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The study of prevalence and prognostic significance of ventricular dyssynchrony in patients with dilated cardiomyopathy

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ABSTRACT

Context: Heart failure has become a major problem in current world with relatively higher rate of readmissions, increasing morbidity and mortality. Due to LV dilatation and systolic dysfunction, heart is susceptible to dyssynchrony which was widely studied to assess prognosis and treatment with cardiac resynchronization therapy (CRT). However so far, dyssynchrony is evaluated mostly by electrocardiographic criteria (prolong QT interval), which have shown poor correlation with echocardiographically documented intraventricular dyssynchrony. Relying on a more mechanistic approach, echocardiography will likely play a central role in the evaluation of dyssynchrony in the near future.

Aims: To assess the prevalence of different types of dyssynchrony in patients with dilated cardiomyopathy and to study the prognosis of dilated cardiomyopathy patients based on type of dyssynchrony using TDI (Tissue Doppler Imaging).

Settings and Design: The study was carried out in Department of Cardiology, Southern Railway HQ Hospital, Perambur, Chennai from September 2017 to April 2019 over a period of 18 months.

Subjects and Methods: The study was conducted on both male and female patients presenting with heart failure (NYHA III/1V) due to ischemic cardiomyopathy or nonischemic cardiomyopathy with left ventricular ejection fraction ≤35%.

Statistical Analysis: Descriptive statistics included computation of percentages, means and standard deviations. The Mann whitney u tests was used for quantitative data comparison of all clinical indicators.

Results: Ischemic DCM has poor prognosis compared to non ischemic ones. Electrical dyssynchrony (QRS≥120 msec), Interventricular dyssynchrony (IVMD ≥40 msec and Intraventricular dyssynchrony (TDI >50msec) is more in ischemic DCM compared to non ischemic DCM. More the dyssynchrony, more poorer the prognosis. Intraventricular dyssynchrony measured as septal to lateral delay by Tissue Doppler imaging is best among all different types of dyssynchronies in predicting the prognosis of DCM patients.{ (p=0.000), odd ratio 0.01 with 95% CI 0.0062 to 0.018.}

Conclusions: The role of TDI in assessing the severity of dyssynchrony as well as prognosis in patients with both ischemic and non ischemic DCM was determined by our study hus opening the window of opportunity to predict the prognosis of heart failure by screening intraventricular dyssynchrony with TDI.

Keywords: Tissue doppler imaging ; Intra ventricular dyssynchrony ; Interventricular dyssynchrony ; mechanical dyssynchrony; Heart failure

INTRODUCTION

Congestive heart failure (CHF) is a major health issue, with as many as 10% of individuals older than 65 years affected (1). Even though the medical management of CHF has improved substantially in recent years, morbidity and mortality remain high, especially for patients with poor functional class, despite optimal therapy (1). The most common cause of heart failure is dilated cardiomyopathy (DCM)(2). Dilated cardiomyopathy (DCM) is best understood as the final common response of myocardium to diverse

