Effect of atrioventricular optimization on circulating N-terminal pro-B-type natriuretic peptide following cardiac resynchronization therapy.

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Abstract

Aims

Following cardiac resynchronization therapy (CRT), atrioventricular (AV) optimization is not routinely practiced. To evaluate its clinical utility, we examined the effect of AV delay optimization on the prognostic biomarker N-terminal fragment pro-brain natriuretic peptide (NT-proBNP).

Methods and Results

We prospectively studied 72 patients (mean age73±12.5y, 70.8%male, 55.6%ischaemic) undergoing iterative AV optimization. Patients were divided into those whose nominal setting appeared ideal and not changed (Group 1, n=22) and those whose AV delay was optimized (Group 2, n=50). All patients underwent NT-proBNP assessment prior to CRT, pre- and a median 5 days post-optimization. Compared with Group 1, NT-proBNP fell significantly in Group 2 patients (median 474pg/ml) following optimization (p=0.00001). A significant change in filling pattern (defined as a change in AV delay>50ms) was required in 30% of patients, and it was this subgroup that derived the greater reduction in NT-proBNP levels(-1407pg/ml, IQR -3042 to -346pg/ml) compared to those requiring <50ms AV delay change(-125 pg/ml, IQR -1038 to 6 pg/ml), p=0.0011. The benefit of AV optimization was principally observed in reverse remodelling non-responders (median -2167pg/ml, IQR-3042 to -305pg/ml) and in patients with pseudonormal or restrictive filling pattern (median -1407pg/ml, IQR-2809 to -342), compared with those with more benign diastolic filling (median – 264pg/ml, IQR -1038 to -21) p=0.033.

Conclusions

In one-third of patients major filling pattern changes are achieved with AV optimization, associated with subsequent rapid falls in NT-proBNP. The greater the AV delay change, the larger the NT-proBNP fall, and non-responders and those with restrictive or pseudonormal filling despite CRT are most likely to benefit.

Key Words

Heart failure; Cardiac resynchronization therapy; Optimization of cardiac resynchronization therapy; Atrioventricular delay; N-terminal fragment pro-B type natriuretic peptide

Introduction

Following cardiac resynchronization therapy (CRT) the atrioventricular (AV) delay can be individually modified to maximally enhance ventricular filling and preload (AV delay optimization)**.** The physiological argument for optimizing preload, particularly in heart failure (HF) patients with progressively increasing age (1-4), is clear and the acute haemodynamic benefits of achieving AV synchrony are well described (5,6). Notably the landmark CRT trials all included AV optimization as standard procedure (7-10). This has led to recent guidelines advocating the role of routine AV delay optimization following CRT (11).

Despite this, AV delay optimization is rarely performed in clinical practice (12). The 2006 ACT registry (3130 patients with St Jude devices at 213 USA centres) showed routine AV optimization to be performed in only 6.3% of patients (13). This under-utilization is likely related in part to logistical issues of coordinating the echocardiographic and pacing services and in part due to the many disparate techniques available to perform AV optimization. Concern also exists around the lack of robust short and long term evidence of the clinical benefits of AV optimization. In the recent SMART-AV trial, using improvement in left ventricular end-systolic volume at 6 months as the primary endpoint, the study demonstrated no significant difference between the fixed AV delay and either echo or EGM derived optimized AV delay (14). The dearth of evidence has led some centres to advocate the use of AV delay optimization only in patients judged to be nonresponders, despite there being no evidence to underpin this practice (14).

For CRT AV delay optimization to become more widely accepted there is still a real need to establish its clinical utility. Further, clarification is also required to identify whether AV delay optimization is worthwhile in all patients who undergo CRT or whether it should be reserved just for nonresponders to CRT. Therefore, using the iterative technique recommended by the American Society of Echocardiography (11), we assessed the impact of AV delay optimization on the powerful prognostic biomarker N-terminal fragment pro-B type natriuretic peptide levels (NT-proBNP) (15,16). By comparing two groups; those whose nominal setting appeared ideal and was not changed (Group 1), and those whose AV delay was optimized (Group 2). We hypothesized that a programmed optimal AV delay would cause an early rapid reduction (within one week) in the NT-proBNP compared to patients not requiring programming of their AV delay.

Methods

Study Population. All patients undergoing clinical CRT implantation in accordance with international guidelines (17) at St George's Hospital between 2009 and 2010 were invited to take part in the study. All patients were required to be more than 3 months post CRT and to demonstrate sinus rhythm, and to be optimised on stable heart failure (HF) medications. All patients had a fixed 'out-of-the-box' AV delay device setting following implantation. Patients were excluded from the study if a technically satisfactory echocardiogram could not be obtained.

Study protocol. The clinical status (New York Heart Association HF classification-NYHA) and left ventricle (LV) functional assessment by 2D-transthoracic echocardiography was assessed prior to CRT implantation and at the time of AV optimization. Blood samples for measurement of NT-proBNP levels were also drawn at baseline (one day prior to CRT implantation), immediately prior to AV optimization and then within 1 week following AV optimization. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the local Research Ethics Committee. All patients provided written informed consent.

