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Comparison of Tissue Doppler Imaging and Radionuclide Multigated Analysis in Assessment of Cumulative Cardiotoxicty to patients receiving Anthracyclines or Multiple Transfusions

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ABSTRACT

Introduction: Anthracyclines and chronic transfusion cause cumulative cardiotoxicity through iron mediated myocardial damage, where early detection could lead to remedial measures. Left Ventricular Ejection Fraction (LVEF) and regional wall motion measurement by Radionuclide Multiple gated Acquisitions (MUGA) scanning is accepted modality to monitor cardiac function in this population. Tissue Doppler Imaging (TDI) offers a sensitive method for earlier detection by assessing myocardial contraction velocity. We compared MUGA & TDI for early detection of cumulative cardiotoxicity.

Material & Methods: Children receiving anthracyclines or chronic transfusion therapy were assessed for cardiac function by MUGA and TDI with baseline studies where feasible and serial measurements thereafter.

Results: 59 MUGA scans and 52 TDI assessments were done in 36 children, 29 with malignancies requiring anthracyclines, and 7 thalasemics requiring chronic transfusions. 9 MUGA scans and 12 TDI studies done pre-exposure were all normal. 50 post-exposure MUGA scans had a mean LVEF of 55.98% as compared to 60.44% pre-exposure with 10 (20%) cases showing a significant decline in function. Mean Anthracycline dose was 317.27 mg/ m^2 (90- 480 mg/ m^2). Mean transfusion dose was 1569.17-ml/ kg (220- 3000 ml/kg). In this post-exposure group, 28 of 40 (70%) TDI assessments showed a significant decline in cardiac function compared to MUGA ($p<0.01$). Serial TDIs available in 15 children showed 10 with progressive decline of cardiac function with increasing exposure.

Conclusions: TDI is more sensitive than MUGA in detecting declining cardiac function in children receiving anthracyclines and chronic transfusion therapy, which needs further validation in a larger study.

Keywords: Thalassemia; Transfusions; Anthracyclines; Cardiotoxicty; Tissue Doppler; Radionuclide Multigated

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INTRODUCTION

Children with malignancies and those exposed to multiple blood transfusions are prone to cardiac dysfunction, which increases with cumulative exposure to drugs like anthracyclines and iron overload syndromes of the chronically transfused.[1,2,3] This becomes a major cause of morbidity in childhood cancer survivors and is the defining factor for mortality in thalassemics.[4,5] The mechanism of myocardial damage in both conditions, though different, is finally iron- metabolite mediated,[6] and the end-result remains decreased functional output of the heart, resulting in dyspnea and other clinical manifestations. Diastolic dysfunction is the primary mechanism responsible for dyspnea in patients with heart failure, irrespective of the presence or severity of systolic dysfunction.[7,8] Conventional 2-D Echo studies have long been the only mode of monitoring such patients which is limited by the dependence of the trans-mitral flow velocity and the Isovolumic Relaxation Time (IVRT) on Left Ventricular (LV) relaxation and left atrial pressure.[9,10] Increase in left atrial pressure override the effects of Impaired Relaxation (IR), resulting frequently in a "pseudonormalization" of the transmitral velocity.[11] Conventional Pulsed-Wave Doppler Echocardiography (CPWDE) provides an assessment of ventricular diastolic function, however, its utility is limited by the significant impact of preload conditions.

Tissue Doppler Imaging (TDI) has emerged as new ultrasound modality in last decade that records systolic and diastolic velocities within the myocardium and at the corners of the mitral annulus.[12-15] The velocity of annular motion reflects shortening and lengthening of the myocardial fibers along a longitudinal plane. The early diastolic velocity recorded at the lateral corner of the annulus (Ea) has been demonstrated to decline progressively with age and to be reduced in pathologic LV hypertrophy as well as in patients with restrictive cardiomyopathy.[16-18] These findings suggest that Ea is an index of LV relaxation that may not be influenced by left atrial pressure, offering considerable advantage for early detection of dysfunction.

Left Ventricular Ejection Fraction (LVEF) and regional wall motion measurement by Radionuclide Multiple gated Acquisitions (MUGA) scanning evolved as an accepted modality to monitor cardiac function but requires extensive infrastructure and trained manpower.[19,20] Few such centers exist in a relatively resource-strapped country like India. On the other hand, most new Doppler machines can perform TDI studies with a software upgrade. This would allow wider application for detecting cardiotoxicity in most pediatric hematology-oncology units with existing cardiology facilities. The benefit of early detection allows corrective measures to be taken in children with malignancies and those with iron overload syndromes. We undertook this study to compare the two methods to see if TDI was indeed a sensitive and reliable tool for the detection of such cases.

