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Right Ventricular Electrical Activation in Heart Failure During Right, Left and Biventricular Pacing

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Abstract

Objective—Compare right ventricular (RV) activation during intrinsic conduction to pacing in heart failure (HF) patients.

Background—Right ventricular (RV) activation during intrinsic conduction or pacing in patients with LV dysfunction (HF) is unclear but may affect prognosis. In cardiac resynchronization therapy (CRT), timed LV pacing (CRT-LV) may be superior to biventricular pacing (CRT-BiV), hypothesized to be due to merging of LV paced and right bundle branch (RBB) mediated wavefronts thus avoiding perturbation of RV electrical activation. We tested this.

Methods—Epicardial RV activation duration (RVAD: onset to end of free wall activation) was evaluated non-invasively by electrocardiographic imaging (ECGI) in normals (n=7) and compared to HF patients (LVEF 23±10%, n=14). RVAD in HF was contrasted during RV, CRT-BiV, and CRT-LV pacing at optimized AV intervals.

Results—During intrinsic conduction in HF (n=12), durations of QRS and precordial lead rS complexes were 158±24 and 77±17 ms respectively, indicating delayed total ventricular depolarization but rapid initial myocardial activation. Echocardiography demonstrated no significant RV disease. RV epicardial voltage, activation patterns and RVAD in HF did not differ from normal (RVAD 32±15 vs 28±3 ms respectively, p=0.42). In HF, RV pacing generated variable areas of slow conduction and prolonged RVAD (78±33 ms, p<0.001). RVAD remained delayed during CRT-BiV at optimized atrioventricular intervals (76±32 ms, p=0.87). In contrast, CRT-LV reduced RVAD to

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P.J. and C.R. are equity holders and paid employees of CIT.
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40±26 ms (p<0.016) comparable to intrinsic conduction (P=0.39) but not when atrioventricular conduction was poor or absent.

Conclusion—In HF patients without RV dysfunction treated with CRT, normal RV free wall activation in intrinsic rhythm indicated normal RBB-mediated depolarization. However, the RV was vulnerable to developing activation delays during RV pacing whether alone or with biventricular CRT. These were avoided by CRT-LV in patients with normal atrioventricular conduction.

Keywords

Right ventricle; Electrocardiographic imaging; LBBB; Heart failure; RV pacing; CRT

Introduction

Right ventricular (RV) electrical activation during intrinsic conduction or ventricular pacing is not well characterized. This understanding may influence cardiac resynchronization therapy (CRT) mode in heart failure (HF) patients. For example, LV pacing only (CRT-LV) may be superior to simultaneous biventricular pacing (CRT-BiV) [1]. However, the postulated mechanism of timed LV paced wavefronts merging with intrinsic conduction, thus avoiding any RV pacing effect, has not been directly tested. The explanation assumes intact right bundle branch (RBB) conduction in patients with both Purkinje system and ventricular disease and also that the RV pacing component of CRT-BiV exerts deleterious effects. Certainly, RV pacing alone increases patient morbidity[2], attributed to detrimental electromechanical effects simulating left bundle branch block (LBBB)[3]. Interestingly, RV pacing increases mortality in HF patients with pre-existing LBBB [4] indicating contributory mechanisms other than altered LV activation alone. These may include pacing-induced alteration of RV activation and ensuing RV contractile dysfunction, which diminishes survival in HF [5–7].

Our preliminary reports indicated that RV epicardial breakthrough in HF patients was delayed compared to normals and duration of RV activation (RVAD) prolonged by RV pacing[8,9]. Here, we extended these observations. We hypothesized that RV pacing as part of CRT-BiV alters RV activation compared to intrinsic RBB-mediated depolarization and may be avoided by CRT-LV. This was tested using electrocardiographic imaging (ECGI) which noninvasively depicts epicardial cardiac excitation with high-resolution [9,10].

Methods

Seven normal, healthy adults (age 21–43 years, 4 male) with normal ECGs formed a control group (data published previously[9]) to enable comparison to baseline RV activation in HF. 14 HF patients (61±18 years, 11 male, LVEF <35 %) receiving CRT were studied 6.8 ±5 months after implant. In 12/14 patients with preserved atrioventricular (AV) conduction, surface ECGs were analyzed for durations of QRS complex and rS intervals in V1/V2[11] and voltage maps generated during intrinsic conduction. ECGI reconstructs epicardial voltages assuming a homogeneous torso without taking into account the conductivities of tissues surrounding the heart. This facilitates practical application of ECGI in patients without compromising accurate reconstruction of voltage patterns (e.g. low voltage regions). While absolute voltage values may not be preserved, relative magnitudes (ratios of potential amplitudes in different regions) are reconstructed under the homogeneous torso approximation[12,13]. This methodology permitted accurate evaluation of epicardial RV voltage relative to LV values.