genetic and environmental insults with left ventricular (LV) dilatation and systolic dysfunction (3). The disruption of the link between the sarcolemma, the cytoskeleton, and the sarcomere has been shown to be associated with the disease-DCM(1). The predominant cause of mortality in these patients is either end-organ dysfunction due to pump failure causing CHF or arrhythmia-related death(4). Due to LV dilatation and systolic dysfunction, DCM is susceptible to dyssynchrony which was widely studied to assess prognosis and treatment with cardiac resynchronization therapy (CRT)(5). However so far, dyssynchrony is evaluated mostly by electrocardiographic criteria(prolong QT interval), which have shown poor correlation with echocardiographically documented intraventricular dyssynchrony(5,6). Relying on a more mechanistic approach, echocardiography will likely play a central role in the evaluation of dyssynchrony in the near future. The echocardiographic assessment includes conventional and/or specific applications ranging from M mode and pulsed/ continuous doppler to pulsed tissue doppler, the off-line analysis of colour tissue doppler, strain rate imaging (SRI)(7-9). Mechanical Dyssynchrony is of 3 types- 1. Atrio-ventricular Dyssynchrony, 2. Inter-ventricular dyssynchrony and 3. Intra-ventricular dyssynchrony. Atrio-ventricular dyssynchrony occurs in patients with DCM and first degree AV block which is measured as AV delay due to mitral inflow(10). Inter-ventricular dyssynchrony represents the discordance between the times of right ventricular (RV) and LV contraction. PW or CW Doppler images of aortic and pulmonary flow velocities are currently used to measure the inter-ventricular mechanical delay (IVMD)(11). Intra-ventricular dyssynchrony is characterized by either premature or late contraction of LV wall segments due to delayed electrical conduction (12). It can be identified by means of simple Mmode, pulsed Tissue Doppler or better by colour Tissue Velocity Imaging (TVI). TDI is a relatively recent imaging modality that allows regional myocardial velocity measurements. Precise determination of the amplitude, timing of onset and peak systolic and diastolic velocities can be obtained in relation to the electrocardiogram signal. Several new techniques have been derived from TDI that yield a quantitative and detailed evaluation of LV dyssynchrony(1). The compared prognostic values of interventricular and left and right intraventricular dyssynchrony have not been previously fully described. Hence this study was planned to study different types of dyssynchronies and their prognostic significance in patients of DCM.

MATERIAL AND METHODS:

Study area- The study was carried out in Department of Cardiology, Southern Railway HQ Hospital, Perambur, Chennai from September 2017 to April 2019 over a period of 18 months. Study population- The study was conducted on both male and female patients presenting with heart failure(NYHA III/1V) due to ischemic cardiomyopathy or nonischemic cardiomyopathy with left ventricular ejection fraction ≤35%.

Inclusion Criteria: Patients with LVEF ≤ 35 % New York Heart Association Class III-IV

Exclusion criteria: Patients with Atrial Fibrillation,Patients with Congenital heart diseases, Patients with rheumatic heart diseases, Patients within one month of acute myocardial infarction, Patients with Myocarditis/ Pericarditis/ Pericardial effusion-Tamponade, Patients who underwent thoracic/cardiac surgery/Pace maker, CRT Implantation/ valve replacement or other alteration of cardiac anatomy even during follow up, Patients with chronic respiratory diseases like COPD/ILD etc., Patients with chronic renal failure, Patients who do not give consent. Patients who are poor compliant to treatment.

Accepting the prevalence according to Bader H etal (13) , sample size was calculated to be ≈ 86, but based on i) Hospital statistics ii) Inclusion and exclusion criteria and iii) Cooperation and non-cooperation of the patients , sample size we included in this study was 71.

Study design- Prospective Observational Study

Study Duration- The study was conducted for 18 months from 1/9/17 to 30/4/19.

Study intervention :Detailed 2D echocardiography was done on patients included in the study at the time of admission and were followed at 1 month, 6 months and 12 month intervals. Symptoms were classified based on NYHA classification at the time of admission and during followup. Every effort was made to maintain all patients on optimum goal

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directed medical therapy(GDMT) as per ACC/AHA guidelines. For patients who did not come for follow up detailed assessment was done telephonically.

Data collection methods: Fully filled consent is obtained from the patients enrolled in study. Patients were classified into 2 groups -ischemic and non ischemic DCM group based on their coronary atherosclerosis status. Patients with non critical coronary artery disease/normal coronaries were classified as non ischemic group whereas patients with significant stenosis were classified as ischemic group as per diagnostic criteria.(16) A detailed history and physical examination was carried out for every subject who entered the study based on pre-designed proforma, inclusion & exclusion criteria along with thorough physical examination and assessment of vital parameters. ECG, echocardiography, laboratory investigations such as lipid profile (cholesterol, LDLcholesterol, HDL-cholesterol, triglycerides), blood sugar level, HbA1C, Chest X ray and other routine investigations were performed as a part of diagnosis and treatment for all the patients. For the first 3 months of study all 3 types of dyssynchronies (Electrical, inter ventricular and intraventricular) were calculated on subjects enrolled and followed for 1 year based on their time of enrollment. Symptom status based on NYHA, any events like rehospitalization, death (due to cardiac symptoms), duration of hospitalization stay were recorded to assess the prognosis. Any patient whose symptom class improved from time of first visit was considered to be in good prognosis group and any patient who remained in same symptom class or further deterioration of symptoms or any admission due to untoward cardiac event/fatality in spite of GDMT was considered in bad prognosis group. (Figure 1)

