretical and practical implications of this hypothesis remain to be proven.

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