In the study group, RV activation times and patterns were contrasted during intrinsic conduction and in different pacing modes. RV activation duration (RVAD) was defined as time difference between onset and end of RV free wall depolarization. Atrial synchronous pacing was performed in all excepting one patient with atrial fibrillation. AV interval was optimized

(AVopt) echocardiographically during CRT-BiV according to Ritter[14]. RV pacing effects were evaluated in DDD-RV with shortened AV interval (30~50 ms) i.e. when ventricular excitation was committed to the paced wavefront. DDD-RV was then repeated at AVopt to permit direct comparison to CRT. CRT was assessed in CRT-BiV and CRT-LV at AVopt when AV conduction was intact. Implanted devices varied in ability to perform RV and LV pacing independently. Thus, both modes were not obtained in every patient.

Data are reported as mean ± SD. Groups were compared by using unpaired two-tailed *t* tests (SPSS software, version 13, Chicago, IL). A probability value of <0.05 was considered significant.

Results

HF patients (ischemic etiology in 50%) had poor functional NYHA class and reduced LV function (ejection fraction 23±9.8 %)[Table 1]. Echocardiographically, RV size was normal in 13/14 patients but enlarged in patient #12. 2/14 patients without intrinsic conduction had received CRT upgrade from chronic RV pacing (QRS >200 ms).12/14 patients exhibited intrinsic conduction (PR interval 203±53, range 140–350 ms) including 2 with QRS<120 ms selected on echocardiographic criteria. AVopt was shorter (143 ± 31, range 80–189 ms, p<0.001). 10 patients conducted with LBBB (QRS 158±24, range 130–194 ms). rS duration in V1/2 was 77±17 ms indicating rapid initial myocardial activation (figure 1a). RV epicardial free wall voltage was preserved in all HF patients, including patient #12, although left ventricular low voltage areas were evident (eg Figure 1b).

Intrinsic conduction

RV activation patterns in HF patients (including patient #12) (Table 2) were similar to normals (although these were not age or gender matched) (Figure 1c and 2a). RV epicardial breakthrough(s) followed QRS onset. Sites varied similarly in both groups. In HF, RV breakthrough occurred at various anterolateral freewall positions in 11/12 patients. In patient #10, earliest breakthrough was inferoposteriorly followed by an independent lateral RV freewall breakthrough 20 ms later. Epicardial activation spread radially from breakthrough sites. Latest RV activation occurred basally. No areas of slow conduction were demonstrated. The duration of entire RV free wall activation in HF patients did not differ to normals (32±15 vs. 28±3 ms[9] respectively, p= 0.42) (figure 2b).

RV pacing

This was performed apically except in patients 1, 6 and 14 in whom leads were sited midseptally. RV pacing (DDD-RV) with minimal AV delay prolonged RV activation by slowing conduction, indicated by crowded isochrones not observed during intrinsic conduction (figure 3). Overall, RVAD was 83±26 compared to 32±15 ms during intrinsic conduction (P<0.001)(figure 4). RV midseptal pacing did not differ. When AV intervals were extended during RV pacing, RVAD remained prolonged (78±33 ms) and unchanged compared to pacing at short AV intervals (p=0.70). In patients #3 and 13, RV pacing did not generate local conduction slowing and RVAD was <45 ms for both short and long AV intervals, similar to intrinsic conduction. This was maintained during CRT-BiV (see below).

CRT

RVAD during CRT-BiV was 76±32 ms. This did not differ to RV pacing only at either short (p=0.56) or extended AV delays (p=0.87, figure 3, 4). In 4 patients with intrinsic conduction, RV epicardial breakthrough sites observed during intrinsic conduction were retained indicating manifestation of RBB conduction during CRT-BiV (figure 3). The effect of this on RV activation was usually negligible and overall RVAD remained prolonged compared to intrinsic

conduction. Again, patients #3 and 13remained exceptional. In these, RVAD during CRT-BiV was as rapid as during RV pacing with extended AV delays or during intrinsic conduction i.e. RV pacing did not generate local slowing and instead contributed to RV activation (figure 5).