Interventricular dyssynchrony was measured as the time interval between the preaortic and prepulmonary ejection times. The aortic pre-ejection time was measured from the beginning of QRS complex to the beginning of the aortic flow velocity curve recorded by pulsed wave (PW) Doppler in apical 5-chamber view. The pulmonary pre-ejection time was measured from the beginning of QRS complex to the beginning of the pulmonary flow velocity curve recorded in the left parasternal short axis view. The difference between the two values determines the interventricular mechanical dyssynchrony (IVMD) and delay> 40 ms indicates significant interventricular dyssynchrony.

Intraventricular Dyssynchrony was measured from the color Doppler images by off-line analysis. Sample volumes were placed at the basal level in the septum and lateral wall (using the four-chamber images) to derive velocity graphs. From these data, the time from the beginning of the QRS complex (on electrocardiogram) to peak systolic velocities in the septum and lateral wall were assessed, and the difference between these two peak systolic velocities was calculated as a measure of intraventricular dyssynchrony (referred to as the septal-to-lateral delay). The delay <50 msec was considered as minimal dyssynhrony, between 50-80msec as intermediate dyssynhrony and >80 msec as extensive dyssynchrony.(64)

Statistical analysis: The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics included computation of percentages, means and standard deviations. The Mann whitney u tests was used for quantitative data comparison of all clinical indicators. Chi-square test and fisher exact test were used for qualitative data whenever two or more than two groups were used to compare. Logistic regression multivariate analysis test was also used. Level of significance was set at $P \leq 0.05$.

OBSERVATION & RESULTS

Our study population was divided into 2 groups- Ischemic DCM -41(57.7%) and Non ischemic DCM - 30(43.3%) based on the coronary status. (Figure 2)

The prevalence of Electrical dyssynchrony (QRS≥120msec) among Ischemic group is 70.8%(n=34) where as in non ischemic group it is 29.2%(n=14) where as the prevalence of Interventricular mehanical dyssynchrony (IVD≥40msec) among Ischemic group is 75%(n=36) where as in non ischemic group it is 25%(n=12) and the prevalence of Intra ventricular mehanical dyssynchrony among Ischemic group is 85%(n=34) where as in non ischemic group it is 15%(n=6). Hence all 3 dyssynhronies are clearly more in Ishcemic group compared to non ischemic group. (Figure 3)

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The mean QRS duration among ischemic group was 132±10.44 msec where as in non ischemic group was 122.8±-10.32 msec(p=0.001), The mean IVMD in ischemic group was 45.58±5.35 msec where as in non ischemic subsets it was 37.23±5.56 msec(p=0.01), The mean Intraventricular dyssynchrony measured by TDI in Ischemic DCM group was 67.17±17.33msec and 38.73±13.56 msec in non Ischemic DCM (p=0.001), Hence patients with ischemic DCM had more dyssynchrony.

In our study out of 41 patients of ischemic DCM, 7(17.1%) found to have minimal dyssynchrony , 23(56.1%) found to have intermediate and 11(26.8%) found to have extensive dyssynchrony. Among 30 patients of non ischemic DCM, 24(80%) were found to have minimal dyssynchrony, 6(20%) belongs to intermediate group and none in extensive group.(p=0.001). Hence severity of Intraventricular dyssynchrony is more in ischemic group compared to non ischemic.

Ischemic DCM patients have spent more time in hospital 22.41±18.67 days during 1 year follow up in comparision to 1.2±2.61 days in non ischemic group.(p=0.001), only 25 patients (61%) of ischemic DCM group showed good prognosis where as all patients among non ischemic group found improvement in clinical status.

The incidence of readmission rate more than once due to cardiac events is more among ischemic group-19 patients(45.9%) and none from non ischemic group(p=0.001), thereby suggesting that Ischemic DCM has poor prognosis.