MATERIAL AND METHODS

Children and adolescents (less than 18 yrs age) attending a Pediatric Hematology- Oncology Unit receiving, or about to start receiving anthracylcines, or being enrolled into a chronic transfusion program were included over a 3 yr

period from Mar 2004 to Mar 2007. In addition, 5 healthy children, in the age group of 5 to 10 years, were taken as controls for serial TDI studies. Pre-exposure studies by MUGA and TDI were done whenever feasible and they served as their own controls for post-exposure studies. MUGA studies were carried out by injecting Stannous pyrophosphate and Technetium-99 followed by assessment in a SEIMENS® E-Soft gamma to obtain measurements of Left Ventricular Ejection Fraction. Interpretation was done by the same observer throughout the period of the study. TDI assessments were similarly carried out by a single observer throughout the duration of the study. All TDI assessments were done within 72 hours of the MUGA studies and in any case before any change in dose exposure. A Philips® R M2424 A ultrasound machine with inbuilt software for TDI imaging was used for assessments and data of 8 parameters including diastolic and systolic measurements of wall motions of both atria, left ventricle and septal wall were measured.

The criteria used to define abnormal TDI were those published earlier by Kapusta et al.[21] The peak velocities during systole, early- and late diastole, within the basal-, mid-, and apical parts of the inter-ventricular septum, and the LV free wall were assessed. These velocities were expressed as positive or negative when directed towards the transducer, or away from it, respectively. In systole, a positive velocity wave is detected, corresponding to the contraction and inward motion of the LV myocardium. The subsequent, biphasic, diastolic TDI pulsed waves are always negative and correspond to the relaxation outward motion of the LV myocardium (early- and late diastolic velocity, respectively). Therefore, a regional wall motion abnormality was defined as a myocardial movement opposite to the one expected from the study of the normal subjects during the diastolic phase of the heart cycle.[22] This abnormal wall motion was detected by visual inspection of the color image as well as by using the single gated TDI method.

MUGA scan was defined abnormal if LVEF was less than 2SD below expected level appropriate for age and sex or decline in LVEF by 10% from baseline.[19]

Both Observers were blinded to anthracycline or transfusion dose received. MUGA results were analyzed in real time and were used for all clinical decision-making, but the cardiologist remained blinded to the results. An interim analysis of the TDI results was made after 18 months and again at completion of the study. Institutional ethical clearance for the study was obtained prior beginning the study. Accumulated data was analyzed and the 2 methods compared using chi- square test for significance.

RESULTS

59 MUGA scans and 52 TDI assessments were done in 36 children over a 3 yr period starting Mar 2004. Cases included children and adolescents (less than 18 years of age) with a diagnosed malignancy receiving anthracyclines, or a chronic anemia enrolled on a regular blood transfusion program. 10 TDI assessments in 5 cases that could not be completed within 72 hrs of the MUGA scan or before a change in anthracycline or blood transfusion dose were discarded for purposes of analysis.

Cases included 29 children with malignancies of which 10 with Acute Lymphoblastic Leukemia (ALL) and 9 with Hodgkin's Disease (HD) formed the dominant groups. Other malignancies included 2 Non-Hodgkin Lymphomas

(NHLs), 2 Acute myelogenous leukemia (AML), and 6 Sarcomas of bones and soft tissues (Ewing's tumor, Primitive neuroectodermal tumor (PNET) Osteogenic sarcoma). All 7 chronic Anemia patients had beta-Thalassemia. Mean age was 8.33 yrs (2- 18 yrs, median 8 yrs). There was a marked male preponderance (M: F 2:1). 9 MUGA scans done pre-exposure to anthracyclines in children with malignancies and no apparent co-morbidities served as controls. Controls for TDI included 7 of these cases and 5 age matched, healthy children (3 Males, 2 Females). All controls had normal MUGA scans and TDI assessments.

When compared individually both tests picked up significant decline in function post-exposure. 50 post-exposure MUGA scans had a mean LVEF of 55.98% as compared to 60.44% pre-exposure with 10 (20%) cases showing a significant decline in function. (Table- 1) The difference in pre and post- exposure assessments was statistically significant.

Table 1: MUGA results Pre- and Post Exposure.

