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The Effect Of Optimal Cardiac Resynchronization Therapy Pacing Rate In Non-Ischemic Heart Failure Patients On The Quality Of Life And Echocardiographic Findings.

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Abstract:

Cardiac resynchronization therapy (CRT) has become an important treatment strategy for a select group of heart failure (HF) patients, few studies have examined the optimal basal atrial pacing rate and its impact on long-term outcome in CRT patients.

30 CRT patients were divided to two groups and programmed to 70 – 80 bpm basal atrial pacing rates respectively for 6 months with comparing the effect of each programming on the quality of life using Minnesota heart failure questionnaire and echocardiographic findings (EF, LVEDD , LVESD , LVEDV, LVESV).

There was a highly significant difference between both groups as group 2 (with basal heart rat=80) had higher MFHQ after the programming with mean=67.2 ±9.1 vs group 1 (with basal heart rate =70) with mean 50.6 ±8.3 (P-value<0.001). Also, there was no significant effect of the programming on NYHA of group I (P-value=0.301) but, the programming increase the NYHA of group II significantly (P-value=0.014). The programming didn't affect the (EF, LVEDD, LVESD, LVEDV, LVESV) of both groups significantly (p-value = 0.916, 0.786 for both groups). The lower basal trial pacing rate the better quality of life and the lower NYHA class.

Keywords: CRT, pacing rate, MLHFQ, quality of life

1. Introduction:

Heart failure (HF) is a global public health problem affecting millions worldwide. Approximately 1–2% of the adult population in developed countries has HF, with the prevalence rising to ≥10% among persons 70 years of age or older. [(1)]

Cardiac resynchronization therapy (CRT) has become an important treatment strategy for a selected group of heart failure (HF) patients with electrical dyssynchrony, and several studies have documented the beneficial effects of CRT on mortality and morbidity in such patients.[(2)] Although the majority of correctly selected patients respond favorably to CRT, 25–30% show little or no improvement after device implantation. To increase response rates, resources have focused on programming optimization, particularly atrioventricular (AV) and interventricular (VV) timing intervals [(3)].

However, few studies have examined the optimal basal atrial pacing rate and its impact on long-term outcome in CRT patients. Increasing pacing rates in BiV mode have demonstrated positive acute hemodynamic effects (e.g., decreased filling pressure and increased cardiac output). Furthermore, an increased atrial basal pacing rate and HR (heart rate) could prove to be favorable in HF patients with chronotropic incompetence (attenuated HR response to exercise) which is associated with increased cardiac and all-cause mortality[(4)].

2. Patients and Methods:

Our study included 30 non responders CRT patients with refractory congestive heart failure to optimum doses of guideline directed medical therapy.The study started in august 2017 and ended in july 2019. All patients provided written informed consent for participation.

2.1 Inclusion criteria:

Patients eligible for this study if they have the following criteria ;-

1) Sinus rhythm.
2) > 95 % biventricular paced complexes.
3) Dilated cardiomyopathy.

2.2 Exclusion Criteria:

Patients will be excluded from the analysis if:-

1) Atrial fibrilation.
2) Malfunctioning ventricular lead.
3) Ischemic cardiomayopathy.

The patients were divided into two groups, the first group is programmed at 70 pacing heart rate and the second group is programmed at 80 pacing heart rate , all patients **subjected before CRT programming to the following**:

A-Demographic data and medical history:

1. Age, gender, risk factors e.g. diabetes mellitus, hypertension, smoking, dyslipidemia and positive family history of cardiac diseases.
2. Symptoms as regard: Nature, duration, severity and impact on patient's quality of life.
3. Degree of symptoms was classified according to NYHA classification.
4.Other predisposing or associated medical problems specially (renal disease, bronchopulmonary disease, neurological disease and chronic hepatic disease).
5. Previous hospital admissions and decompensation.
6. Minnesota living with heart failure questionnaire.

Minnesota Living With Heart Failure Questionnaire (MLHFQ):[(5)]

It was designed in 1984 by Thomas S. Rector to measure the effects of heart failure and treatments for heart failure on an individual's quality of life. It is one of the most widely used health-related quality of life questionnaires for patients with heart failure (HF). It provides scores for two dimensions, physical and emotional, and a total score . The patients were given an Arabic translated form of the questionnaire and we asked the patient to assess how much his heart condition affects his life during the past month (4 weeks). After each question, he circled the 0, 1, 2, 3, 4 or 5 to show how much his life was affected. If a question does not apply to him, he should circle the 0 after that question.