Imaging

The echocardiographic images were recorded with a Vivid 7 ultrasound system (Vingmed Ultrasound AS, General Electric, Horten, Norway) equipped with a 2.5- to 5-MHz imaging probe and off-line cine-loop analysis software. Measurements made included left ventricular ejection fraction (LVEF), LV dimensions/volumes, severity of

mitral regurgitation (MR) and trans-mitral pulsed-wave (PW) Doppler derived diastolic parameters including the early diastolic (E) and atrial (A) wave velocities, the E/A ratio, the deceleration time (DT) of the E-wave and the annular septal tissue velocity (E') . In our study the presence of mitral E/A ratio of <0.8 or DT >200ms was considered evidence of abnormal relaxation (IR). A pseudonormal (PN) was defined by the presence of mitral E/A of 0.8 to 1.5 and DT of 160 to 200ms, but distinguished from normal filling pattern by a septal E' of <8cm/s. Restrictive diastolic filling was defined as mitral E/A >2 or DT < 160ms. (18)

AV Optimization

The iterative method was used for the optimization of the AV delay (7,11). The technique involves observing the mitral PW Doppler LV filling waves as the AV delay is programmed long (240ms) and progressively decreased in 20ms steps until there is compromise of the left atrial contribution to LV filling (minimum AV delay 40ms). The AV delay is then increased in 10ms increments till there is no further A wave attenuation and the diastolic filling time has been maximised. This process takes approximately 15 to 20 minutes. The interventricular delay was set at 0 ms (simultaneous LV and RV pacing).

Plasma NT-proBNP measurements.

Patients rested in the supine position for at least 15 min before blood sampling. All samples were analysed for NT-proBNP using an Immulite 2500 (Siemens Healthcare Diagnostics). The interassay coefficient of variation was 5.0% at 380 ng/L, 4.4 at 8700 ng/L, 5.0% at 13000 ng/L, with detection limit 20 ng/L and upper measuring limit 35000

ng/L. All kits had the same lot number. The normal NT-proBNP range of a healthy population is <125 pg/mL, Analysis of the samples was performed by an operator blinded to the results of the optimization process.

Data Analysis

For the purposes of data analysis patients were divided into 2 groups: Group 1-Patients who did not require alteration to their trans-mitral filling pattern. Group 2- Patients who required modification of their AV delay. Results are presented as mean ±1 standard deviation (SD) for continuous normally-distributed variables, as median [interquartile range] for continuous skewed distributed data, and as percentages for categorical data. Analysis of normality was performed with the Kolmogorov–Smirnov and Shapiro-Wilk test. Comparison of normally distributed continuous variables was performed using Student's t test for paired and unpaired data. Non-normally distributed variables were compared using Mann-Whitney Rank Sum tests and Kruskal-Wallis tests. Comparison of categorical data was performed using Chi-square and Fisher's Exact Tests where appropriate. Linear regression analysis was calculated to evaluate the association between changes in AV delay and NT-proBNP. Using the median reduction of NT-proBNP observed in Group 2 (>474 pg/ml) as the cut off threshold, sensitivity, specificity, likelihood ratio, accuracy and p values were calculated individually at each tabulation (from 30ms up to 100ms change in AV delay). The best cut-off point corresponds to the AV delay change with the best likelihood ratio, highest accuracy, and the most significant p value. Statistical significance was established as $p<0.05$. All analyses were performed with SPSS statistical package for Windows (SPSS 17.0, Chicago, Illinois).

Results

Study Population

One hundred and sixty three patients were considered for enrolment into the study. After meeting exclusion criteria (atrial fibrillation in 28 patients, medication change required in 21 patients), 114 patients were considered for recruitment into the study. A further 33 patients declined to consent and 9 patients were unable to attend for repeat blood test, leaving a final study population of 72.

The baseline patient demographics and echocardiographic characteristics prior to CRT implantation and at the time of AV optimization are shown in Table 1. All study patients had LBBB morphology with QRS duration > 120ms. No patient had RBBB or nonspecific interventricuular conduction delay. The majority of patients were clinical responders (improvement by at least 1 NYHA classification from baseline) with 69.5 % found to be in NYHA class I or II functional class. Moreover, 35% (25/72) of patients demonstrated evidence of significant LV reverse remodelling post CRT, as defined by ≥ 15% reduction in LV end systolic volume. With regard to lead positioning the LV lead was placed in a posterolateral (n=29), posterior (n=27), or lateral (n=16) cardiac vein. The right atrial lead was positioned in the right atrial appendage and the right ventricular lead was placed in the septum (n=53) or apex (n=19) of the right ventricle. AV delay optimization took place after a median 93 (IQR 79-111) days following CRT. Of the 72 patients, 22 (30.5%) did not require change to their 'box setting' AV delay (Group 1).

Comparison of Groups.

Pre-CRT. Both Group 1 and Group 2 had similar baseline demographics (Table 1). However, there was evidence of greater electrical dyssynchrony prior to CRT in Group 1 (QRS duration 176 ± 29 ms versus 152 ± 26 ms, p=0.005) compared to Group 2.

At the time of AV optimization. Both groups were observed to have a similar response to CRT, albeit with a trend towards more positive LV reverse remodelling in Group 1, with 45% of patients in Group 1 (with pre-existing optimal delay) showing evidence of ≥ 15% reduction in LV end systolic volume compared to the 30% of patients requiring AV optimization (p=0.2). Patients in Group 2 were also observed to have more severe MR with 42% in Group 2 vs. 18.2% in Group 1 demonstrating evidence of MR grading 3 and 4 (p=0.044). Group 2 patients also had correspondingly higher median NT-proBNP following CRT compared to Group 1 (Group 2: 2915 pg/ml (IQR 1386-8398 pg/ml) vs. Group 1: 1272 pg/ml (IQR 603-3246 pg/ml, p=0.022).

Atrioventricular delay optimization

The AV delay required alteration in 69% of patients (50/72) with the majority of these patients requiring atrial sense programming (66.7%). (The baseline and final median AV delay were 120ms and 100ms (IQR 60-170ms) respectively).