MUGA Results	Pre- Exposure	Post- Exposure	Total
Normal	9	40	49
Abnormal	0	10	10
Total	9	50	59

Mean anthracycline dose was 317.27 mg/ m^2 (90- 480 mg/ m^2). 2 had also received radiation to the chest. Mean transfusion dose was 1569.17-ml/ kg (220- 3000 ml/kg). However, number of cases detected to have decline in cardiac function by TDI was much higher in the same post-exposure group. 28 of 40 (70%) TDI assessments showed a significant decline in cardiac function as compared to nil in the pre- exposure group. The difference was highly significant. (Table- 2)

Table 2: TDI Results- Pre and Post Exposure.

TDI Results	Pre- Exposure	Post- Exposure	Total
Normal	12	12	24
Abnormal	0	28	28
Total	12	40	52

TDI- Tissue Doppler Imaging, MUGA- Multiple gated Acquisitions.

When the 2 methods were compared to each other, the difference in number of cases detected with decreased cardiac function by TDI compared to MUGA was found to be statistically highly significant ($p<0.01$) as reflected in Table-3.

Table 3: Comparison of MUGA *vs* TDI in Post- Exposure Cases.

MUGA vs TDI	Normal TDI	Abnormal TDI	Total
Normal MUGA	11	17	28
Abnormal MUGA	0	9	9
Total	11	26	37

TDI- Tissue Doppler Imaging, MUGA- Multiple gated Acquisitions.

This indicates that TDI assessment is superior to MUGA scan in detecting declining cardiac function in these children. To see whether those detected by TDI had truly declining cardiac function or were false positives, we looked at data in which serial TDI assessments were available in the same child on 2 or more occasions post exposure to increasing doses of anthracyclines or transfusions. Serial TDIs available in 15 children showed 10 with progressive decline of cardiac function with increasing exposure. This included all 5 detected by MUGA. In 4 of these latter cases, initial post exposure MUGA scans were normal while TDI showed decline, while both showed decline in the subsequent assessment. In the 5th case TDI became abnormal at the same time as MUGA. In the remaining 5 children in whom TDI had shown significant decline in cardiac function with increasing exposure, MUGA scans had remained in the normal range and showed no decline. None of the 5 healthy controls showed any decline in TDI assessments in a single follow- up done 6 to 9 months after initial evaluation. The numbers were too small however to be subjected to statistical tests of significance.

DISCUSSION

Our study, is first novel study, done at that time period, directly comparing the two non-invasive modalities, TDI versus MUGA, for assessing cumulative cardiotoxicity in two different population groups who were likely to suffer cardiac dysfunction either as a result of anthracycline exposure or recurrent blood transfusions leading to iron overload syndrome. Though the mode of injury is multi-factorial and slightly different in both cases, the final pathway for both is iron-metabolite mediated myocardial damage resulting in decreased function.[6] Moreover, as both TDI and MUGA measured the end product that was cardiac function, the mode of damage would not influence the outcome; therefore the two types of cases were clubbed in the study.

Both methods individually showed a significant decline in cardiac function post-exposure as compared to normal pre-exposure studies in all cases. However, the number of cases with significantly decreased cardiac function detected by TDI was far higher (70%) as compared to MUGA (20%). The comparative difference between two modalities was found to be statistically highly significant ($p<0.01$). This indicates that TDI assessment is superior to MUGA scan in detecting declining cardiac function in these children. The cases detected early by TDI were true positives as MUGA picked them up subsequently in 4 out of 5 cases. In another 5 cases TDI became abnormal and showed progressive decline with increasing exposure while MUGA remained normal. TDI did not show any false positive results in any of the controls over a period of 6-9 months. However, a larger prospective trial would be required to conclusively prove this assertion about true and false positive results with additional markers of cardiac damage. There are studies comparing TDI with standard Doppler or with Tissue-velocity magnetic resonance imaging but no studies compared TDI with MUGA.[23,24]

Children with malignancies exposed to anthracylines and radiation suffer significant cardiac dysfunction, which has become one of the principal causes of morbidity and limited life spans in survivors.[25,26] Clinically evident cardiotoxicity was initially reported as high as 18% to 26% which can be increased to 36% in patients receiving more than 600 mg/m^2 of anthracycline leading to recommendations to maintain cumulative anthracycline dose at < 250 mg/m^2.[27,28] Congestive heart failure may even present up to 20 years after successful therapy with

anthracyclines.[29,30] Similar cardiotoxicity is also seen in chronically transfused patients who suffer from iron overload syndromes, where cardiac dysfunction remains the main cause of death in those who remain on transfusion regimes into the 2nd and 3rd decades.[31,32] The mechanism in both cases is through iron metabolites mediated cardiac damage resulting in cardiac dysfunction.[33] In fact, iron-chelation remains an accepted mode of treatment for cardiotoxicity from both causes.[6] Sensitive and specific methods of early detection are of paramount importance as early diagnosis can enable intervention in both cases.[34,35] Alternatives to conventional anthracyclines, addition of cardio-protective agents, and use of iron-chelators are effective alternatives. Though adding to costs, they could become justified in those suffering from early cardiac damage.[36]

