SREE CHITRA TIRUNAL INSTITUTE OF MEDICAL SCIENCES AND TECHNOLOGY

PROJECT REPORT

CANDIDATE: DR. HEMANT MADAN

PROGRAMME: DM CARDIOLOGY

MONTH AND YEAR OF SUBMISSION: NOV 2003

CERTIFICATE

I, Dr **Hemant Madan**, hereby declare that the projects included in this book were undertaken by me under the supervision of the faculty, Department of Cardiology, SCTIMST.

Trivandrum,

1-11-2003

Dr. Hemant Madan

Forwarded,

The candidate, **Dr Hemant Madan**, has carried out the minimum required procedure.

Trivandrum,

1-11-2003

Prof. JaganMohan.A.Tharakan
Professor and Head
Department of Cardiology
SCTIMST

No:	PROJECT	PAGE
1	**Angiographic morphology of patent ductus arteriosus – Is Krichenko classification still relevant?**	2
2	**Doxorubcicin induced diastolic heart dysfunction An echocardiographic study**	25

ANGIOGRAPHIC MORPHOLOGY OF PATENT DUCTUS ARTERIOSUS – IS KRICHENKO CLASSIFICATION STILL RELEVANT?

ANGIOGRAPHIC MORPHOLOGY OF PATENT DUCTUS ARTERIOSUS – IS KRICHENKO CLASSIFICATION STILL RELEVANT?

INTRODUCTION

Persistent patency of ductus arteriosus (PDA) in the postnatal period is among the commonest congenital heart diseases. The incidence of PDA varies from 1 in 2000 to 1 in 5000 live births and it accounts for 10 to 12 percent of all congenital heart diseases. [1, 2] Though surgical closure of PDA, when indicated, is the established form of treatment for the condition, the availability and feasibility of percutaneous closure for PDA has become increasingly safe and acceptable.

Improvements in technology and cardiac catheterization techniques have ensured ease of deployment and effective closure in a large percentage of patients with isolated PDA. The initial device occlusion of PDA was carried out with a Rashkind double umbrella device [3]. Subsequent development saw the introduction of Gianturco coils – previously used for occlusion of tumour vascular supplies and arteriovenous malformations – for closure of PDA [4]. Closure of large PDAs still remained a relative contraindication for percutaneous closure till the introduction of PDA occluder devices – the Amplatzer occluder device being the most popular at present.

Krichenko first proposed a classification of PDA based on angiographic appearance in 1989 [5]. While there has been significant progress in the designing and manufacture of PDA occluding hardware, the basic angiographic appearance of PDA has received little attention. This is paradoxical because the shape of PDA may in part determine the designing of various types of occluding devices (coils included).

The present study was a retrospective analysis of angiographic appearance of PDAs planned for percutaneous closure at a single center.

AIM AND OBJECTIVES

The study was conducted with the overall aim of analyzing the morphological angiographic appearance of PDAs planned for percutaneous closure at a single tertiary care center. The specific objectives of the study were:

1. To define the shapes of PDA at angiography.
2. To measure the size of various anatomical components of the ductii in order to have a standard of measurement for the population.
3. To classify ductii according to the shapes encountered.
4. To compare the classification of ductii with the one proposed by Krichenko.

MATERIAL AND METHODS

This study was a retrospective analysis of angiogram films of all patients planned for a percutaneous PDA closure over a period of 4 years at a single center.

Review of angiograms

Cineangiogram films were reviewed on standard display equipment (TAGARNO). Catheter size, which was known from the procedure report, was measured on the screen. Measured value divided by the actual catheter size gave the calculated magnification factor:

Magnification factor = Catheter size measured on screen ÷ Actual catheter size

Thereafter, measurement of various anatomical components of the ductus was carried out on screen. Each of these measurements divided by the magnification factor gave the actual measurement.

Eg **Ampulla size = Ampulla measured on screen ÷ Magnification factor.**

Measurements of ductii on digital angiogram films (after January 2001) were done using standard quantitative angiogram software (Phillips Inturis).

Angiographic assessment of PDA was usually done in the lateral view. Appropriate cranial or caudal angulation was given to profile the ductus when indiacted. Right anterior oblique view (RAO 30 degrees) was done in a few cases to highlight the ampulla at the pulmonary artery (PA) end (when it was present).

Measurements of anatomical components of ductii

Ductii were measured at the following points (Fig 1):

1. Ampulla at the aortic end.
2. Narrowest portion of the ductus.
3. Ampulla at the pulmonary end – if present.
4. Total length of the ductus
5. Depth of the ampulla.
6. Angle of the ductus with the descending thoracic aorta.

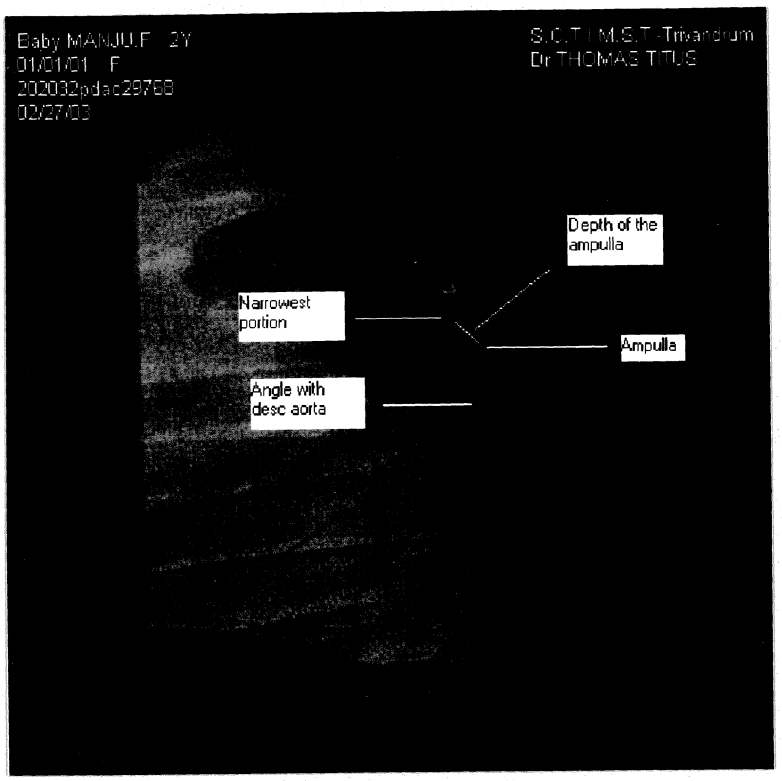


Fig 1: Description of various anatomical components of the ductii.