There was an observed wide spectrum of change in the AV delay with a median change in AV delay of 50 ms from baseline (IQR 40 to 60 ms). (Figure 1)

Effect of AV delay programming on NT-proBNP

Change in NT-proBNP. After a median 5 days (IQR 2-5) following AV optimization, the NT-proBNP significantly dropped by a median of 474 pg/ml (IQR -61 to -1822 pg/ml reduction, p=0.000005) following AV delay manipulation in Group 2. In comparison the NT-proBNP increased by a median 80 pg/ml (IQR -32 to +244 pg/ml, p=0.12) in Group 1 after a median 5 days (IQ 5 to 7 days). (Figure 2) To verify that the significant difference between the groups was not simply a factor of the larger initial NT-proBNP in Group 2 (which would be expected to result in larger absolute changes in NT-proBNP), we also examined percentage change. In the optimised Group 2 the mean percentage change in NT-proBNP following optimisation was a fall of 21% (mean fall of 1081ng/l) whereas in the non-optimised Group 1, the mean percentage change in NT-proBNP was a small rise of +7% (mean rise of 171ng/l, p= 0.0004).

Relationship of AV programming and change in NT-pro BNP.

An inverse regression equation was found to best-fit with the variation of change to the AV delay from baseline with NT-proBNP fall (Figure 3). The reduction in NT-proBNP observed in those patients requiring AV delay optimization yielded a median value of 474 pg/ml. An adjustment of the AV delay of 50ms from baseline was found to have the highest accuracy in producing a NT-proBNP reduction of greater than 474 pg/ml. This was reached in 32% (23/72) of all study patients with an associated likelihood ratio for a reduction in NT-pro BNP (of > 474 pg/ml) of 2.21 with an accuracy of 0.76. (Figure 4) Moreover patients requiring AV delay change ≥ 50 ms showed a median fall in NT-proBNP of 1407 pg/ml (IQR -3042 to -346 p/ml)) compared to a fall of 125 pg/ml (IQR -

1038 to +6 pg/ml) (p=0.0011) observed in those patients with a ≤ 50 ms AV delay change.

Effect of AV delay programming on NT-pro BNP in specific subgroups

Responders versus Nonresponders. Absence of response to CRT at the time of AV optimization (in terms of LVESV reduction <15% and no improvement in NYHA class) was noted in 15/50 (30%) of the patients in Group 2, and it was this cohort who derived the most benefit following AV delay adjustment with a median drop in NT-proBNP of 2167 pg/ml (-3042 to -305), with 73% showing a NT-proBNP reduction greater than median threshold observed in the study (474 pg/ml). Also, amongst patients who derived symptomatic benefit (improvement >1 NYHA class) but showed no evidence of significant LV reverse remodelling (n=20/50 40%) there was a modest reduction in the NT-proBNP following AV optimization (median -694.5 pg/ml (-1279 to -248)). In contrast, those patients who showed a positive response to CRT (n=15, 30%) as evidenced by positive reverse LV remodelling (>15% reduction in LVESV) appeared not to derive so much benefit with only a slight reduction seen in their median NT-proBNP (-65.5 pg/ml (-262 to +25)). Despite this, 3/15 patients (20%) from the responder cohort demonstrated a NT-proBNP reduction greater than 474 pg/ml after AV optimization. All three of these patients had required a change in AV delay >50ms. Furthermore, there was no significant difference in the magnitude of change in AV delay between CRT responders and nonresponders (p=0.22).

Doppler transmitral LV filling pattern. At the time of the AV delay optimization, the majority of patients 54% (n=27) exhibited an IR diastolic filling pattern by Doppler echocardiography. A further 38% (n=19) patients showed PN or restrictive LV filling. Interestingly, those patients demonstrating a normal or IR pattern often required the AV delay to be reduced to prevent E/A fusion due to the prolonged relaxation time (median reduction in AV delay of 40ms IQR -58 to +38), whereas in patients with PN or restrictive filling, a longer AV delay was required (median increase in AV delay of 35ms IQR -43 to +65). Furthermore, it was the PN/restrictive group who showed a significantly more marked reduction in the NT-proBNP (median -1407 pg/ml, IQR -2809 to -342) following AV adjustment compared to those patients with less severe diastolic filling patterns (normal or IR) (median – 264 pg/ml, IQR -1038 to -21) p=0.033 (Figure 5).

Follow up LV remodeling data

At a median follow up period of 121 days (IQR 91- 175), 34 out of the 50 patients in Group 2 had a follow up echocardiogram performed. When subgrouping patients with regard to the response in NT-proBNP change following AV optimization it was reassuring to note that there was a trend towards improved LV remodelling at follow up [although not statistically significant] in those patients with a > 474pg/ml fall in NT-proBNP, despite clearly demonstrating evidence of worse LV function at the time of optimization compared to the group with less < 474pg/ml fall in NT-proBNP. (Table 2)

Discussion

This is the first study to report the neurohormonal impact, as assessed by NT-proBNP, of iterative AV delay optimization on HF patients following CRT. In 70% of individuals, AV delay continued to be suboptimal 90 days post CRT implantation and subsequent modulation of the AV delay initiated a significant drop in NT-proBNP (median 474 pg/ml) within a week following optimization compared with those patients not requiring AV optimization (p=0.00001). Furthermore, a significant change in filling pattern was required in 30% of patients, defined as a change in their AV delay of greater than 50 ms, and it was this subgroup that derived the greatest reduction in NT-proBNP levels (1407 pg/ml (IQR -3042 to -346 pg/ml) compared to those patients requiring less than a 50 ms AV delay change (median reduction 125 pg/ml (IQR -1038 to 6 pg/ml) (p=0.0011).