During CRT-LV in patients with preserved AV conduction (n=10), the RV was activated more rapidly (40±26 ms) compared to either RV pacing or CRT-BiV ($p<0.016$, figure 3, 4). RV excitation was unaccompanied by regions of conduction slowing as observed during RV pacing or CRT-BiV. Overall, RVAD was similar to intrinsic conduction (40±26 vs 32±15 ms, $p=0.39$). During CRT-LV, RV breakthrough sites and activation patterns were identical to intrinsic conduction ie determined by intrinsic RBB conduction (figure 3) except in patient #4. Here, AVopt (130 ms) was considerably shorter than PR interval (350 ms). Hence, LV pacing did not permit intrinsic conduction, and prolonged RVAD (91 vs 25 ms during intrinsic conduction) indicated slow depolarization from LV pacing without RBB effect. When intrinsic conduction was absent (#2, 6), RV activation was similarly committed to the LV paced wavefront. RVAD determined by LV pacing without RBB participation in cases #2, 4, and 6 was 79 ±15 ms, indistinguishable to RV pacing (78 ±33 ms).

Discussion

Survival in HF patients is reduced with LBBB and RV pacing, but improved by CRT[2,15,16]. Hence, electrical activation sequences affect prognosis. However, human cardiac activation under these conditions has usually reported LV effects only[17]. RV activation has been sparsely studied although RV dysfunction further increases mortality in HF patients[6,7]. Normally, RV contraction is a complicated peristaltic movement beginning in the inflow region and extending to the outflow tract[18]. Altered electrical activation with RV pacing may perturb RV hemodynamics[1]. However, electrical characterization poses technical difficulties. The RV is largely silent during conventional electrocardiography since it generates weak electrical forces completed early in the QRS and mostly concealed by LV depolarization. However, ECGI reveals RV free wall electrical activation in detail.

Intrinsic Conduction

In HF patients studied, echocardiography indicated minimal RV disease. Voltage maps revealed no regions with diminished potential, in contrast to the LV [figure 1]. In patients with LBBB (or narrow QRS configuration), surface ECG recordings demonstrated rapid initial myocardial activation (short rS duration) suggestive of intact RBB conduction[11] despite the presence of LV conduction abnormalities[8]. ECGI activation maps supported this: after delayed RV breakthrough, both pattern and speed of RV epicardial free wall activation were similar to normals [figure 2]. (In contrast, the same patients exhibited LV conduction delay/block during intrinsic activation). Following this, there was radial and rapid centrifugal spread of activation across the RV free wall [figure 2]. These results in HF patients are consistent with previous observations[8] and similar to normal hearts [9,19]. The activation pattern likely reflects the course of the RBB, which passes down the septum to the base of the anterior papillary muscle, then fans out into multiple free running false tendons terminating in the free wall as a profuse subendocardial Purkinje network. This generates near simultaneous activation of the free wall in a radial manner, likely responsible for initiation of RV contraction from the inflow to outflow tract[20,21]. (In contrast the LV free wall depolarizes from apex to base). RV activation duration in this study was determined from completion of free wall depolarization. Previous invasive endocardial mapping in similar patients revealed lateral wall activation times near-identical to those obtained here with ECGI[22].

Right Ventricular Pacing

The electrical effects of RV pacing are conceived as reproducing those of LBBB. In support, QRS configurations are similar and LV activation occurs transseptally following RV depolarization in both. For RV pacing to truly simulate LBBB, it should replicate RV activation by the RBB. However, ECGI, which discloses electrical activation not evident from the conventional electrocardiography, demonstrated that RV pacing significantly altered pattern and velocity of RV depolarization. RV paced wavefronts propagated slowly from apex to base contrasting with rapid and radial spread during intrinsic activation. RVAD was prolonged almost threefold. Activation maps revealed conduction slowing, with isochronal crowding around pacing sites [figure 3]. This indicates development of functional delays, presumably due to predominant cell-to-cell propagation, with limited or no engagement of intact His-Purkinje conduction system tissue. This is similar to mechanism of LV activation during RV pacing [3,23]. When AV delay was extended in patients with preserved AV conduction, RV depolarization was still initiated by RV apical pacing but intrinsic RBB conduction also manifested itself. RV activation then was determined by the sum effect of these wavefronts. Overall, there was no change in RVAD compared to RV pacing at shorter AV delays because pacing effects dominated, although in two cases (#3 and 13) RV pacing generated comparatively less functional free wall conduction slowing and RVAD remained below 45 ms, comparable to intrinsic conduction (figure 5).