Angiographic types of ductii

After noting the measurements at various anatomical points, the ductii were classified into the following types as defined:

Saucer shaped: When the total length of the ductus < 6 mm with a narrowing at the PA end by more than 50 percent of the width of ampulla (Fig 2)

Cylindrical (Tubular ductus) – When the length of the ductus was more than 6 mm with a narrowing at the PA end by < 50 percent of the width of the ampulla. (Fig 3)

Conical ductus (Cup shaped): When the total length of the ductus was more than 6 mm with a narrowing at the PA end by > 50 percent of the ampullary width and the length of this narrow portion (stem of the ductus) < one-third of the total length of the ductus.(Fig 4)

Funnel shaped ductus: When the ductus was similar to a conical ductus but had a longer stem (more than one-third of the total length of the ductus) [Fig 5]

Hourglass shaped ductus: When the ductus had an ampulla at both the PA and the aortic end (Fig 6)

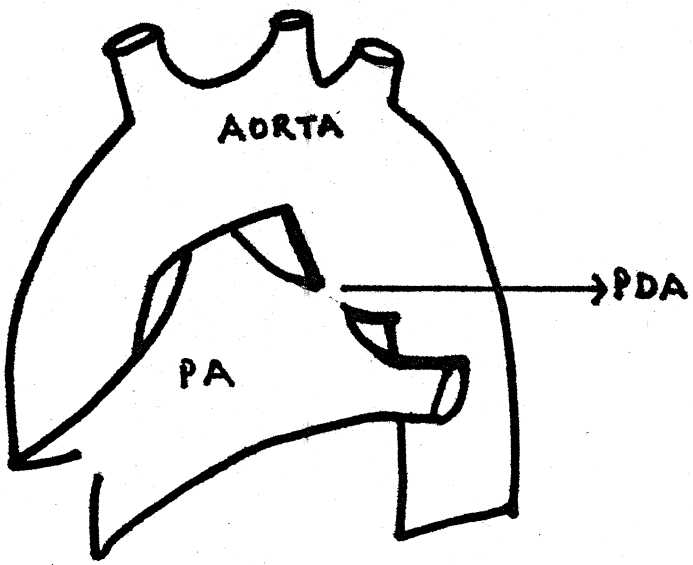
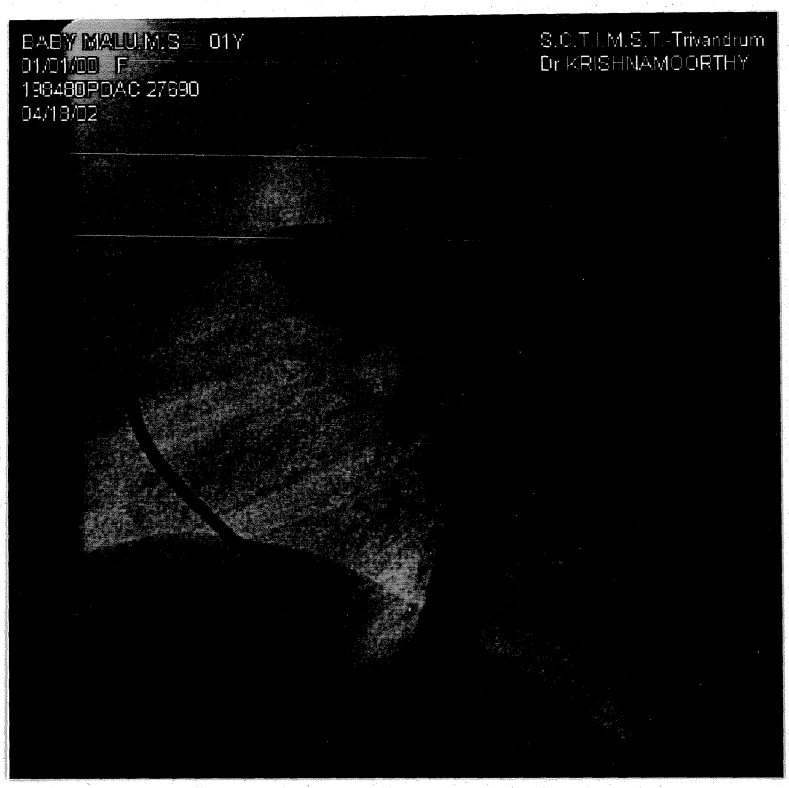


Fig 2:Saucer shaped ductus – note the shallow depth of the ductus with hardly any narrowing at the PA end



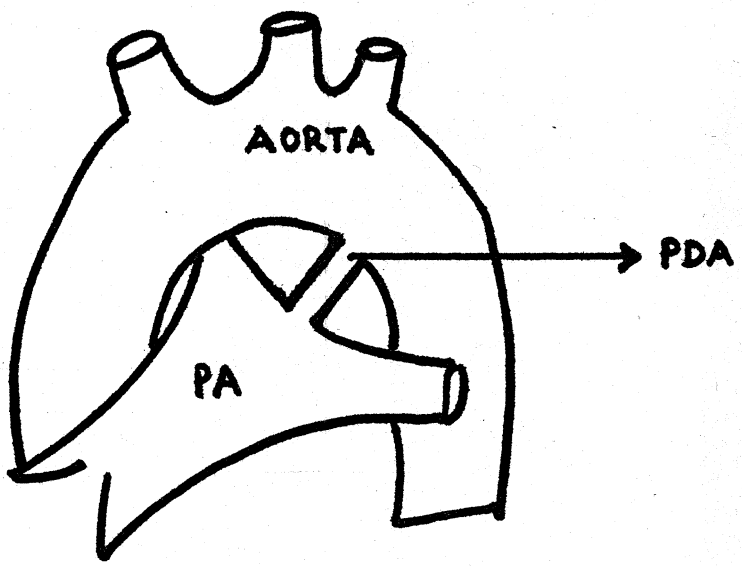
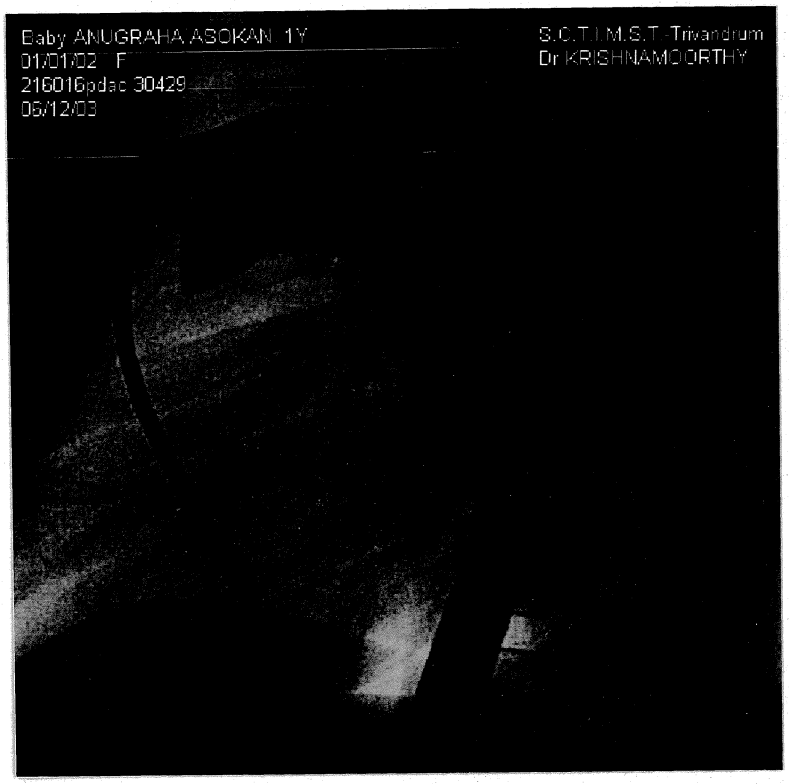


Fig 3: Tubular ductus – note the length of the ductus > 6mm with a < 50% narrowing at the PA end.