Moreover, the benefit of AV optimization as defined by the magnitude of reduction in NT-proBNP was principally observed in 2 categories of patients at the time of optimization:

1- Nonresponders to CRT with respect to reverse remodelling plus symptoms (defined as those patients who demonstrated ≤ 15% reduction in their LV end systolic volume). Seventy three percent of non-responders demonstrated a fall > 474pg/ml in NT-proBNP post AV optimization.
2- Severe heart failure with pseudonormal or restrictive filling pattern despite CRT.

Physiological impact of AV optimization.

Understanding the pathophysiology underpinning BNP synthesis and function provides a valuable insight into the possible mechanistic benefit seen in patients undergoing AV delay optimization. The natriuretic peptide hormones are produced as a consequence of

cardiac myocyte stretching due to increased intracavity pressures in both atria and ventricles. Thus an AV delay programmed too long can cause early LV filling (E wave) to coincide with atrial contraction (A wave), and consequently reduce diastolic filling. A long AV delay may also lead to diastolic MR in heart failure patients due to high LV end diastolic pressures and the hiatus between atrial contraction and subsequent ventricular contraction. Conversely, an over-short AV delay prevents completion of ventricular filling, because ventricular contraction closes the mitral valve, truncating or even obliterating the atrial filling 'A' wave. Thus normalization in the mechanical timing between the LA and LV contraction during AV optimization may lead to:

-improved LV diastolic filling and corresponding reduction in left atrial (LA) pressures

-subsequent enhanced LV systolic function

-and reduced diastolic mitral regurgitation

and may account for the reduction in the NT-proBNP observed in our study.

Of note in atrial fibrillation patients with normal systolic function, there is an acute drop in natriuretic peptides (within 24 hours) following electrical cardioversion to sinus rhythm (19). The mechanism for this reduction in NT-proBNP is thought to be due to restoration of LA systole and thus alleviation of the elevated LA pressure and corresponding improvement in LV diastolic filling. Similarly a properly timed, effective atrial contraction after AV optimization may cause a similar drop in the LA mean pressure and may contribute to the reduction in NT-proBNP observed in our study, particularly in patients with elevated LV end diastolic pressures and left atrial pressures.

With maximization of the LV preload, studies have clearly shown that the addition of an optimal AV delay is associated with a clear haemodynamic benefit and improvement in systolic function. In PATH-CHF study cohort, Aurrichio et al were able to demonstrate that individualized AV delay manipulation lead to a significant ($p<0.0001$) acute increase in invasive LV systolic parameters including the systolic pulse pressure (+16%) and LV dp/dt (a preload dependent marker of LV contractility) by approximately 25% (5). Similarly, this was non-invasively shown by Jansen et al, who observed a +32 ± 21% increase in LV dp/dt (derived from the mitral regurgitant jet on echocardiography) following AV optimization (20). Although, an acute increase in LV dp/dt that does not necessarily translate into clinical benefits (21).

Additional improvement in diastolic function has also been reported following AV delay intervention. In a retrospective 215 patient study, 9% patients showed improvement in ≥ 1 diastolic function stage after undergoing AV optimization (Ritter or iterative method) (22). Stahlberg et al, by means of an indirect estimate of the left atrial end-diastolic pressure - derived from the estimated pulmonary artery diastolic pressure obtained from a sensor in the right ventricular outflow tract (Implantable Haemodynamic Monitor (IHM) Chronicle®, Medtronic Inc, USA) - were able to show lower LA derived pressures following AV optimization (21.9 ± 8.1 mmHg vs. 23 ± 7.7 mmHg respectively, $p<0.05$) (23). Recently, using a novel direct continuous invasive ambulatory LA monitoring system (HeartPOD™ ISL St Jude Medical) the optimal AV delay (also using the transmitral iterative method) clearly correlated with a reduction in the LA pressures and improved LA filling profile (24).

Who should undergo AV optimization?

Some have advocated AV delay optimisation only in the 'nonresponder' group to CRT (14). To date there has been no published evidence to substantiate this position. Our data to some extent supports this viewpoint, in that the derived benefit from AV optimization appeared to have the greatest impact on those patients with worse systolic function at the time of optimization. However, leaving a suboptimal AV delay after an expensive device implant would seem counterintuitive, and 3 out of 15 responder patients (20%) showed a >474pg/ml improvement in NT-proBNP following AV optimization, indicating that even in the responder group, if the AV delay changes required are large, then a further improvement in BNP is seen, above that for CRT alone**.** Notably in our study the benefit of AV optimization was also observed in patients who improved their clinical status (NYHA class reduction ≥ 1) without evidence of positive reverse remodelling. Often it is this subgroup of symptom responders who are denied access to CRT optimization clinics. Furthermore, the entire concept of response to therapy is problematic.(25) Not only is there no agreed consensus on the definition of response but clinical improvement derived from NYHA can be biased by 'placebo-related improvement' and can account to 15-30% of patients labelled as clinical responders (26), thereby excluding potential nonresponders wrongly labelled as clinical responders.