Conventional 2-D echo, with measurements of LVEF, is limited in its capacity to detect cardiac dysfunction till significant decline has occurred.[9,37] Left Ventricular Ejection Fraction (LVEF) and regional wall motion measurement by Radionuclide Multigated Analysis (MUGA) scanning overcame this limitation by providing sustained and sensitive recordings over a period of time resulting in more accurate measurement of LVEF.[19,38] It thus evolved as an accepted modality to monitor cardiac function but required extensive infrastructure and trained manpower. The basic limitation of using LVEF as a tool for assessment of cardiac function however remained.

TDI has evolved as a novel echocardiographic technique, which overcomes these limitations by measuring regional systolic and diastolic velocities within the myocardium and at the corners of the mitral annulus.[13,14] The velocity of annular motion reflects shortening and lengthening of the myocardial fibers along a longitudinal plane. The early diastolic velocity recorded at the lateral corner of the annulus (Ea) has been recently demonstrated to decline progressively with age and to be reduced in pathologic LV hypertrophy,[16] as well as in patients with restrictive cardio-myopathy.[17] These findings suggest that Ea is an index of LV relaxation that may not be influenced by left atrial pressure, offering considerable advantage for early detection of dysfunction. Stapleton et al in their study population of 151 children after anthracycline treatment of childhood malignancies demonstrated abnormalities of both LV and right ventricular longitudinal diastolic function at all dosages of anthracyclines, including decreased early annular velocities and Ea/Aa ratios and compensatory increases in late diastolic tissue Doppler velocities.[39]

The concept behind tolerable cumulative dose for antracyclines has changed over the last few decades due advances in field of non-invasive imaging. It was initially thought that cumulative doses less than 500 mg/m^2 carried a low risk of anthracycline-induced cardiotoxicity. However, numerous subsequent reports have demonstrated evidence of cardiac dysfunction with cumulative anthracycline dosages less than 250 mg/m^2.[21] TDI can pick up more abnormalities at relatively low to moderate (120-450 mg/m^2) cumulative anthracycline doses as demonstrated by Kapusta and colleagues with regional LV free wall motion abnormalities in more than 80% of pediatric oncology patients.[21] In our study mean cumulative anthracycline dose was 317.27 mg/ m^2 (90- 480 mg/ m^2) and carditoxicity was picked up in 70% of exposed patients (28/40).

TDI was also effective in early diagnosing transfusion associated cardiotoxicity.[40] Silvilairat and colleagues in their study of thirty-one pediatric patients with transfusion-dependent beta thalassemia demonstrated that diastolic dysfunction was absent in all patients with serum ferritin <2500 ng/mL, and was present in all patients with serum ferritin >5000 ng/mL and Deceleration Time (DT) has a significant correlation with serum ferritin ($r = -0.59$, $p <$

0.0001).[41] In the present study, the mean transfusion dose was 1569.17-ml/ kg (220- 3000 ml/kg), however, we did not correlate it with serum ferritin levels. Published studies demonstrate correlation between cumulative transfusion dose with biochemical markers like serum ferritin, amino terminal pro-brain natriuretic peptide (NT-proBNP) and liver iron concentration (LIC).[8]

TDI has also advantages of relatively lower cost of upgrading existing cardiology facilities, which are more widely available, making it an attractive alternative to the existing modes of performing this vital assessment. Other markers of cardiac damage including Cardiac Troponins, Atrial Natriuretic Peptide exist, but their role in predicting cardiac damage remains limited due to lack of consistent evidence of efficacy.[34,35] Therefore a need was felt to objectively compare this newer modality with existing standards to test efficacy and establish its utility.

A limitation of the present study remains the small sample size, and the results would need further validation. Sufficient grounds exist, however, based on this study, to explore this modality as a standard test for early detection of cumulative cardiotoxicity in patients exposed to anthracyclines and chronic transfusions.

CONCLUSIONS

TDI emerged as a more sensitive method for early and reliable detection of cardiac dysfunction in children exposed to anthracyclines and multiple blood transfusions as compared to current methods which have significant limitations. In addition abnormal TDI precedes detection by the latter providing an opportunity for earlier intervention. The markedly higher numbers of cases detected by TDI as compared to MUGA appear to be “true positives”. However, this remains unproven in our study and needs verification in a larger prospective trial.

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