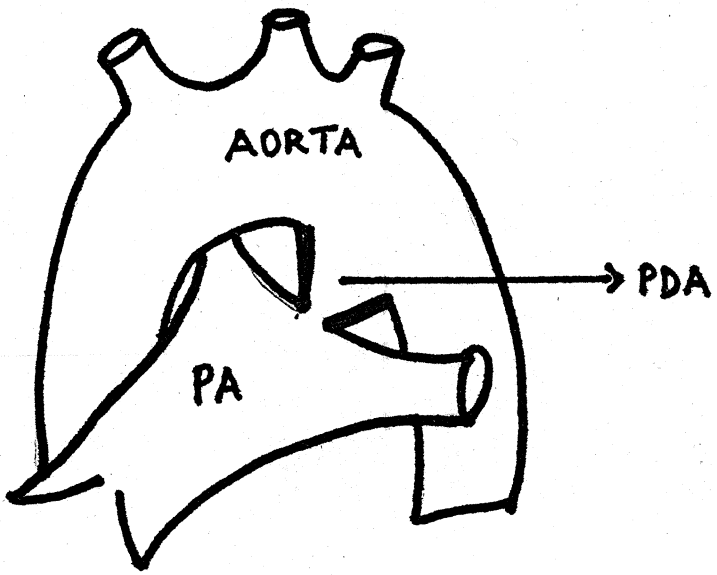
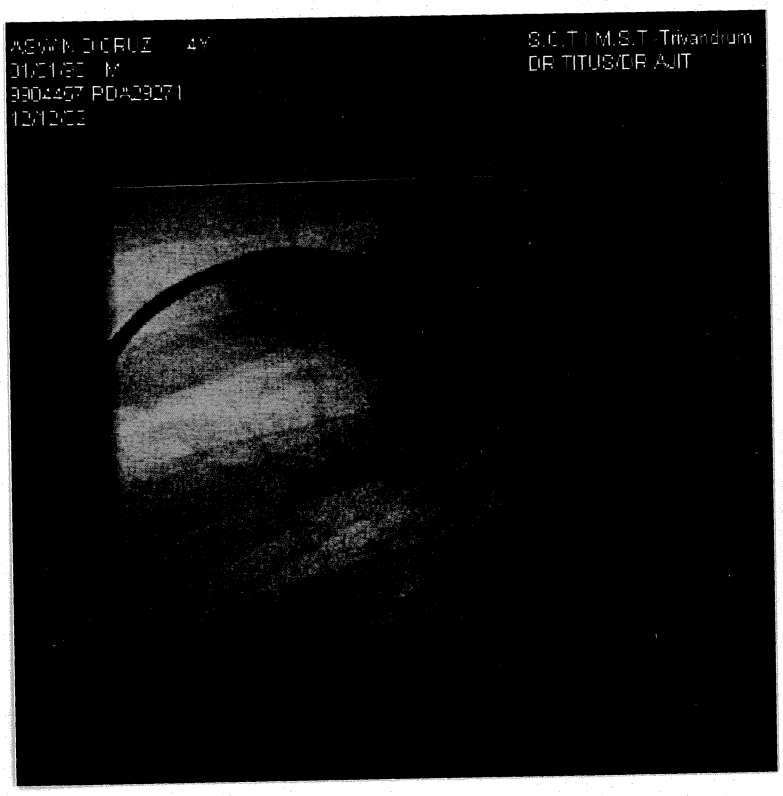


Fig 4: Conical Ductus – note the narrowing at the PA end by > 50% of the ampullary width and small stem of the ductus.



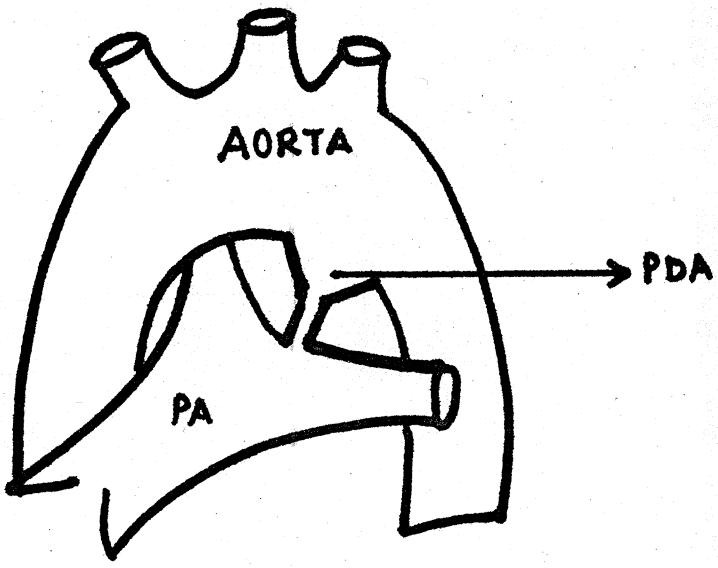


Fig 5 Funnel shaped ductus – note the relatively long stem of the ductus as compared to the conical ductus

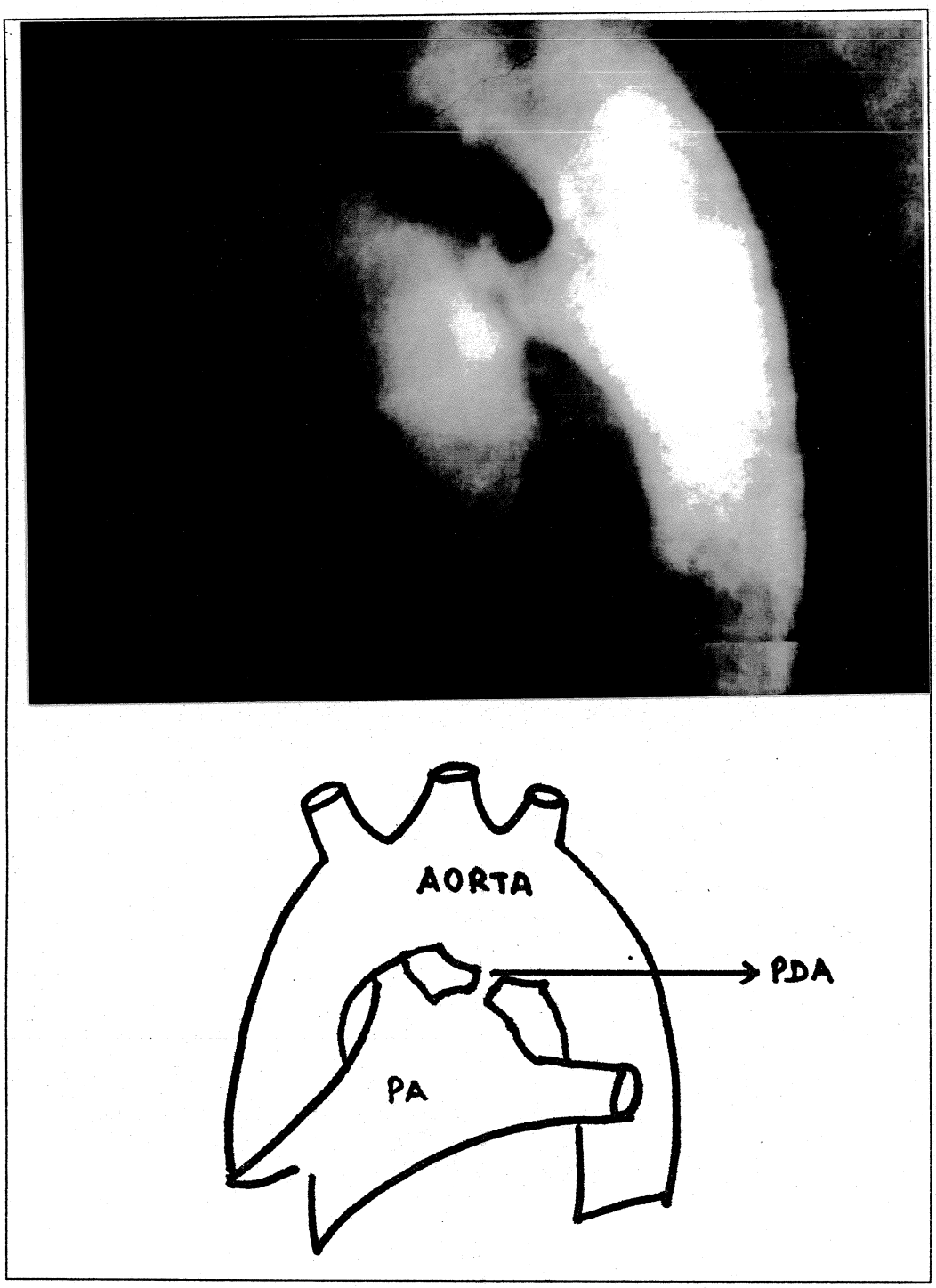


Fig 6: Hourglass shaped ductus – note the narrowest mid-portion of the ductus with a dilatation at both the aortic and PA end

Comparison with Krichenko Classification:

All the ductii were also classified based on Krichenko classification and the prevalence of various types of ductii was noted.