A clear benefit was also observed in those patients with moderate to severe diastolic LV impairment as evidenced by transmitral PW Doppler inflow patterns (PN and restrictive filling patterns) at the time of AV optimization. Our findings would concur with previous studies that have shown that increases in stroke volume (as measured by aortic VTI) are

greater in those patients with PN/Restrictive filling patterns compared to the IR group following AV optimization. (27)

Clinical applications

Although our data has demonstrated that AV optimization post CRT can produce a significant reduction in NT-proBNP, there is a more pronounced impact in patients deemed to be nonresponders to CRT. Nonresponse to CRT remains a major clinical concern and the profound fall in NT-proBNP observed in this cohort confirms the importance in obtaining an optimal AV delay post CRT. Moreover, there is a need for further evaluation in a larger prospective study to assess if AV delay manipulation can convert so-called nonresponders to responders as judged by symptoms and LV reverse remodeling.

Study limitations

Firstly, it is difficult to separate those effects due to CRT alone from those due to AV delay optimization on the trajectory fall observed in the NT-proBNP. However due to the rapid fall seen in the NT-proBNP over a median 5 day period following AV optimization, one can infer that AV delay manipulation was the main contributor to the reduction seen in the NT-proBNP. Furthermore, the dose response relationship between fall in NT-proBNP and extent of change in optimal AV delay supports causality. Secondly, the short term nature of our study does not provide information about the long term clinical outcome of AV optimization. However, the inclusion of NT-proBNP, a useful prognostic marker in HF patients, may provide some clues to the possible translation to long term prognosis. We did not perform ventriculoventricular (VV) optimization as randomised

trials have shown lack of benefit following VV optimisation (27, 28). Hence, we cannot exclude the impact that VV optimization may have had on our study results.

Conclusion

Routine post CRT AV optimization employing the iterative method results in changes to the AV delay in the majority patients. In almost one third of patients, major changes to filling pattern can be achieved, associated with a subsequent rapid, significant fall in NT-proBNP. The greater the change needed in AV delay, the larger the fall in NT-proBNP and non-responders and those with severe heart failure and restrictive or pseudonormal filling despite CRT are most likely to benefit.

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Figure legends

Figure 1. Change made in AV delay (ms) during AV delay programming in the Group 2 cohort (n=50).

Figure 2. The effect of AV optimization on plasma NT-proBNP levels (pg/ml).
Comparative distribution of NT-proBNP levels pre and post AV optimization in Groups 1 and 2 are illustrated. Corresponding median NT-proBNP are presented as median values (interquartile range) for pre CRT, pre and post AV optimization.

Figure 3. Inverse regression analyses correlating the change made in AV delay and the change observed in NT-proBNP in the Group 2 cohort. [pre and post AV optimization]

Figure 4. Sensitivity and specificity cut off assessment with an adjustment of the AV delay >50ms from baseline found to have the highest accuracy in producing a NT-pro BNP reduction of greater than 474 pg/ml.

Figure 5. Effect of AV delay programming on plasma NT-proBNP sub-grouped on the basis of Doppler transmitral LV filling pattern. [pre and post AV optimization]
IR= impaired relaxation
PN= pseudonormal

Figure 1

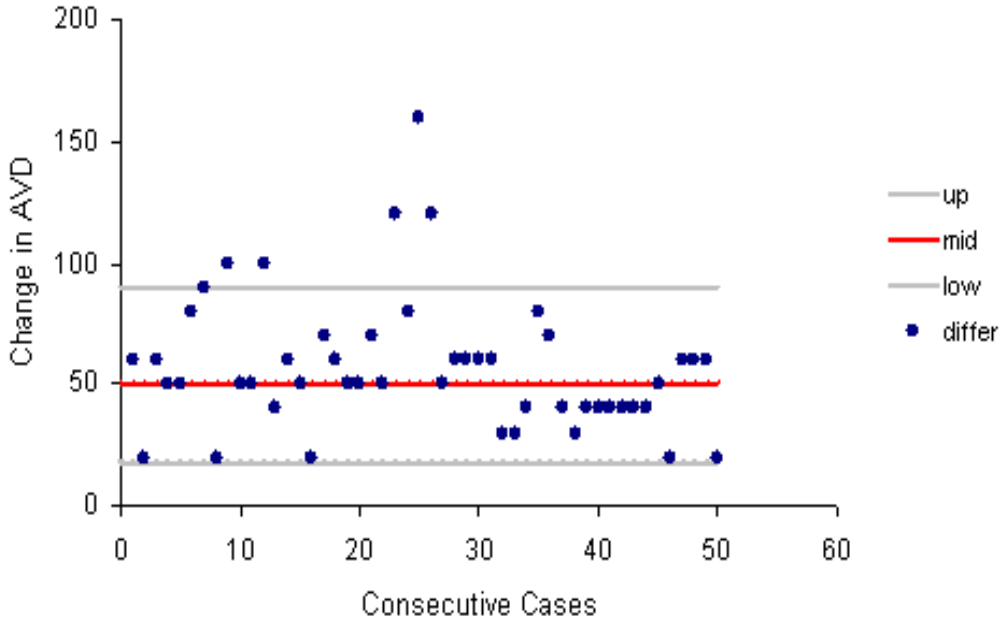
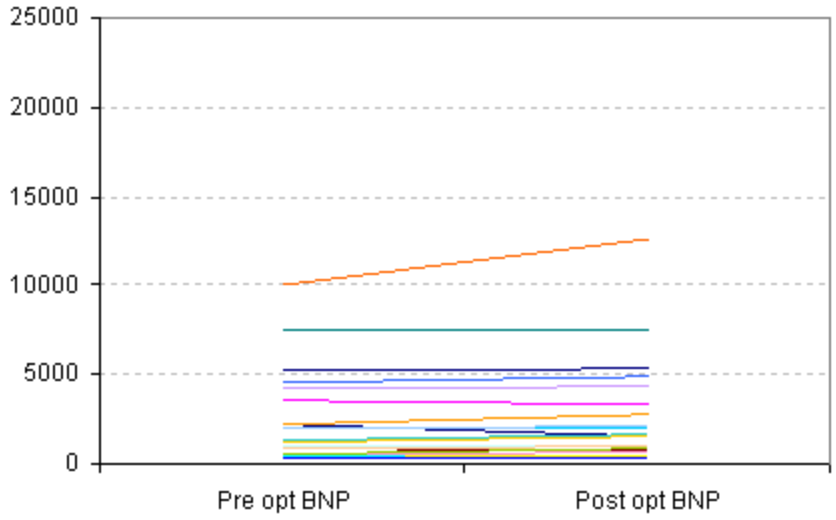