MLHFQ provides additional clinical information regarding disease course and outcome that is not captured by traditional indices of clinical status. It is very useful in monitoring response to HF therapy.

B-Examination:

1. General examination: Full examination with special stress on weight, height, heart rate and rhythm, blood pressure (supine and standing) and signs of systemic congestion.

2. Cardiac examination: All patients were subjected to full local cardiac examination with special stress on the presence of signs of failure as: mitral regurgitation, S3 gallop, basal crepitations...etc.

C- Investigations:

1. Twelve lead resting ECG .

2. Trans-thoracic 2D echocardiographic examination

Standard images were obtained in the parasternal (long- and short-axis views), apical (2 and 4 chamber views) and subcostal view. Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cineloop format. M-mode, two-dimensional as well as pulsed and continuous Doppler flow across the different heart valves in all the standard views were done with particular emphasis on:

Left ventricular end diastolic and end systolic volumes (LVEDV, LVESV) and LVEF were

calculated using biplane Simpson‘s method interface (endocardial borders) in the apical four and two chamber views excluding papillary muscles. At the mitral valve level, the contour is closed by connecting the two opposite sections of the mitral ring with a straight line, with normal range for LVEDV 62–150 ml in males and 46–106 ml in females, LVESV 21–61 ml in males and 14–42 ml in females and LVEF 52–72 % in males and 54–74 % in females.

D. CRT Programming:

- All patients gave written informed consent for CRT programming after full explanation about the procedure in details. The patients were divided into two groups ,the first group is programmed at 70 pacing heart rate and the second group is programmed at 80 pacing heart rate, Beta blockers and ivabradine with or without digoxin were prescribed to both groups to the maximum tolerated dose to maintain heart rate less than 70 bpm in the 1st group and less than 80 bpm and more than 70 bpm in the 2nd group to ensure the maximum atrial pacing .

- The A-V delay and V-V delay were optimized in each patient using (**QuickOpt** in S.t jude devices and **AdaptiveCRT** alogrithm in medtroinc devices).

E. Follow up:

- **for 6 months as regards: Patient clinical improvement through:**

which is based on tracings of the blood–tissue

A. Assessment of patient clinical condition, NYHA class and history of decompensation or hospital admission.

B. Minnesota living with heart failure questionnaire.

C. Echocardiographic assessment of left ventricular function and volumes as done before device implantation.

D. Regular clinical follow up (Pulse tacking) to ensure adequate heart rate below the basal pacing rate and adjusment of the dose of B blockers, ivabradine and digoxin.

Statistical Analysis:

Analysis of data was performed using SPSS v. 23 (Statistical Package for Social science) for Windows.

Description of variables was presented as follows:

Description of quantitative variables was in the form of mean, standard deviation (SD), median and range (min-max) Description of qualitative variables was in the form of numbers (No.) and percent’s (%).

Data was explored for normality using Shapiro/Kolomogrov tests of normality.

Comparison between quantitative variables was carried out by independent t-test which was used to test the difference between the means of the two groups for parametric data and Mann whitney U test for non-parametric data.

Comparison between categorical data was done using the Chi square test, to test the statistical difference between the two groups. Paired t-test was used to illustrate changes in quantitative parameters after the programming (for parametric data and Wilcoxon test for non-parametric data.

The significance of the results was assessed in the form of P-value that was differentiated into:

Non-significant when P-value > 0.05

Significant when P-value ≤ 0.05

Highly significant when P-value ≤ 0.001

3. Results:

This study was conducted to investigate the short-term impact of 70-bpm (DDD-70) and 80-bpm (DDD-80) basal atrial pacing rates on the quality of life and echocardiography in 30 CRT patients; patients were allocated randomly into the 2 groups.

Before programming the two groups to the new pacing atrial rate ,the devices already programed at 60 bpm while the precent of atrial pacing is 1-2 % while after 6 months of programming to 70 & 80 bpm ,the precent of atrial pacing of the former group is 40-50% and 70-80% in the latter group which obtained from histogram of the devices.