The results illustrate that prolongation of duration of global RV activation by RV pacing was driven by slow conduction areas generated locally around the stimulus site. These were usually small in extent. Delay permitted intrinsic RBB-mediated conduction to contribute to RV free wall depolarization resulting in varying degrees of wavefront fusion. (RV pacing may disturb septal depolarization also but this is not depicted by epicardial mapping). Hence, pattern and duration of RV free wall activation was the outcome of the balance of intrinsic (centrifugal) and RV paced (centripetal) wavefronts. When RV paced delays were less, global RV activation duration was not delayed (although direction of depolarization was different to intrinsic conduction). In contrast, when intrinsic AV conduction was absent or poor the RV was committed to activation by the RV pacing and RVAD was longer.

Cardiac Resynchronization

RV activation duration and pattern were unaltered by CRT-BiV compared to effects of RV pacing alone at the same AV delay. Thus, RV depolarization in CRT-BiV was governed by RV electrode excitation (figure 3). Overall, CRT-BiV slowed RV activation while simultaneously causing LV pre-excitation. LV pacing with optimized AV interval (CRT-LV with preserved AV conduction) produced strikingly different effects on RV activation compared to those of CRT-BiV or RV pacing. In the majority, CRT-LV permitted RV activation via intact RBB with centrifugal RV activation, avoiding functional delays generated by RV stimulation. Swifter RV activation was reflected by shorter overall RVAD comparable to intrinsic conduction in the same patients (figure 4, 5). In three cases, CRT-LV did not diminish RVAD compared to CRT-BiV. In two (#3,13), RVAD during CRT-LV and CRT-BiV were short (<45 ms) because RV paced wavefronts synergized with intrinsic RBB conduction and maintained normal RVAD. In patient #4, RVAD remained delayed compared to intrinsic conduction because AVopt was considerably shorter than the intrinsic PR interval (130 vs 350 ms respectively), preventing emergence of RBB-mediated activation. In this case, and in those with absent intrinsic conduction (#2, 6) when RV activation resulted from LV pacing, RVAD was 79±15 ms, indistinguishable to RV pacing (78±33 ms) suggestive of a propagating mechanism of slow cell to cell conduction.

Clinical Implications

Here, in patients with poor LV function and preserved AV conduction treated with CRT, ECGI demonstrated intact RBB conduction and electrically normal RV function despite LBBB. In these, intrinsic rapid and confluent RV free wall activation could be retained with CRT-LV, avoiding RV delays generated by RV pacing either alone or as part of CRT-BiV.

These data provide a mechanistic explanation for previous assumptions that avoidance of RV pacing by timed LV pacing may have hemodynamic benefit [1]. RV pacing-induced changes in activation sequence and prolongation of activation duration may all potentially perturb the normal sequential pattern of RV inflow to outflow contraction. However, the current study also demonstrated that improvement of RV activation by CRT-LV cannot be expected to occur consistently even in those with intact RBB conduction, as observed in 3/10 cases. Thus, CRT-LV did not further improve RV activation when RVAD remained normal during CRT-BiV or RV pacing (eg patient #3 (figure 5)), or when paced AV interval was much shorter than the intrinsic PR interval (#4) and the RV was committed to electrode stimulation in any case. AV optimization is an important feature of correct post-implant programming[24] and the influence of the AV interval on the contribution of intrinsic conduction to ventricular activation was illustrated previously[8]. The current study illustrates that any incremental electrical benefit to be gained by CRT-LV in terms of RV activation (observed in 7/10 patients) depends on the balance between intrinsic vs. paced atrioventricular intervals and effects of functional conduction slowing with pacing, which are unpredictable.

Limitations

The study in an unselected CRT population is limited by small volume and thus findings may not be characteristic of all CRT patients eg RV activation may differ in patients with RV dysfunction[25]. Examination was performed at variable time intervals after implant (Table 2) and a remodeling effect affecting the results cannot be excluded. CRT-LV advantage with respect to RV activation, suggested by the current study, may be diminished if pacing cannot be timed with RBB conduction (changing AV intervals with activity or irregular conduction in atrial fibrillation) or if RBB conduction is absent. Chronic effects of pacing on RV function may be complex and ultimate CRT response likely determined by both LV[17] and RV effects. For example, during chronic CRT-BiV, RV mechanical dysfunction improvement may occur from LV remodeling[26] or by RV septal site pacing[25].