In our study at the end of 1 year follow up none of the patients with minimal intraventricular dyssynchrony (<50msec) showed bad prognosis, where as 5(17.2%) showed bad prognosis in intermediate intraventricular dyssynchrony group and 8 (72.7%) showed bad prognosis in extensive intraventricular dyssynchrony group(p=0.001). Hence Comparing the 3 different types of dyssynchronies, intraventricular dyssynchrony by TDI is best in predicting prognosis(p=0.000), odd ratio 0.01 with 95% CI 0.0062 to 0.018. Thus role of TDI in assessing the severity of dyssynchrony as well as prognosis in patients with both ischemic and non ischemic DCM was determined by our study with small period of follow up which was well supported by various previous studies thus opening the window of opportunity to predict the prognosis of heart failure by screening intraventricular dyssynchrony with TDI.

DISCUSSION

The present study was done on 71 patients of DCM, both ischemic as well as non ischemic subtypes. In this study different types of dyssynchrony i.e., electrical, interventricular and intraventricular mechanical dyssynchrony has been studied and compared with each other in relation to the prognosis of DCM based on severity of dyssynchrony.

Study population was divided into 2 groups- Ischemic DCM -41(57.7%) and Non ischemic DCM - 30(43.3%) based on the coronary status. This is in line with Morshed et al (14)

AGE & Gender: The mean age in ischemic DCM group was 61.87± 10.75 where as in non ischemic it was 58.9±9.53(p=0.23), 2 groups were age matched. This was almost similar to study done by Edner M et al,(15) Citro et al.(16)

Among ischemic group 23(56.1%) were men and 18(43.9%) were women where as in non ischemic group 17(56.7%) were men and 13(43.3%) were women patients(p=0.96, sex matched), This was consistent with western berg et al.(64) We have found no significant association between ischemic and non ischemic group with respect to Ejection fraction, hypertension, diabetes, baseline clinical functional status (NYHA). The prevalence of all 3 types of dyssynchronies is certainly more in ischemic group compared to non ischemic group, which is in accordance to Morshed et al (14)

Electrical dyssynchrony:

The mean QRS duration among ischemic group was 132±10.44 msec where as in non ischemic group was 122.8±10.32 msec(p=0.001), electrical dyssynchrony was found to be significantly more in ischemic group. This was in line with Anzouan et al (17) and Citro et al.(16)

Intraventicular Mechanical Dyssynchrony (IVMD) The mean IVMD in ischemic group was 45.58± 5.35 msec where as in non ischemic subsets it was 37.23±5.56 msec(p=0.01), IVMD is significantly more in ischemic compared to non ischemic DCM. Morshed et al (14) observed that the mean IVMD

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was 35±12.4 msec in ischemic group and 30±14.7 msec in non ischemic group. Thus interpreting IVMD is more in ischemic compared to non ischemic. This was also supported by Bader et al,(18) Anzouan et al.(17) .

Intraventricular Mechanical Dyssynchrony: The mean Intraventricular dyssynchrony measured by TDI in Ischemic DCM group was 67.17±17.33msec and 38.73±13.56 msec in non Ischemic DCM (p=0.001) which is also a feature in a study conducted by Morshed et al(14), the mean TDI in Ischemic group was 68..5±19.8msec and in non ischemic group it was 54.6± 15.0msec According to JB Anzouan-Kacou et al(17) in 2009 studied the prevalence of inter-VD and intraLVD was respectively 47.5 and 70% in patients of DCM, thereby signifying intraventricular dyssynchrony is clearly seen in most of DCM patients Similarly in a study done by westernberg et al(19) in a head to head comparison between TDI and MRI among 20 patients of heart failure revealed the mean TDI was 55±37 msec.