Table (1) Baseline characteristics of the two groups under the study:

(1) Demography		**Group .1**	**Group .2**	**P.value**
Age		54.7±7.9	57.6 ±7.7	0.935
Sex	**Males**	11(73.3)	9(60)	0.800
	Females	4(26.7)	6(40)	
QRS Duration		144±10	147±10	0.9
QRS Morphology		LBBB (100%)	LBBB (100%)	1
NYHA Classification		4.2±1.1	4.3±1	0.796
MHFQ		51.1 ±8.1	51 ±8.2	0.967
(2) Echocardiographic Findings				
LVEDD		7.03 ±0.924	7.23 ±1.26	0.9
LVESD		6.23±0.832	6.34±1.11	0.967
LVEDV		267.93 ±80.03	284.27 ±114.03	0.967
LVESV		200.13 ±62.43	220 ±82.43	0.567
EF%		33.13 ±1.64	33.3 ±1.23	0.870
MR	**Non significant**	8(53.3)	9(60)	0.713

	Significant	7(46.7)	6(40)	
(3) Medical Therapy				
B Blocker		(15)100%	(14)93.3%	0.309
ACEI		(13)86.7%	(12)80%	0.624
MRA		(12)80%	(12)80%	1.000
Ivabradine		(3)20%	(2)13.3%	0.624
Digoxin		(4)27%	(3)20%	0.666

There were no statistically significant difference between both groups regarding their MFHQ before the programming (P-value=0.967) but after the programming there was a highly significant difference between both groups as group 2 (with basal heart rat=80) had higher MFHQ after the programming with mean=67.2 ±9.1 vs group 1 (with basal heart rate =70) with mean 50.6 ±8.3 (P-value<0.001).

Table (2) Comparison between MFHQ of the two groups before and after the programming and the effect of the programming on MFHQ in each group:

MFHQ	**BHR 70 No=15(100%)**	**BHR 80 No=15(100%)**	**P-value (groups)**
Pre-programming			
Mean±SD	51.1 ±8.1	51 ±8.2	
Range(min-max)	(39-67)	(39-67)	0.967
Median	50	50	
Post-programming			
Mean±SD	50.6 ±8.3	67.2 ±9.1	
Range(min-max)	(39-67)	(51-81)	**<0.001****
Median	50	67	
P-value (pre-post)	0.150	**0.001****	

*Scale data was presented as mean±SD with median *P-value is significant at <0.05*
***P-value is highly significant*

Regarding the effect of the programming on MFHQ in each group; it was found that there was no significant effect of the programming on MFHQ of group 1(P

value=0.150) but, the programming increase the MFHQ of group 2 from 51 ±8.2 to 67.2 ±9.1 (p-value=0.001) as in figure (1)

- There were no statistically significant difference between both groups regarding their LVEDV before and after the programming (P-value=0.967 and 0.673; respectively). Regarding the effect of the programming on LVEDV in each group; the programming didn't affect the LVEDV of both groups significantly (p-value=0.546, 0.554 for both groups).

Table (3) Comparison between LVEDV of the two groups before and after the programming and the effect of the programming on LVEDV in each group:

LVEDV	**BHR 70 No=15(100%)**	**BHR 80 No=15(100%)**	**P-value (groups)**
Pre-programming			
Mean±SD	267.93 ±80.03	284.27 ±114.03	
Range(min-max)	(153-404)	(153-516)	0.967
Median	255	247	
Post-programming			
Mean±SD	264.3 ±78.32	281.4 ±114.1	
Range(min-max)	(153-404)	(153-516)	0.637
Median	247	239	
P-value (pre-post)	0.546	0.554	

- There were no statistically significant difference between both groups regarding their LVESV before and after the programming (P-value=0.567 and 0.624; respectively).
- Regarding the effect of the programming on LVESV in each group; the programming didn't affect the LVESV of both groups significantly (p-value=0.211, 0.145 for both groups).