In conclusion, although CRT–LV was non-inferior to CRT-BiV in one trial[27], the significant variations reported here suggest that demonstration of CRT-LV benefit requires attention to individual electrical substrate. Device programming may be guided non-invasively by dynamic 3D mapping such as ECGI and merits prospective evaluation.

Acknowledgments

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Abbreviations

ECGI	Electrocardiographic imaging
RV	Right ventricle
LV	Left ventricle
CRT	Cardiac resynchronization therapy
HF	Heart failure

AV	Atrioventricular
RBB	Right bundle branch
LBBB	Left bundle branch block

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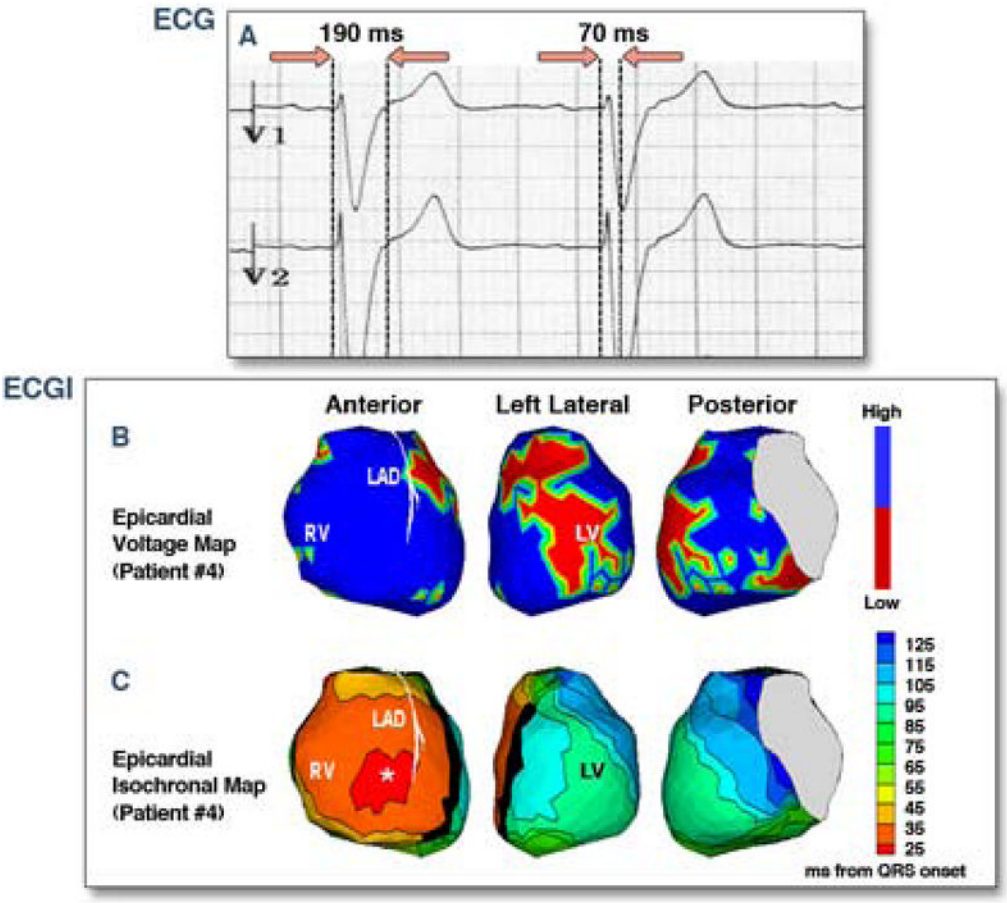

Figure 1. Heart Failure Patients with LBBB

A. 70 ms rS duration in V1/V2 indicates rapid initial myocardial activation via intact RBB despite LBBB.

ECGI Maps Epicardial surfaces of both ventricles are displayed in 3 views. "Anterior" depicts the RV free wall. Left anterior descending (LAD) artery is marked..

B Normal RV epicardial voltage (blue, anteriorly) contrasts with extensive LV disease.

C RV breakthrough (*) occurs laterally within 25 ms. Following RV activation is even, radial, and rapid (widely spaced isochrones) and completes within 45 ms. The LV is then depolarized. Thick black markings indicate line/region of conduction block.