Westerberg et al (19) studied the severity of dyssynchrony using TDI among patients with DCM and classified them as minimal (TDI <50 msec), intermediate (TDI 50-80 msec) and extensive dyssynchrony (TDI >80msec). In our study out of 41 patients of ischemic DCM, 7(17.1%) found to have minimal dyssynchrony, 23(56.1%) found to have intermediate and 11(26.8%) found to have extensive dyssynchrony. Among 30 patients of non ischemic DCM, 24(80%) were found to have minimal dyssynchrony, 6(20%) belongs to intermediate group and none in extensive group.(p=0.001). According to our study severity of Intraventricular dyssynchrony is more in ischemic group compared to non ischemic group. This is in line with Bader et al(18) and western berg et al.(19)

PROGNOSIS: Ischemic DCM patients have spent more time in hospital 22.41±18.67 days during 1 year follow up in comparision to 1.2±2.61 days in non ischemic group.(p=0.001), only 25 patients(61%) of ischemic DCM group showed good prognosis where as all patients among non ischemic group found improvement in clinical status. The incidence of readmission rate more than once due to cardiac events is more among ischemic group-19 patients(45.9%) and none from non ischemic group(p=0.001). So above data revealed that Ischemic DCM has poor prognosis. In our study at the end of 1 year follow up, 32 patients with electrical dyssynchrony (QRS≥120 msec) showed good prognosis where as 12 didn't do well (p=0.01), Similarly in patients with IVMD≥40msec, 30 patients showed improvement and 13 showed deterioration (P=0.001), where as patients with intraventricular mechanical dyssynchrony (TDI>50msec), 27 Patients showed improvement in the clinical status where as 13 worsened (p=0.001). Hence dyssynchrony predicts the prognosis, specifically intraventricular mechanical dyssynchrony. This is well supported by 7 meta analysis conducted by BAX and colleagues,(20,21) Bader and coworkers.(18) Infact prognostic value of LV dyssynchrony, was first reported by Bader and co-workers(18) in 2004 as the presence of intra-LV (but not inter-V) dyssynchrony was identified as an independent predictor of severe cardiac events (hazard ratio 3.39, p < 0.0001), independent of the LVEF and QRS width.

In our study at the end of 1 year follow up none of the patients with minimal intraventricular dyssynchrony (<50msec) showed bad prognosis, where as 5(17.2%) showed bad prognosis in intermediate intraventricular dyssynchrony group and 8 (72.7%) showed bad prognosis in extensive intraventricular dyssynchrony group(p=0.001), incuding 3 deaths due to cardiac cause.

Comparing the 3 different types of dyssynchronies, intraventricular dyssynchrony by TDI is best in predicting prognosis(p=0.000), odd ratio 0.01 with 95% CI 0.0062 to 0.018. Bax and colleagues(20,21) in their meta-analysis concluded that TDI could predict responders to resynchronisation therapy with 87-97% sensitivity and 55-100% specificity. Further, a septal to lateral delay of 65 msec, had prognostic value, which is clearly seen in our case. Thus role of TDI in assessing the severity of dyssynchrony as well as prognosis in patients with both ischemic and non ischemic DCM was determined by our study with small period of follow up which was well supported by various previous studies thus opening the window of opportunity to predict the prognosis of heart failure by screening intraventricular dyssynchrony with TDI.

CONCLUSION

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Ischemic DCM has poor prognosis compared to non ischemic ones. Electrical dyssynchrony (QRS≥120 msec), Interventricular dyssynchrony (IVMD ≥40 msec and Intraventricular dyssynchrony (TDI >50msec) is more in ischemic DCM compared to non ischemic DCM. More the dyssynchrony, more poorer the prognosis. Intraventricular dyssynchrony measured as septal to lateral delay by Tissue Doppler imaging is best among all different types of dyssynchronies in predicting the prognosis of DCM patients.{ (p=0.000), odd ratio 0.01 with 95% CI 0.0062 to 0.018.} Severity of intraventricular dyssynchrony assessed by TDI helps in predicting prognosis during long term there by pressing the need for aggressive medical management/ CRT implantation in patients with extensive dyssynchrony.

CONFLICT OF INTEREST: NIL

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'as done using PHILLIPS I.E Matrix 33-Advanced echo machine.