Table (4) Comparison between LVESV of the two groups before and after the programming and the effect of the programming on LVESV in each group:

LVESV	BHR 70 No=15(100%)	BHR 80 No=15(100%)	P-value (groups)
Pre-programming			
Mean±SD	200.13 ±62.43	220 ±82.43	
Range(min-max)	(118-316)	(118-390)	0.567
Median	186	208	
Post-programming			
Mean±SD	197.73 ±61.22	217.6 ±82.67	
Range(min-max)	(118-307)	(118-390)	0.624
Median	179	208	
P-value (pre-post)	0.211	0.145	

There were no statistically significant difference between both groups regarding their EF before and after the programming (P-value=0.870 and 0.595; respectively).

- Regarding the effect of the programming on EF in each group; it was found that there was no significant effect of the programming on EF of both groups (P-value=0.2 and 0.317 in both groups respectively).

Table (5) Comparison between EF of the two groups before and after the programming and the effect of the programming on EF in each group:

EF	BHR 70 No=15(100%)	BHR 80 No=15(100%)	P-value (groups)
Pre-programming			
Mean±SD	33.13 ±1.64	33.3 ±1.23	
Range(min-max)	(29-35)	(31-35)	0.870
Median	33	34	
Post-programming			
Mean±SD	33.53 ±1.4	33.2 ±1.5	
Range(min-max)	(30-35)	(30-35)	0.595
Median	34	34	
P-value (pre-post)	0.2	0.317	

- There were no statistically significant difference between both groups regarding their mean NYHA before the programming (P-value=0.796) but, there was a statistically highly significant difference between both groups after the programming (P-value=0.003)
- Regarding the effect of the programming on mean NYHA in each group; it was found that there was no significant effect of the programming on mean NYHA of group I (P-value=0.500) but, the programming worsened the mean NYHA of group II significantly (P-value=0.002).

Table (6) Comparison between mean NYHA of the two groups before and after the programming and the effect of the programming on mean NYHA in each group:

Mean NYHA	70 BHR	80 BHR	P. value
Pre programming	**4.2±1.1**	**4.3±1**	**0.796**
Post programming	**4±1.2**	**5.6±1.5**	**0.003****
P-value	**0.500**	**0.002****	

*P-value is significant at <0.05 **P-value is highly significant

4. Discussion:

In our study,we examined the effects of a basal pacing rate of 80 bpm compared to 70 bpm in CRT patients on the quality of life and echocardiographic findings (LVEDV ,LVESV and ejection fraction).

We found that programming the basal atrial pacing rate of CRT to 80 bpm significantly imapirs the quality of life by increasing the MHFC score.This finding matches **GhotbiAA et al.(2015)** which stated that the higher the pacing atrial rate the higher score in Qol survey (indicates more limitation of Qol).[6]

Also , we found that programming the basal pacing atrial rate to 80 bpm increase the NYHA class of the patients which matches with **D. Logeart et al. 2009** concluded that The mean NYHA class was lower at the low pacing rate (55 bpm) compared with the high pacing rate (75 bpm) (2.2+0.6 vs. 2.6+0.5, P-value 0.03).[7]

A high frequency of atrial pacing may compromise CRT response by disrupting optimal left-sided AV coupling. Programmed paced AV (PAV) delays differ significantly from sensed AV (SAV) delays during sinus rhythm.This is because of (1) latency in atrial capture and sensing, (2) interatrial conduction delay, (3) latency in ventricular capture, and (4) interventricular conduction delay.(8)

Capture latency refers to the delay between emission of the right atrial pacing stimulus and atrial contraction (Fig. 1). Sensing latency refers to the delay between the onset of atrial depolarization and the time at which the local endocardial signal is sensed (Fig. 1). Because of latency in atrial capture and sensing, the optimal AV delay for sensed and paced P-waves may differ. During sinus rhythm, the programmed SAV delay begins when the native P-wave is sensed but the physiologic AV interval, which begins with atrial depolarization and the onset of mechanical contraction, may be delayed due to sensing latency. [(8)]

The mean latency between the beginning of atrial depolarization and the time of atrial sensing is 30–50 ms. Thus, the physiologic AV interval is longer than the programmed SAV delay. The opposite situation occurs during atrial pacing. The programmed AV delay begins with emission of the atrial pacing stimulus, but the physiologic AV interval begins with atrial depolarization and mechanical contraction. The mean latency between atrial output and capture is reported to be 30–50 ms, however it may be >300 ms (Figs. 2 and 3). The physiologic AV interval is therefore shorter than the programmed PAV delay.[(8)]