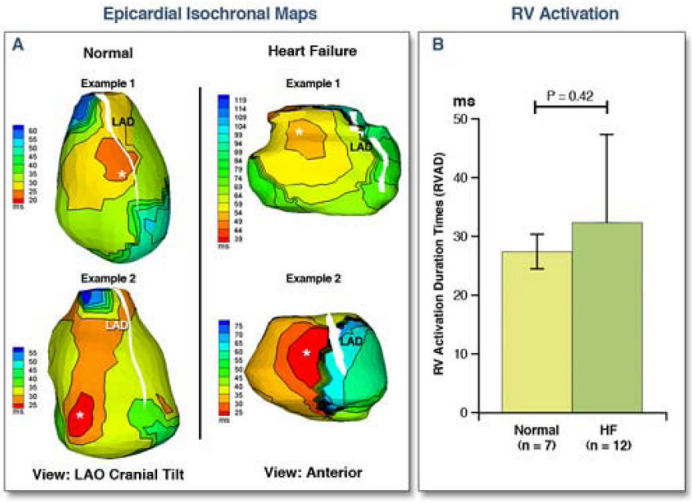

Figure 2. Intrinsic Conduction in Normals Contrasted to Heart Failure

A. Examples of 2 normal and 2 HF patients. RV breakthroughs (*) vary in both, normal for RBB-mediated depolarization. Following RV activation is radial and rapid.

B. RVAD in normals was similar to HF.

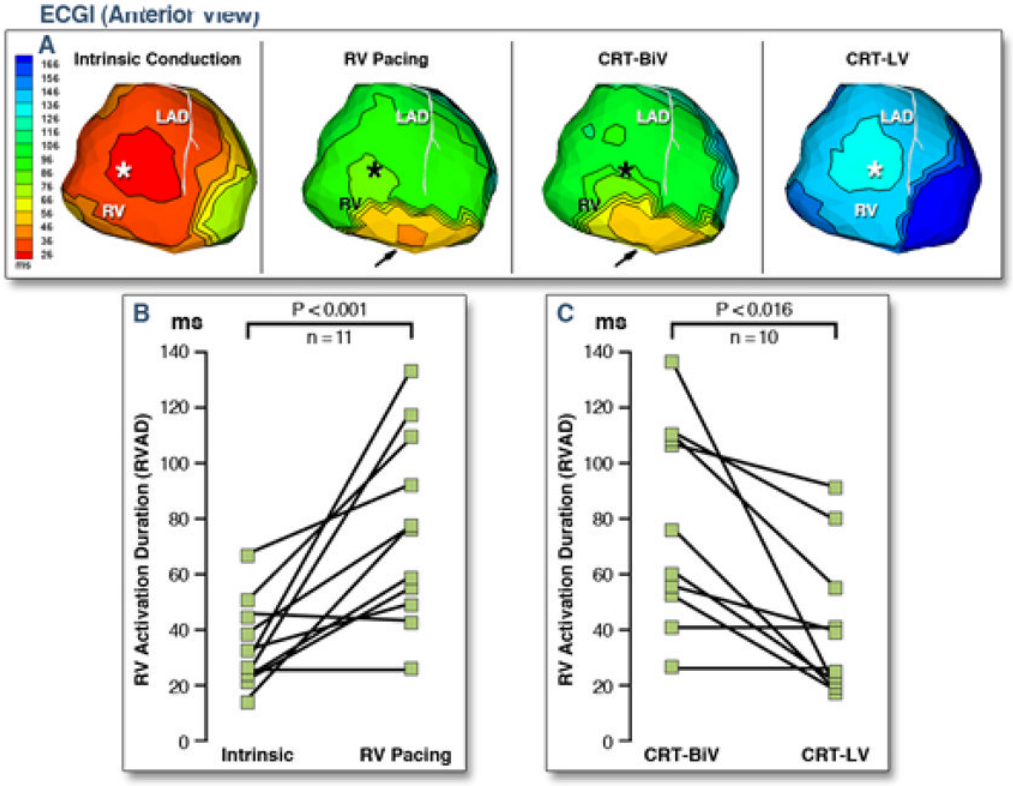

Figure 3. RV activation contrasted in different pacing modes

A. RV activation in a HF patient during intrinsic conduction contrasted with different pacing modes at identical atrioventricular intervals. During ***RV pacing***, isochronal activation crowding surrounds the paced site (arrow) indicating local conduction slowing not present during intrinsic conduction. Lateral wall breakthrough (*) from RBB conduction persists. ***CRT-BiV*** causes no appreciable change. During ***CRT–LV***, RV activation is identical to intrinsic conduction.