Clinical and hemodynamic data:

The following clinical and hemodynamic parameters were also noted as a part of the study:

a. Demographic variables – age and sex.
b. Symptomatology and associated cardiac diseases.
c. Basal left to right shunt as assessed by the ratio between pulmonary blood flow (Qp) and systemic blood flow (Qs)
d. Presence of pre – procedure pulmonary hypertension.
e. Number of coils (in case of coil occlusion) or size of device used for closure of the PDA.

Statistical analysis:

The collected data was analyzed using the SPSS Version 10 software. Descriptive variables were defined using mean and standard deviation while correlation was described using t test for dependant or independent variables.

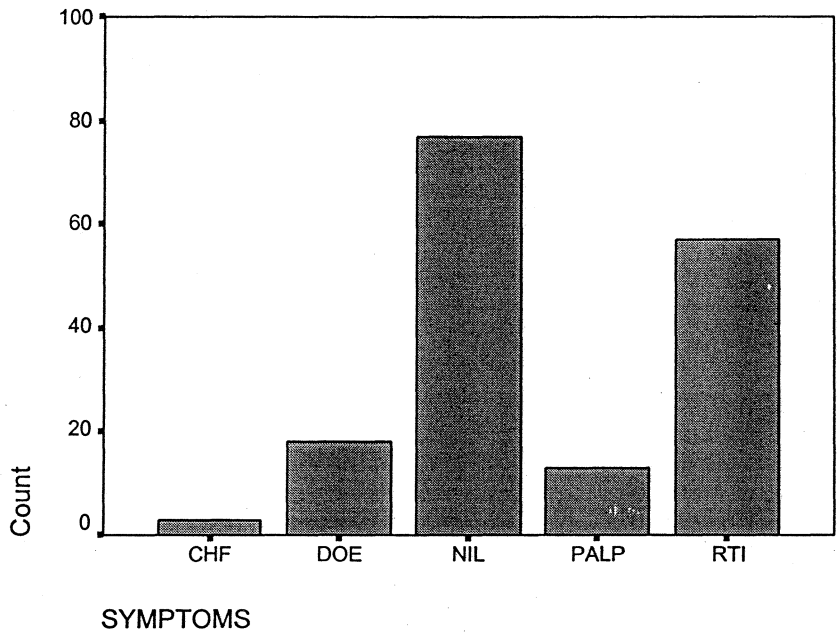
RESULTS

Angiographic appearance of ductus arteriosus in one hundred and sixty eight consecutive patients undergoing cardiac catheterization with an aim to perform percutaneous closure of the ductus was analyzed. The study cohort included 112 females (66.7%). The mean age of patients was 4.6 + 9.74 years (range = 9 months to 52 years.

Clinical and hemodynamic variables

The frequency of occurrence of various symptoms is shown in Figure 7. As evident, a majority of patients were asymptomatic with an incidental diagnosis of PDA. .

Fig 7 Distribution of symptoms



(DOE – dyspnoea on exertion, CHF – congestive heart failure, NIL – no symptoms, PALP – palpitations, RTI – frequent respiratory infection)

The mean shunt (Qp / Qs) in the study cohort was 1.76 $\pm$ 0.483 : 1 (Range 1 – 5). The mean shunt was significantly higher in the subgroup of 10 patients who underwent a PDA device closure (Qp/Qs = 2.488 $\pm$ 1.195) as compared to the patients who underwent a coil closure.

Sixteen patients (9.5%) had pulmonary artery hypertension (PAH) on hemodynamic assessment. The incidence was significantly higher in the patients who

underwent a device closure (60%). All patients had only mild to moderate PAH with no significant pulmonary vascular disease.

Associated cardiac disease

Overall 14 patients (8.3%) of cases had associated mild cardiac disease. The commonest associated disorders were bicuspid aortic valve (n=2) and peripheral pulmonary stenosis (n=2). 2 additional patients had Down's syndrome. A small ventricular septal defect and an operated case of atrial septal defect were also among the group of patients who underwent percutaneous closure.

Performance of procedure

One hundred and sixty seven patients underwent a successful percutaneous closure of the ductus. Coil closure could not be carried out in one patient due to failure to deploy coils. The ductus was closed with coils – detachable or non-detachable – in 157 patients and using PDA occluder device in 10 patients. The number of coils used for closure was – 1-coil in57.3% (n=90) patients, 2 coils in 36.9% (n=58) and 3 coils in 5.7% (n=9) patients. (Fig 8) A bioptome-assisted deployment of multiple coils was done in 23 patients.

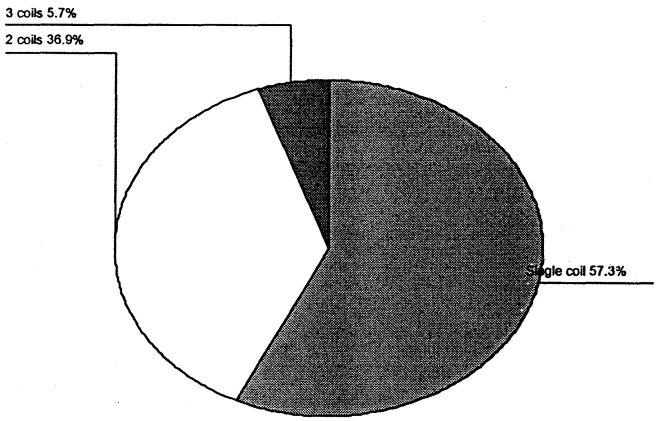


Fig 8 – Number of coils used for PDA coil embolization.

Ten patients underwent a successful device closure of the PDA. The indication for device closure in all these patients was a large ductus. The size of devices used was – 8/6mm in 5 cases, 10/8mm 4 cases and 12/10mm in 1 case.

Ductus morphology

Description of various anatomical parameters of the ductii is shown in Table 1.

	Value (range)
Width of the ampulla (mm)	11.52 ± 4.27 (2.7 – 27.3)
Length of the ductus (mm)	8.99 ± 2.97 (2.4 – 22.7)
Depth of the ampulla (mm)	6.57 ± 2.68 mm (1.2 – 17.99)
Naorrowest portion (mm)	2.53 ± 1.25 mm (0.7 – 6.6)
Angle with descending aorta (degree)	141.4 ± 13.56 (110 – 170)

Table 1: Anatomical parameters of the ductii studied

When a separate analysis was performed for patients who underwent device closure (as compared to coil embolization), these patients had larger left to right shunts (Qp / Qs 2.48 ± 1.2 Vs 1.34 ± .31 in PDA coil group), larger ampullae (18.29 ± 5.08 Vs 11.11 ± 3.87 mm), larger diameter at the narrowest points (5.05 ± 1.15 Vs 2.38 ± 1.08 mm) and longer lengths (12.56 ± 3.03 Vs 8.78 ± 2.83mm). However patients in the device closure group also tended to be older (mean age 16.4 ± 15.49) as compared to the patients in the coil group. None of the differences in the size assumed statistical significance.