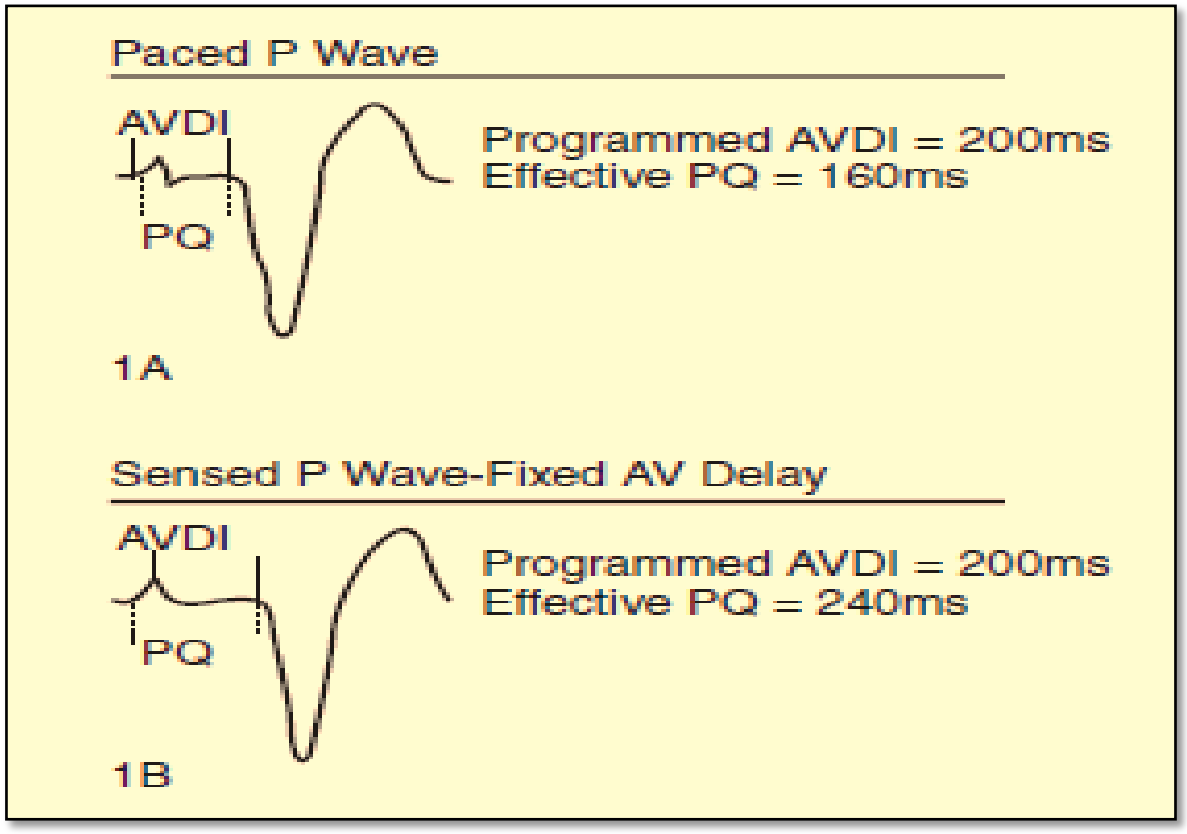
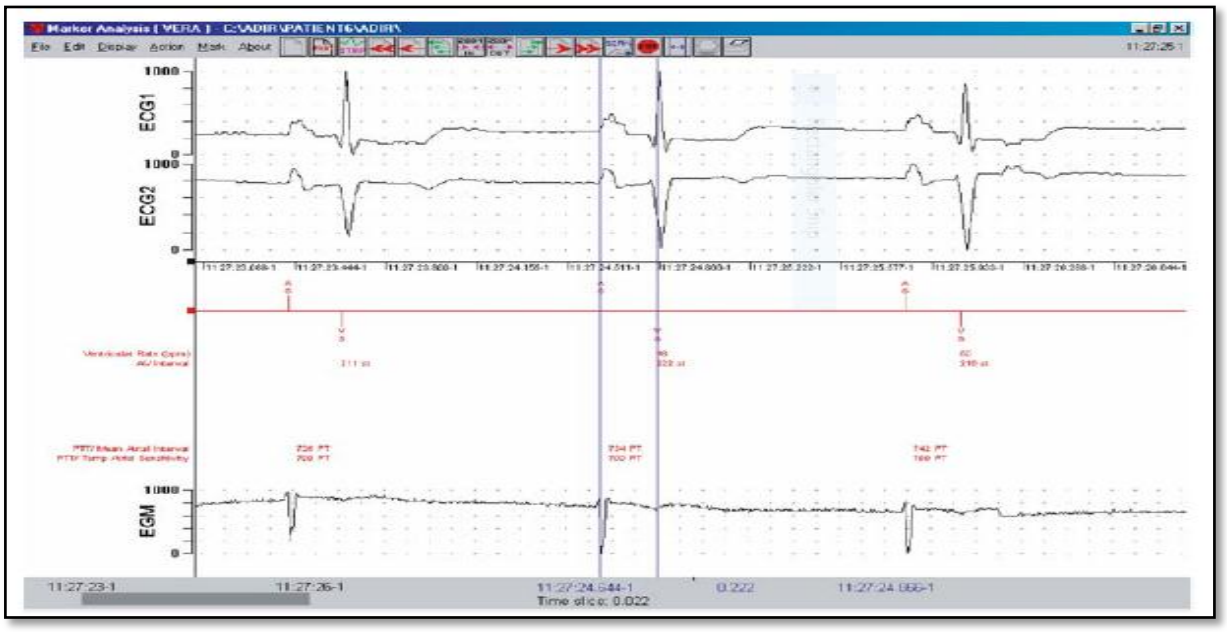