200
150
100
50
0
Change in AVD
0
10
20
30
40
50
60
Consecutive Cases
up
mid
low
differ

Figure 2

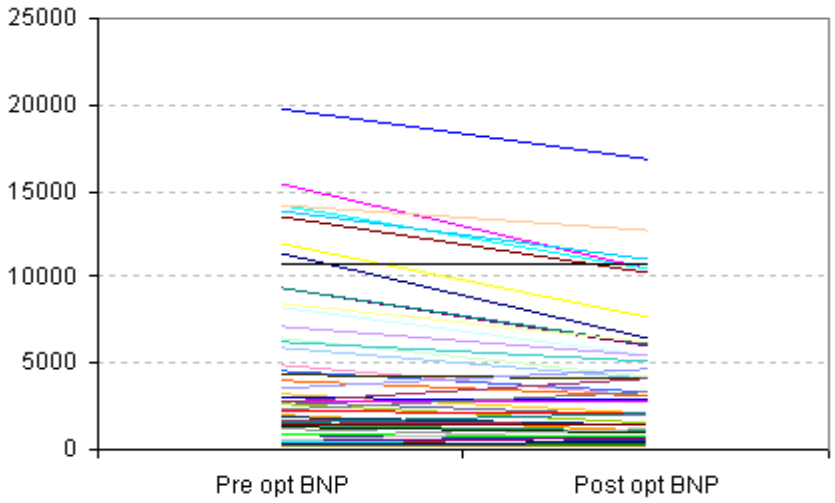
Group 1



BNP	pre CRT	pre OPT	p value
1st Q	1712	603	
median	3517	1272	**0.0009**
3rd Q	5603	3246	

BNP	pre OPT	post OPT	p value
1st Q	603	734	
median	1272	1578	0.12
3rd Q	3246	3158	

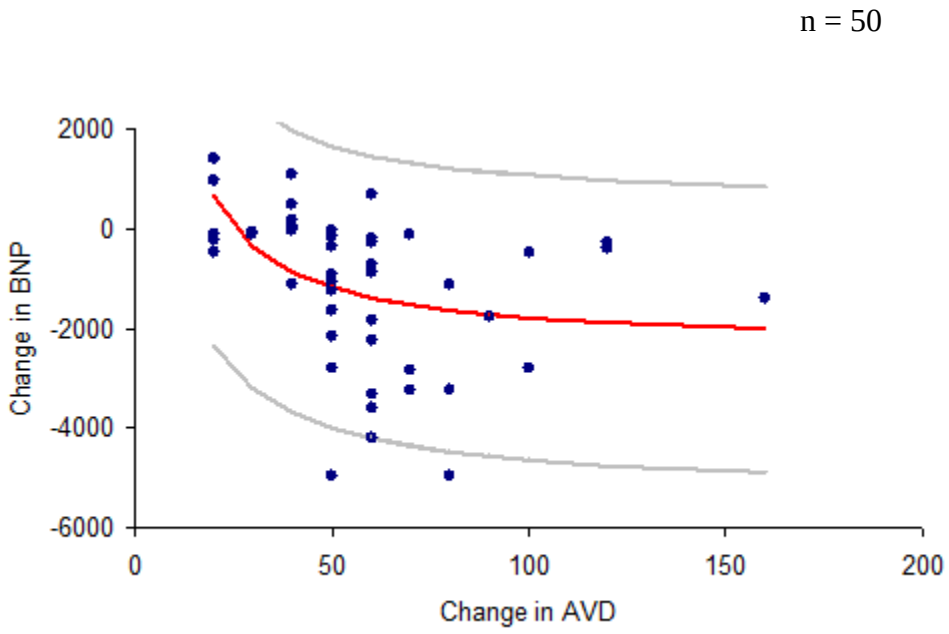
Group 2



BNP	pre CRT	pre OPT	p value
1st Q	2154	1386	
median	5916	2915	**0.000009**
3rd Q	13317	8398	

BNP	pre OPT	post OPT	p value
1st Q	1386	1069	
median	2915	2924	**0.000005**
3rd Q	8398	5499	