Morphological Types of PDA

A distribution of the various ductii as classified according to the Krichenko classification is shown in Fig 9. As evident, Type A ductii (ampulla at the aortic end accounted for the majority of cases (92.1%). Tubular ductii accounted for the rest.

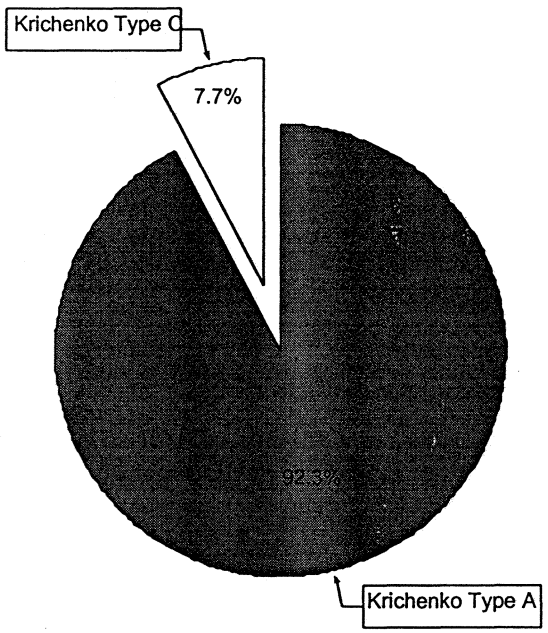
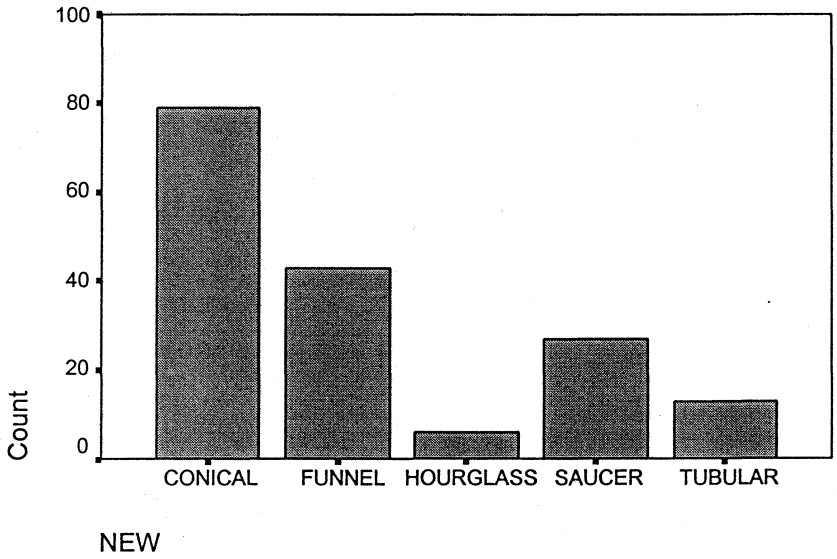


Fig 9 - Distribution of various types of ductii according to Krichenko classification

An analysis of the shapes of ductii as per the proposed classification given before is shown in Fig 10. Conical type of PDA was the commonest accounting for 47% of all cases (n = 79). The frequency of occurrence of other shapes was funnel shaped 25.6% (n = 43), saucer shaped 16.1% (n = 27), tubular 7.7% (n= 13) and hourglass shaped 3.6% (n = 6).

Fig 10 - Distribution of PDA types according to angiographic appearence



DISCUSSION

Antoninho Krichenko first proposed a classification for PDA based on angiographic appearance 1989. The study included a total of 79 patients planned for percutaneous closure of the PDA. PDA was classified into 5 types based on aorticopulmonary configuration, relation ship to tracheal air shadow and areas of narrowing. The description of various types of PDA is given in Table 1 and Fig 11.

An alternative system of classification- based on the morphological appearance was used in the European registry of transcatheter coil occlusion of PDA [6]. This registry, which reported results of attempted coil occlusion of PDA in 1258 patients analyzed the shapes of ductii according to angiographic appearance. The types of ductii in this study were conical in 43.8%, tubular in 9.5%, window like in 4.4%, complex in 5.2%, elongated in 15% and unclassified in 8%. The study also included a large percentage (14.1%) of residual ductii.

Table 1 – Description and distribution of angiographic types of PDA – as originally proposed by Krichenko (*Am J Cardiol 1989, 63: 877 – 880*)

Type of PDA	Description	Frequency
Type A	Narrowest segment at the PA end with well defined ampulla at the aortic end	64.6%
❖ A1	❖ Constriction anterior to trachea	o 34.2%
❖ A2	❖ Constriction at trachea	o 17.7%
	❖ Constriction posterior to trachea	o 12.7%
❖ A3		
Type B	Narrow segment at the aortic end	17.7%
❖ B1	❖ Constriction anterior to trachea	o 3.8%
❖ B2	❖ Constriction at trachea	o 8.9%
	❖ Constriction posterior to trachea	o 5%
❖ B3		
Type C	Tubular ductus without constriction	7.6%
Type D	Multiple constrictions	3.8%
Type E	Bizarre confguration with constriction remote from trachea	6.3%

The present study, which was a retrospective analysis of the morphological appearance of the ductii, found significant differences form Krichenko's classification. A large majority of ductii in the present study fulfilled angiographic appearance of Krichenko Type A. This percentage (92.3%) was much higher than the 64.6% reported by the author. It was also more than the reported incidence of this type of ductus in the European registry (conical - 43.8% + elongated - 15%).

The second major difference from Krichenko's study was the complete absence of Type B ductus in the present study. This type accounted for 17.7% percent of Krichenko's cases. Though ductii with a small ampulla at the PA end were seen in a

small number of cases (3.6%) all of them had larger ampullae at the aortic end and were hence classified as hourglass shaped in the present study.

The reason for the higher prevalence of so called Krichenko Type A ductii and the absence of Type B ductii may be demographic. Alternatively, the difference may be a limitation of the angiographic demonstration of the ductus. This study relied predominantly on lateral view (with or without minor angulation) for profiling the ductii since the PDA is best profiled in this view. Whether this could lead to an inadequate profiling of the PA end of the ductus is not certain. However, since lateral view is the view used by most interventional cardiologists during percutaneous occlusion of PDA, a system of classification based on the angiographic appearance in this view is more relevant in clinical practice.

Another important observation of the study was that ductii classifiable as Krichenko Type A included ductii with more than one angiographic appearance. It was noted that conical, saucer, funnel and hourglass shaped ductii fulfilled criteria for inclusion in Type A Krichenko but were actually quite different from each other in their angiographic appearance. Hence the present study relied more on angiographic descriptive characteristics of the ductus shape rather than on the classification type of ductus. This feature may have potentially utility in deciding the type of percutaneous intervention hardware planned for a PDA – coil embolization or device occlusion.

An observation also confirmed in the present study was the relative infrequent prevalence of tubular (Krichenko Type C) ductus. This type, which constituted 7.6% of Krichenko's series and 9.5% in the European registry, was seen in 7.7% of the present series. This favorable statistic is important, as this type of ductus is difficult to close by percutaneously and is also likely to have residual flow more often than ductii with large ampullae. [6]

The mean ampulla size of 11.52 mm, size at the narrowest portion of 2.53 and a mean length of 8.99 mm was similar to the statistics reported by Krichenko.