B. RV pacing increased RVAD in all except cases #3, 13.

C. CRT-LV reduced RVAD in all except case #4.

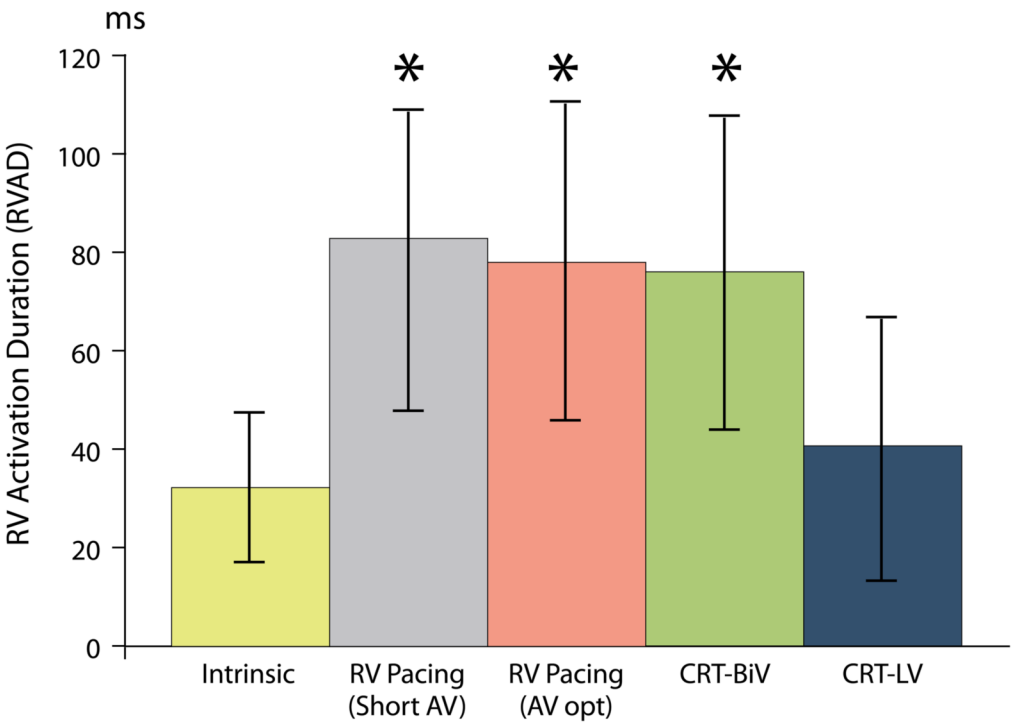

Figure 4. Effects of Pacing on RV Activation Durations in Heart failure

Summary of effects of RV activation in heart failure patients during intrinsic conduction vs. different pacing modes. RV activation durations were increased with RV pacing (short or optimized AV intervals) and during CRT-BiV but returned to normal with CRT-LV. *P<0.01 compared to intrinsic conduction.