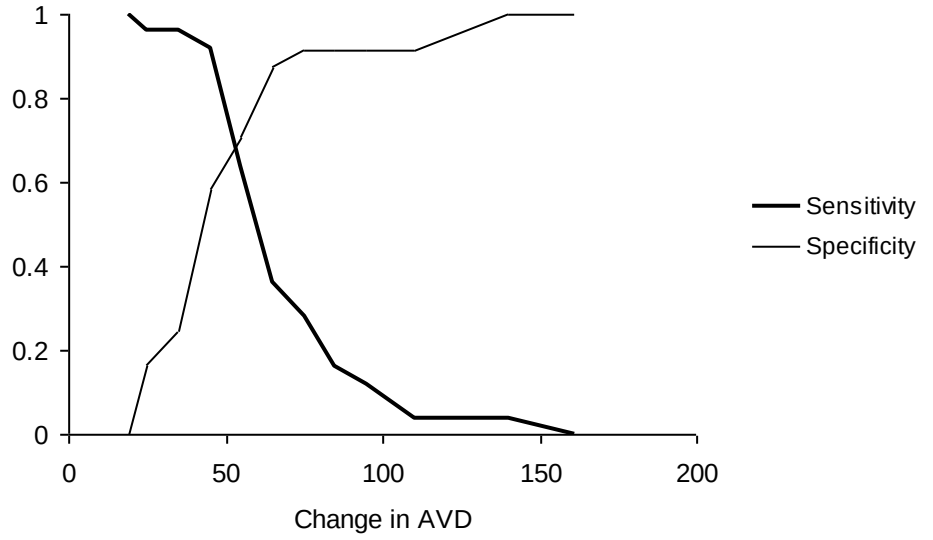
Figure 3



Best Fit Line = Inverse regression with 95% prediction intervals

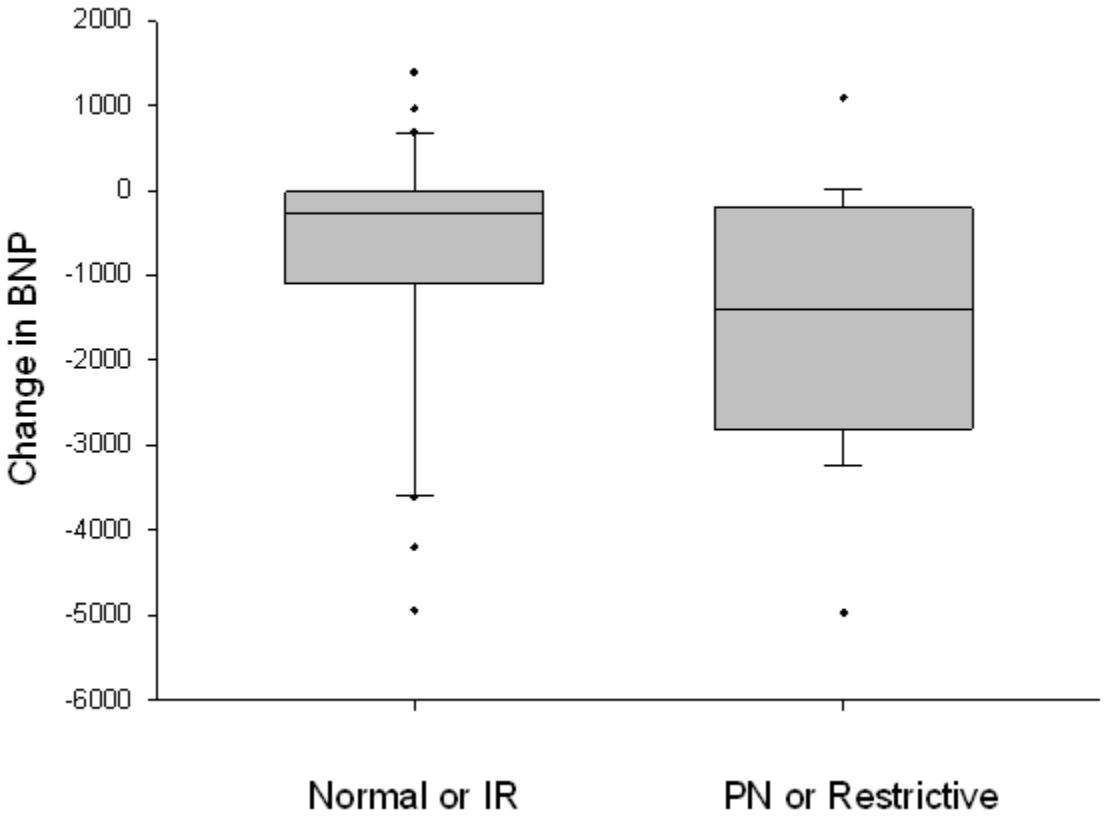
Equation	R	F	df1	df2	Sig.	Constant	b1
Inverse	-0.445	11.64	1	47	0.0013	-2391	60604

Figure 4



AVD change (ms)	n	sensitivity	specificity	likelihood ratio	accuracy	p value
30	24	0.96	0.17	1.15	0.57	0.19
40	24	0.96	0.25	1.28	0.61	0.049
50	23	0.92	0.58	2.21	0.76	0.0002
60	16	0.64	0.71	2.19	0.67	0.015
70	9	0.36	0.88	1.47	0.61	0.06
80	7	0.28	0.92	3.36	0.59	0.14
90	4	0.16	0.92	1.92	0.53	0.67
100	3	0.12	0.92	1.44	0.51	1.00

Figure 5



Median change NTproBNP	**-264 pg/ml**	**-1407 pg/ml**	**p=0.033**
IQR	**[-1038 to -21]**	**[-2809 to -342]**	