CONCLUSION

This study was a retrospective analysis of the angiographic appearance of PDA planned for a percutaneous occlusion with coils or device. This aspect of percutaneous closure of PDAs has not received significant attention in the past. We observed that the types of PDAs encountered in the present study were significantly different from Krichenko's classification – which is the only established system of PDA types based on shape. A predominant majority of PDAs have an ampulla at the aortic end thus making them easily amenable to percutaneous closure. Significantly, no PDA was found to have an isolated ampulla at the PA end.

We have also proposed a lose classification of the shapes of PDA – as visualized angiographically. Future studies will need to address whether this information is of help in deciding the choice of occluding hardware (coil Vs device).

REFERENCES

1. Anderson RC: Causative factors of congenital malformations.1, Patent ductus arteriosus. Pediatrics 14: 143; 1954.

2. Cargen LE. The incidence of congenital heart diseases in children born in Gothenberg 1941 – 1951. Br Heart J 21: 40; 1959

3. Rashkind WJ, Mullin CE, Hellenbrand WE et al.: Non surgical closure of patent ductus arteriousus: clinical application of the Rashkind PDA occluder system. Circulation 1987, 75:583-592.

4. Lloyd TR, Fedderly R, Mendelsohn AM et al. Transcatheter occlusion of patent ductus arteriosus with Gianturco coils. Circulation 1993, 88:1412 – 1420.

5. Krichenko A, Benson LN, Burrows P, Moes CAF, McLaughlin P, Freedom RM. Angigraphic classification of isolated, persistently patent ductus arteriosus and implications for percutaneous catheter occlusion. Am J Cardiol 1989, 63: 877 – 880.

6. Magee AG, Huggon IC, Seed PT, Qureshi SA, Tynana M on behalf of Association of European pediatric cardiology.Transcatheter coil occlusion of the arterial duct. Eur Heart J 2001, 22: 1817 – 1821.

DOXORUBCICIN INDUCED DIASTOLIC HEART DYSFUNCTION - AN ECHOCARDIOGRAPHIC STUDY

DOXORUBCICIN INDUCED DIASTOLIC HEART DYSFUNCTION - AN ECHOCARDIOGRAPHIC STUDY

INTRODUCTION

Anthracyclines are potent anticancer drugs that form an important component of various chemotherapeutic regimes for commonly occurring malignancies including acute leukemia, lymphoma, sarcomas and carcinoma of breast. Doxorubicin is the most commonly used anthracycline in clinical practice. The mechanism of action (cytotoxicity) of these drugs is by inhibition of Topoisomerase II, an enzyme that is responsible for DNA repair in replicating cells.

Though extremely efficacious as anti malignancy drugs, prolonged and high dose therapy with anthracyclines is limited by cardiotoxicity – which is the chief side effect of these drugs. Though variously reported, the incidence of anthracycline induced cardiotoxicity may be as high as 10 percent in certain subsets of patients such as children and patients receiving concomitant mediastinal radiotherapy.[1] Anthracycline induced cardiotoxicity is due to generation of free radicals – particularly the hydroxyl ion.[1] This leads to defective calcium handling by sarcolemma, reduced actin and myosin synthesis, release of vasoactive amines and proinflammatory cytokines culminating in cell death.

The clinical manifestations of anthracycline induced cardiac dysfunction include a rare acute myopericarditis like syndrome, chronic cardiomyopathy, which is the commonest variety and late onset cardiac toxicity. Though various clinical variables including female sex, older age and underlying heart disease have been identified as risk factors for development of cardiac toxicity,[2] cumulative dose of the drug is the most important variable correlated with a higher incidence of toxicity. Doses in excess of 550-mg/m^2 result in an unacceptably high incidence of cardiotoxicity.[3]

Many investigative modalities have been used to detect early cardiotoxicity. These include radionuclide ventriculography,[4,5] endomyocardial biopsy,[6] blood estimation of cardiac enzymes (including Troponins[7], brain natriuretic peptide [8]), exercise testing and echocardiography.[9,10,11] Serial echocardiography, due to the wide availability, ease of performance, cost efficacy and repeatability is the investigation of choice for

baseline assessment and follow up of patients receiving anthracycline based chemotherapeutic regimes.

It is now known that extensive myocyte loss may have occurred by the time anthracycline induced systolic dysfunction becomes manifest.[11] Up to 15 percent of myocardial loss may have already occurred before early symptoms of cardiac dysfunction develop and more than 25 percent of myocardial loss is present by the time overt cardiac failure is present.[12] Diastolic dysfunction, on the other hand, appears earlier and may be a more sensitive marker of anthracycline cardiotoxicity. [13,14, 15]

Tissue Doppler echocardiography is a relatively new modality for assessment of cardiac diastolic function.[14] Evaluation of both global and regional diastolic function, preload independence and the feasibility of performing the test even in patient with atrial fibrillation and in patients with poor echo window are among the many advantages of this technique.[14] The modality has recently been evaluated in monitoring doxorubicin cardiotoxicity in pediatric population. [15]

The present study was a serial follow-up analysis of ventricular diastolic function in patients receiving doxorubicin chemotherapy with a comparison of the efficacy of pulse wave versus tissue Doppler indices of diastolic dysfunction.

AIM AND OBJECTIVES

The study was aimed at analyzing the effect of chemotherapy with doxorubicin on the diastolic performance of the heart in patients receiving this drug as a part of chemotherapy schedule for various malignant disorders. The study design was a prospective follow-up single center study.

The specific objectives of the study were:

1. To assess the baseline and serial ventricular systolic and diastolic performance in patients receiving chemotherapy with doxorubicin based regimes.
2. To assess the sensitivity of multiple tissue Doppler parameters in evaluation of diastolic dysfunction.
3. To compare two different modalities viz. Pulse wave and tissue Doppler in early detection of diastolic function.
4. To study the effect of various clinical parameters including drug dosage on the diastolic performance.

MATERIAL AND METHODS

Fifty-five patients planned for chemotherapy with anti cancer regimes, which included doxorubicin, were studied at baseline and follow-up. The study subjects underwent a pre-chemotherapy baseline assessment, which included a detailed cardiovascular history – including risk factors for coronary artery disease, other conditions such as hypertension and diabetes which may pre-dispose to diastolic dysfunction, functional status and co- existent cardiac disease (such as valvular heart disease, cardiomyopathy etc) which may alter echocardiographic assessment. A detailed clinical examination with particular emphasis on cardiovascular system was also done at baseline. Baseline investigations included a 14 lead electrocardiogram and chest X Ray (PA view). Follow-up clinical assessment included an assessment of the functional status and echocardiographic assessment of the patients. A detailed clinical examination and subsequent ECG and X Ray were done only for patients who had cardiac symptoms.

EXCLUSION CRITERIA

The following patients were excluded from the study:

a. Known underlying ischemic, valvular, congenital or any other form of structural heart disease.
b. Patients with conduction abnormalities like bundle branch blocks, which may impair assessment of diastolic function due to abnormal depolarization of the myocardium.
c. Co-existent pericardial effusion.
d. Subjects planned for concomitant radiotherapy.
e. Patients with a very poor functional status or far advanced malignancy with an expected survival of less than 3 months.