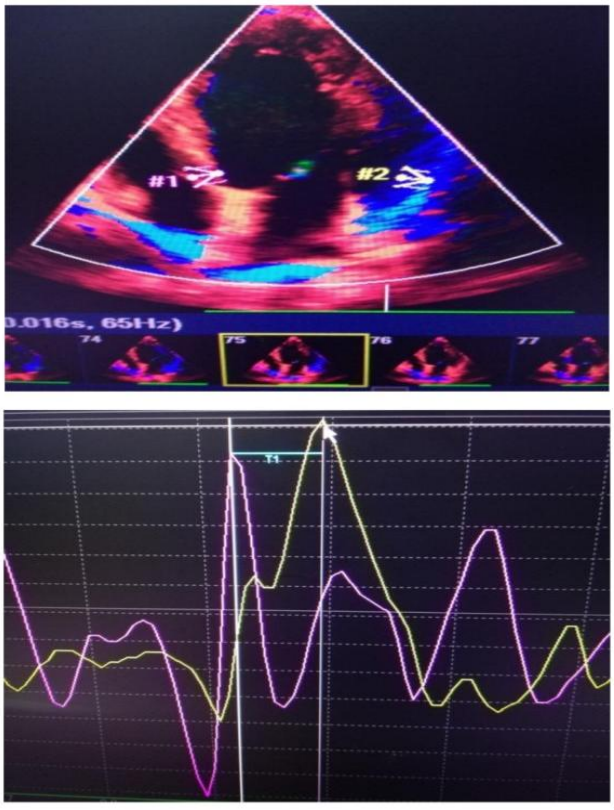

Figure 1- TDI with Intra ventricular dyssynchrony

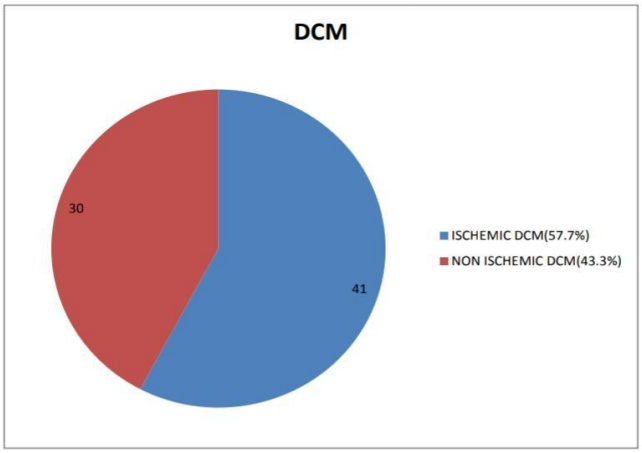

Figure 2- Distribution of DCM patients

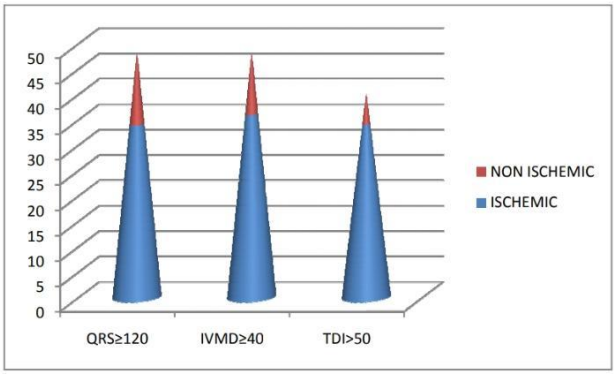

Figure 3- various types of dyssynchronies

DYSSYNCHRONY	ISHCEMIC DCM	NON ISHCEMIC DCM
ELECTRICAL (QRS≥120) (N=48)	34(70.8%)	14(29.2%)
INTERVENTRICULAR (IVMD ≥ 40 MSEC) (N=48)	36(75%)	12(25%)
INTRAVENTRICULAR (TDI > 50) (N=40)	34(85%)	6(15%)

P=0.28

Table 1 - various types of dyssynchronies

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Severity of Intraventricular Dyssynchrony

Table 11: TDI

			TDI scores(msec)			
			minimal<50	Intermediate 50-80	Extensive >80	Total
Groups	ISCHEMIC DCM	N	7	23	11	41
		%	17.1%	56.1%	26.8%	100.0%
	NON ISCHEMIC DCM	N	24	6	0	30
		%	80.0%	20.0%	.0%	100.0%
Total		N	31	29	11	71
		%	43.7%	40.8%	15.5%	100.0%

P value=0.001 (S)

Table 2- severity of intraventricular dyssynchrony

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