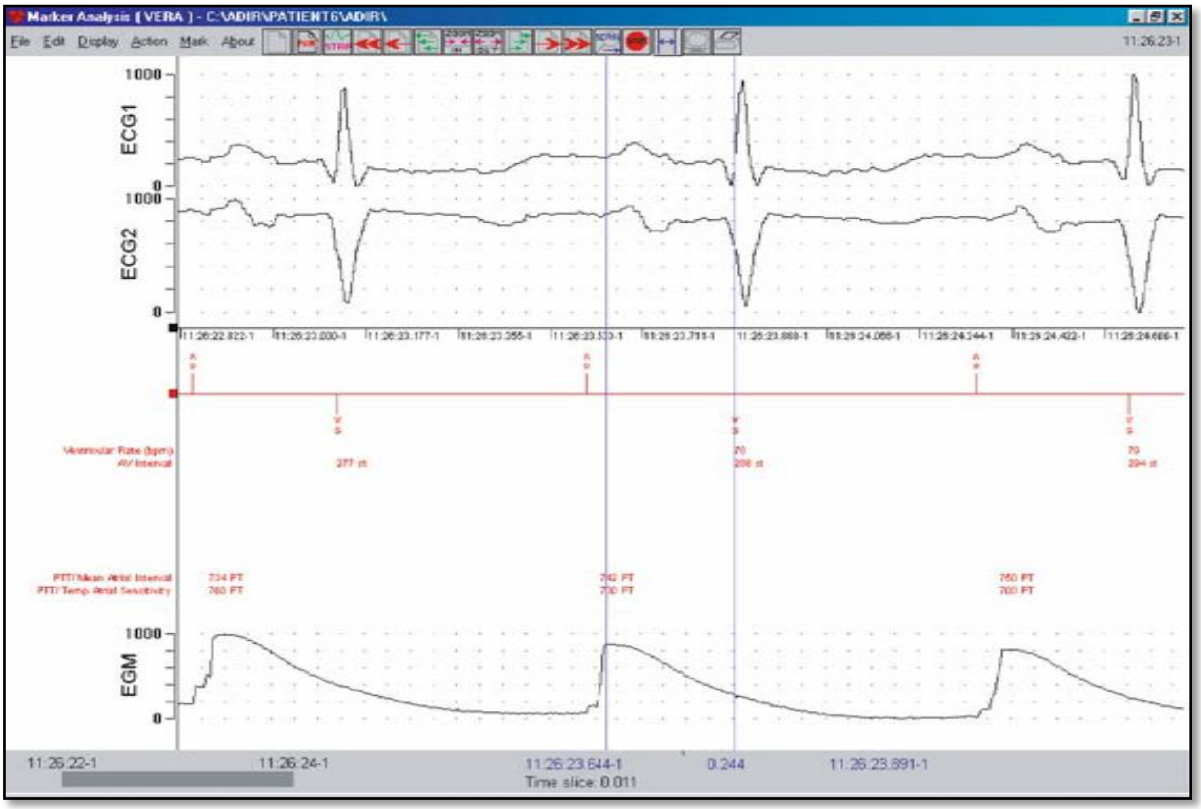