Table 1. Patient Characteristics including subgroup demographics

Variable Baseline Patient Characteristics	Total Study Population (N=72)	Group 1 No AVD change (N=22)	Group 2 AVD change (N=50)	Global P Value Grp 1 vs. 2
PRE CRT				
Male	**51 (70.8%)**	14 (63.6%)	37 (74.0%)	**0.37**
Age (years)	**73±12.5**	72±9.7	74±13.5	**0.16**
QRS (ms)	**160±29**	176±29	152±26	**0.005**
PR interval (ms)	**200(166-238)**	198 (157-238)	200 (174-236)	**0.53**
Non Ischemic	**32 (44.4%)**	8 (36.4%)	24 (48.0%)	**0.15**
NYHA III	**50 (69.4%)**	19 (86.4%)	31 (62.0%)	
NYHA IV	**22 (30.6%)**	3 (13.6%)	19 (38.0%)	**0.039**
Diabetes	**13 (18.1%)**	5 (22.7%)	8 (16.0%)	**0.52**
Hypertension	**30 (41.7%)**	8 (36.4%)	22 (44.0%)	**0.54**
NT pro-BNP (pg/ml)	**5105 (1750-11712)**	3517 (1712-5603)	5916 (2154-13317)	**0.072**
LVEDV (ml)	**218±60**	228±68	212±56	**0.41**
LVESV (ml)	**160±59**	165±65	157±57	**0.55**
EF (%)	**29±7.6**	28±8.6	29±7.1	**0.86**
LV inflow pattern				
Normal/ IR	**26**	11	15 (30%)	
PN/ Restrictive	**42**	10	32 (54%)	**0.19**
MR grading				
1-2	**30 (41.7%)**	10 (45.5%)	20 (40.0%)	
3-4	**35 (48.6%)**	10 (45.5%)	25 (50.0%)	**0.68**
POST CRT at the time of AV optimization				
Time to AV Opt (days)	**93 (79-111)**	99 (92-116)	91 (64-99)	**0.027**
NYHA I	**4 (5.56%)**	2 (9.09%)	2 (4.0%)	
NYHA II	**46 (63.9%)**	16 (72.7%)	30 (60%)	**0.26**
NYHA III	**22 (30.6%)**	4 (18.2%)	18 (36%)	
Creatinine (umol/L)	**112 (88-141)**	117 (89-137)	109 (85-147)	**0.80**
NT proBNP (pg/ml)	**2302 (901-6275)**	1272 (603-3246)	2915 (1386-8398)	**0.022**
ACEI	**62 (86.1%)**	19 (86.4%)	43 (86.0%)	**0.65**
Beta-Blockers	**57 (79.2%)**	19 (86.4%)	38 (76.0%)	**0.48**
Diuretics	**55 (76.4%)**	18 (81.8%)	37(74.0%)	**0.74**
Spironolactone	**21 (29.2%)**	7 (31.8%)	14 (28.0%)	**0.77**
Digoxin	**2 (2.78%)**	1 (4.55%)	1 (2.0%)	**0.53**
Amiodarone	**11(15.3%)**	3 (13.6%)	8 (16.0%)	**1.00**
LVEDV (ml)	**187±61**	185±63	187±61	**0.80**
LVESV (ml)	**121±60**	113±52	125±64	
EF (%)	**39±12**	40±11	37±12	**0.17**

LV inflow pattern				
Normal/ IR	49 (68.1%)	19 (86.3%)	30 (60%)	
PN/ Restrictive	23 (31.9%)	3 (13.6%)	20 (40%)	**0.08**
MR grading				
1-2	**46 (63.9%)**	18 (81.8%)	28 (56.0%)	
3-4	**25 (34.7%)**	4 (18.2%)	21 (42.0%)	**0.044**
Clinical Responder*	**52 (72.2%)**	17 (77.3%)	35 (70.0%)	**0.53**
Echo Responder	**25 (34.7%)**	10 (45.5%)	15 (30.0%)	**0.20**

Data are presented as the mean value±SD for continuous variables and number and percentage of patients for nominal data and median (25^{th}-75^{th} percentile) for non-parametric variables.

CRT-P= cardiac resynchronization therapy- biventricular pacing only; ACEI= angiotensin converting enzyme inhibitor; EF= ejection fraction NYHA= New York Heart Association; LVEDV= left ventricular end diastolic volume; LVESV= left ventricular end systolic volume; IR= impaired relaxation; PN= pseudonormal.

* Clinical responder defined as ≥ 1 reduction in NYHA class post CRT.

 Echo responder defined as patients exhibiting ≥ 15% reduction in LVESV post CRT.

Table 2. Comparison of echocardiography follow up data for patients with > 474pg/ml fall in NT-proBNP versus patients with < 474pg/ml fall in NT-proBNP post AV optimization.

	> 474pg/ml fall in NT-proBNP n=17		**p**	**< 474pg/ml fall in NT-proBNP n=17**		**p**
	CRT Opt	**Follow up***		**CRT Opt**	**Follow up***	
LVED	6.4 (0.6)	6.4 (0.7)	1.0	5.7 (0.9)	5.7 (1.0)	0.69
LVEDV	231 (46)	218 (55)	0.31	160 (51)	169 (50)	0.44
LVES	5.6 (0.74)	5.4 (1.1)	0.26	4.5 (1.0)	4.3 (1.2)	0.17
LVESV	168 (77)	163 (57)	0.74	96 (50)	93 (48)	0.67
EF	30 (9) 30 (25-35)	33 (12) 34 (25-40)	0.16	38 (13) 40 (25-50)	45 (15) 45 (30-57)	**0.05**

*Follow up median 120 days (IQR 91-175) post CRT optimization

Data are presented as the mean value±SD for continuous variables and median (25^{th}-75^{th} percentile) for non-parametric variables.

EF= ejection fraction LVEDV= left ventricular end diastolic volume; LVESV= left ventricular end systolic volume.