ECHOCARDIOGRAPHY

Echocardiographic assessment was done for all patients at baseline. Echocardiography was performed by a single operator on GE System 5 echocardiography equipment. Follow-up echocardiography was done on 3 occasions - after the patients had received a cumulative dose of 100, 200 and 300 mg / m^2 body surface area (BSA) of doxorubicin. Echocardiographic examination included the following:

M Mode and Two Dimensional (2D) Echocardiography

- Chamber measurements
- Evaluation of systolic function by calculation of ejection fraction and fractional shortening (by M mode analysis).
- Color flow assessment for any valvular or congenital heart disease.

Doppler Study:

Mitral Valve Inflow:

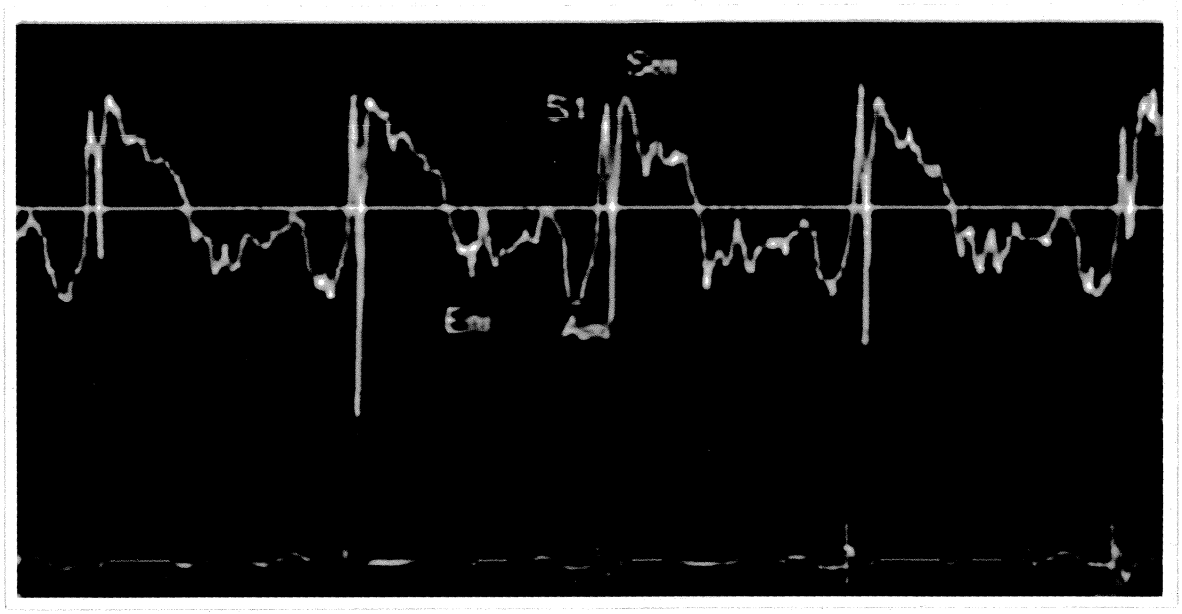
a. E and A Velocity
b. E/A ratio
c. Velocity time integral (VTI)
d. Isovolumic relaxation time (IVRT)
e. E deceleration time (EdT)

Pulmonary Venous Flow:

1. Pulmonary vein systolic and diastolic velocities. (PV S and D)
2. Reversal of pulmonary venous flow with atrial systole (PV AR)

Tissue Dopple (see glossary of terms page 30):

a. Em, A, S1 and Sm measurement,
b. Em/Am ratio
c. Acceleration and deceleration time of E myocardial
d. Tissue Tei's index



Tissue Doppler - Glossary of Terms

- Em velocity – early diastolic velocity – corresponds to the myocardial Doppler velocity during early rapid filling phase of ventricle
- Am velocity - late diastolic velocity – corresponds to the myocardial Doppler velocity during late rapid filling phase of ventricle (atrial contraction)
- S1 velocity – Early systolic Doppler velocity – corresponds to isovolumetric contraction of ventricles
- Sm velocity – Systolic velocity – corresponds to ejection phase velocity
- Sm duration – Duration of ejection phase myocardial velocity
- Q – Sm peak – duration from onset of systole (Q on ECG) to the peak of ejection phase velocity
- A – E duration – duration from the trough of Am wave to the peak of ensuing Em wave (includes the periods isovolumetric contraction time + ejection period + isovolumetric relaxation time)
- Tei's index – derived from the formula {(A to E interval – Sm duration) ÷Sm duration – represents the proportion of time of isovolumetric relaxation + isovolumetric contraction with the ejection time (represents a composite index of diastolic function of the ventricle.

Definition of diastolic dysfunction

Table 1: Definitions and types of diastolic dysfunction on pulse Doppler analysis

	Normal	Impaired relaxation	Pseudo-normalization	Restrictive Pattern
MitralE& A	E >A	E < A	E >A (E/A 1-2)	E>>A (E/A> 2)
E dT	200–250 ms	> 220 ms	150 – 200 ms	< 150
PV S & D	S > D	S>D	S < D	S < D
PV AR	< 35 cm/s	< 35 cm/s	> 35 cm / s	> 25

Features accepted as diagnostic of diastolic dysfunction on pulse wave and tissue Doppler were:

1. Reversal of E / A ratio of mitral valve velocity on pulse Doppler assessment.
2. Presence of pseudo-normalization / restrictive pattern of filling on mitral valve pulse Doppler evaluation.
3. Tissue Doppler Em / Am < 1.
4. Tissue Doppler Em velocity < 8 cm/s.

A left atrial (LA) size of more than one and a half times the aortic size or an absolute increase in the left atrial size by more than 10 mm over baseline LA size, in the absence of systolic dysfunction or mitral regurgitation, was also noted, though this criteria alone did not constitute a definition of diastolic function. Similarly, tissue Tei's index was calculated for all patients at baseline and follow- up echocardiograms but this criterion alone was not used to define diastolic dysfunction.

Definition Of Systolic Dysfunction

The values of ejection fraction below 50% or an absolute reduction in ejection fraction by more than ten percent from baseline was used to define systolic dysfunction.

STATISTICAL ANALYSIS

The data collected during the study was analyzed using the SPSS Version 10 statistical software. Demographic features were analyzed using the Chi square test and continuous variables were analyzed using the unpaired t test

RESULTS

CLINICAL PARAMETERS

A total of fifty-five patients were accrued in the study. The mean age of patients was 51.9 $\pm$ 12.34 years (Range 10 – 75 years). The age distribution of patients is shown in Fig 1.

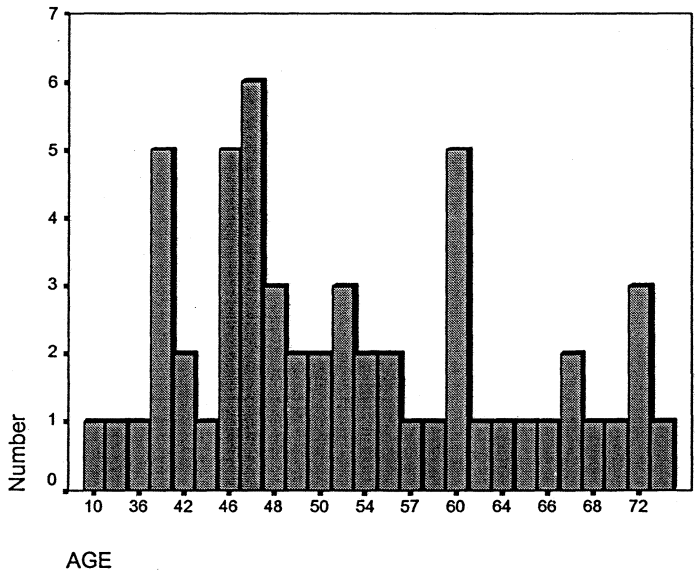
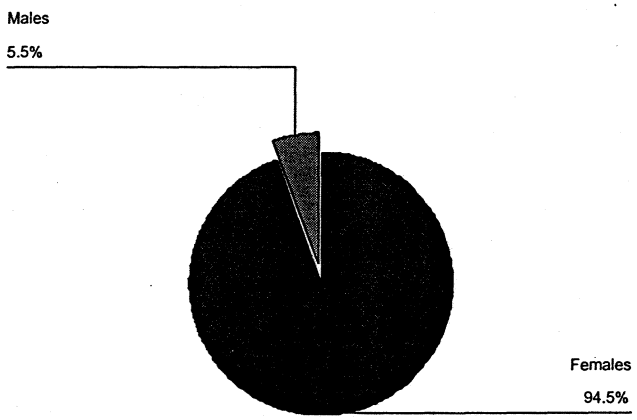