Fig. (1) Effect of atrial capture and sensing latency on the physiologic AV interval.

Fig. 2 AV intervals during atrial sensing. AS and VS occur at the start of the P- and R-waves, and the AS-VS time of 222 ms corresponds well with the surface ECG P-Q time





measured by the cursors.

Fig. 3 Effect of atrial capture latency on AV interval during atrial pacing. AP occurs sooner than the P-wave is seen on the surface ECG. The AP-VS time is measured at 288 ms,but the time from the start of the P-wave–VS time is nearer to 244 ms. Thus, the AP-VS time is overreported by the device, versus the surface ECG

Additionally, Interatrial conduction delays are common during right atrial pacing , The common consequence of these effects is that the optimized AV delay is already in progress before left atrial contribution to ventricular filling has begun (Figs. 4). In this situation, the optimized AV delay during sinus rhythm may be too short during atrial pacing with adverse effects on left ventricular pumping function. [8]

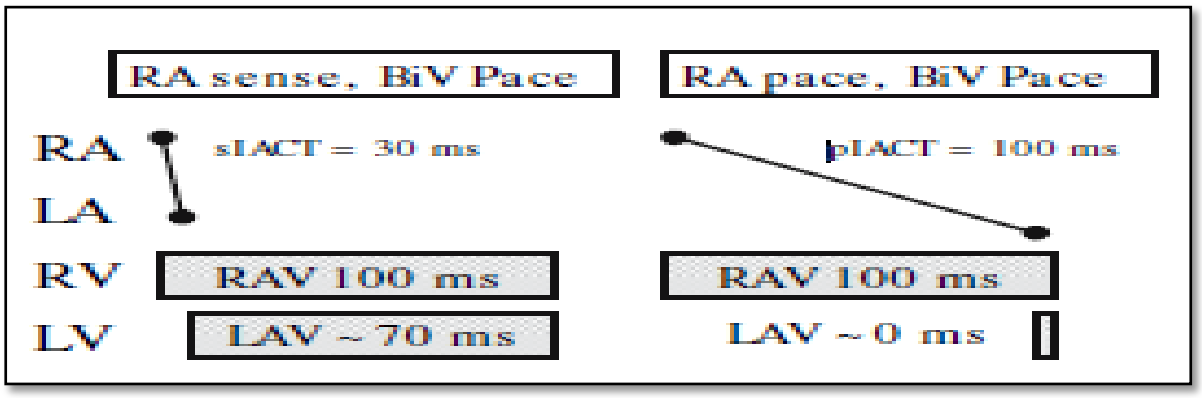


Fig. 4 Effect of right-sided AV delays on left-sided AV coupling during simultaneous biventricular pacing. iACT, intrinsic interatrial conduction time; pACT, paced interatrial conduction time; iVCT, interventricular conduction time.

From all of the above reasons, high frequency of atrial pacing may compromise CRT response by disrupting optimal left-sided AV coupling.

On the other hand , we found that there is no effect of programming the basal atrial pacing rate to 70 or 80 bpm on the echocardiographic parameters (LVEDV ,LVESV and ejection fraction) , which matches GhotbiAA et al.(2015) which stated that there is no significant changes were observed in the echocardiographic parameters including (LVEDV , LVESV and EF).[6]

5. Conclusion:

The lower the better. However , there is no strict recommendation about the optimal basal atrial pacing rate and few studies have examined the optimal basal atrial pacing rate and its impact on long-term outcome in CRT patients :

1. We conclude that the higher the basal atrial pacing rate the worse quality of life and the more increase of the heart failure symptoms.
2. There is no effect of both atrial pacing rates on the echocardiographic paramateres.

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