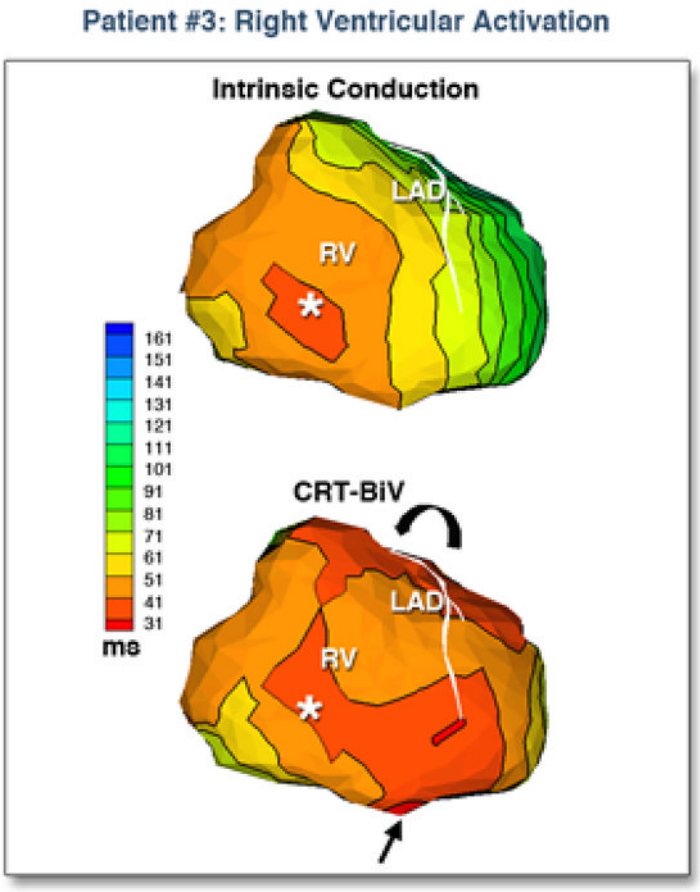

Figure 5. Patient #3: Right Ventricular Activation

During pacing, normal intrinsic breakthrough is preserved (*). The RV pacing electrode (straight arrow) contributes to inferoapical free wall activation and LV pacing to a superior wavefront (curved arrow). All 3 propagating wavefronts (red) merge from differing directions causing rapid free wall activation. Thus, although pacing altered activation pattern, functional conduction delays did not develop and RVAD (<30 ms) remained similar to intrinsic conduction.

Table 1

Demographics of heart failure patients and surface electrocardiogram (ECG) and baseline echocardiographic characteristics

Pt#	Gender	Age *(yrs)*	Pathology	LVEF *(%)*	ECG *(ms)*				Right Ventricle	
					QRSd	rS	PR	AVopt	Size	TR
1	M	75	ICM	25	160	100	210	180	Normal	Mild
2	M	76	ICM	10	*No AV conduction*			140	Normal	Mild
3	F	72	ICM	35	180	80	160	160	Normal	Mild
4	M	45	NICM	15	140	90	350	130	Normal	Mild
5	M	72	ICM	40	180	90	195	130	Mildly enlarged	Mild
6	F	71	ICM	20	*No AV conduction*			AF	Normal	Mild
7	M	72	ICM	20	140	80	160	130	Normal	Mild
8	M	82	NICM	20	130	85	140	130	Normal	Mild
9	M	53	ICM	10	194	94	199	189	Normal	Mild
10	M	50	NICM	20	138	80	220	180	Normal	None
11	F	40	NICM	35	86	60	180	80	Normal	None
12	M	68	NICM	25	100	50	220	180	Enlarged	Mild
13	M	54	NICM	35	130	60	200	180	Normal	None
14	M	19	NICM	15	180	50	200	120	Normal	None

M: male; F: female; ICM: ischemic cardiomyopathy; NICM: non-ischemic cardiomyopathy; LVEF: LV ejection fraction; QRSd: QRS duration; rS: duration of rS forces in precordial leads V1/2; AV opt: echocardiographically optimized atrioventricular interval; TR: tricuspid regurgitation.

Table 2

ECGI: Right ventricular activation duration (RVAD) during different pacing modes in HF patients

Pt#	Interval from CRT Implant to ECGI Study *(months)*	Intrinsic Conduction *(RVAD, ms)*	RV Pacing		CRT-BiV *(RVAD, ms)*	CRT-LV *(RVAD, ms)*	LV Lead Location
			Short AV Delay *(RVAD, ms)*	Optimal AV Delay *(RVAD, ms)*			
1	1.3	22	-	59	61	22	Lateral
2	8	-	67	-	67	63	Anterolateral
3	0.7	25	-	26	26	24	Anterolateral
4	7	25	116	117	107	91	Anterolateral
5	12	21	51	55	53	17	Lateral
6	5	-	96	98	96	84	Lateral
7	5	33	44	49	47		Lateral
8	15	20	-	-	76		Lateral
9	0.7	38	57	76	56	39	Lateral
10	6	28	119	133	137	22	Lateral
11	17	15	74	78	76	19	Lateral
12	8	50	110	110	110	45	Inferolateral
13	4	45	91	43	41	41	Lateral
14	5	67	87	92	109	80	Anterolateral
Mean	***6.8***	***32***	***83***	***78***	***76***	***46***	
SD	***5***	***15***	***26***	***33***	***32***	***27***	

AVD: atrioventricular delay; CRT: cardiac resynchronization therapy; BiV: simultaneous biventricular pacing mode; LV-left ventricular pacing.

RV free wall activation duration during intrinsic conduction in normals (n=7, not shown) was 28 ±3 ms[9]