Fig 1: Age distribution of patients (n=55)

Females constituted 94.5 percent (n = 52) of the patients. (Fig 2)

Fig 2: Sex distribution of patients



The distribution of various malignancies among patients included in the study is depicted in Table 2. Carcinoma breast (pre or post operative) constituted an overwhelming majority (81.8%) among the patients included in the study.

Table 2: Distribution of types of malignancies among patients in the study (n=55)

	Number	Percent
ALL	1	1.8
Ca Breast	45	81.8
Hodgkin's disease	4	7.3
NHL	3	5.5
Carcinoma ovary	1	1.8
Soft tissue sarcoma	1	1.8
Total	55	100.0

ALL – Acute lymphatic leukemia, NHL – Non Hodgkin's lymphoma.

The prevalence of various coronary risk factors in the study cohort was – hypertension 20% (n=11), diabetes mellitus 14.5% (n=8), smoking 3.6% (n=2, both males), dyslipidemia 5.5% (n=3) and postmenopausal status 76.9% (n=40). 80 percent of the patients were in New York Heart Association (NYHA) functional class I whereas 11 patients (20%) complained of mild exertional dyspnoea (NYHA Class II) at the time of initial recruitment into the study. None of the patients included in the study had clinical or radiological evidence of cardiomegaly or pericardial effusion. No patient had ECG findings of left ventricular hypertrophy, left atrial enlargement or left ventricular strain.

BASELINE ECHOCARDIOGRAPHIC PARAMETERS (N = 55)

2 D ECHOCARDIOGRAPHY AND M MODE INDICES

Baseline M mode and echocardiographic findings are depicted in Table 3.

Table 3: Baseline M mode and 2 D echocardiographic characteristics of patients (n = 55)

	Mean (Range)
LVEDD	43.33 ± 4.78 (34 – 56)
LVESD	25.58 ± 4.05 (19 – 38)
EF	71.45 ± 6.54 (61 – 83)
FS	40.91 ± 6.51 (29 – 54)
LA	32.36 ± 4.07 (22 – 43)

No patient had echocardiographic evidence of left ventricular hypertrophy, pericardial effusion or regional wall motion abnormality.

PULSE WAVE DOPPLER INDICES

The mean aortic and pulmonary velocities were 1.25 ± 0.2 and 1.16 ± 1.6 m/s respectively.

Mitral Valve Doppler

The mean mitral valve E velocity was 0.79 ± .18 m/s with a mean E velocity time integral (VTI) of 11.78 ± 3.6m. The mean mitral A velocity was 0.69 ± 0.17 m/s with an A VTI of 9.05 ± 3.1 m. The mean mitral E velocity to A velocity ration (E/A) ratio at baseline was 1.07 ± 0.31 (range – 0.54 – 1.78). Patients had diastolic dysfunction (all with of the impaired relaxation type) at baseline. The mean E dT was 166.35 ± 43.7 ms (range 80 – 270 ms).

Pulmonary Vein Doppler

The mean pulmonary vein systolic velocity was 0.68 ± 0.16 m / s (range 0.16 – 1.3 m/s) and the mean diastolic velocity was 0.53 ± 0.14 m/s (range 0.12 – 0.9). The mean atrial reversal velocity (AR) was 0.34 m/s (range 0.14 – 0.5).

TISSUE DOPPLER ANALYSIS

Baseline tissue Doppler analysis parameters are shown in Table 4. As evident, the mean Em value at baseline (9.38 m/s) was higher than the mean Am value (8.43 m/s). The mean Em / Am ratio was greater than 1 suggestive of an overall normal diastolic function at baseline. The mean baseline tissue Tei's index was 0.85 $\pm$ 0.18 (Range – 0.20 – 1.52).

Table 4: Tissue Doppler indices of patients in the study (n = 55)

	Minimum	Maximum	**Mean**	Std. Deviation
Em velocity(m/s)	4.00	14.00	**9.3**	2.1
Am velocity (m/s)	3	13.00	**8.4**	2.0
Em /Am	0.44	3.3	**1.2**	0.5
S1velocity (m/s)	2.00	11.00	**5.7**	1.9
Sm velocity (m/s)	5.00	12.00	**8.2**	1.7
E acceleration time (ms)	30.00	130.0	**67.27**	19.86
E deceleration time (ms)	30.00	110.0	**72.18**	17.29
Q - Sm peak (ms)	60.00	190.0	**116.55**	33.9
A to E time (ms)	330	580	**474.18**	53.98
Sm duration (ms)	200	330	**256.55**	30.08
Tissue Tei's Index	.0.20	1.5	**0.8**	0.1

BASELINE ECHOCARDIOGRAPHIC CHARACTERISTICS OF PATIENTS WHO COMPLETED FOLLOW-UP (N = 36)

PULSE WAVE DOPPLER PARAMETERS

Mitral Valve And Pulmonary Vein

Doppler characteristics of patients who completed follow up in the study is shown in Table 5. Overall 16.6% (n = 6) of patients were diagnosed to have baseline diastolic dysfunction on the basis of mitral and pulmonary Doppler studies. All of them had impaired relaxation type of diastolic dysfunction.

Table 5: Description of pulse Doppler findings in patients who completed follow-up (n = 36)

	Range	**Mean**	SD
MVE	.44 - 1.20	**.88**	.16
MVA	.54 - 1.60	**.75**	.20
EARATIO	.54 - 1.78	**1.22**	.30
EdT	90 - 270	**172.73**	46.45
PVs	.16 - .90	**.64**	.16
PVd	.12 - .90	**.54**	.16
AR	.14 - .50	**.35**	0.07

BASELINE TISSUE DOPPLER CHARACTERISTICS

Baseline tissue Doppler characteristics of patients who completed follow-up in the study are depicted in Table 6.

Table 6: Baseline tissue Doppler characteristics of patients who completed follow-up (n = 36)

	Minimum	Maximu	**Mean**	SD
Em	6.00	14.0	**10.17**	1.9
Am	3.00	12.0	**7.8**	2.1
S1	2.00	10.0	**5.6**	1.9
Sm	5.00	12.0	**8.1**	1.8
Em/Am ratio	.75	3.3	**1.4**	.69
EAT	30.00	130.0	**68.61**	18.85
EDT	30.00	110.0	**74.17**	16.63
Q - Sm peak	60.00	190.0	**114.7**	33.93
A to E duration	330	58	**468.8**	54.55
Sm duration	200	33	**262.2**	30.34
Tissue Tei's index	0.39	1.1	**0.8**	0.1

The mean Em velocity was higher than the mean Am velocity with a mean Em / Am ratio of 1.45. The mean tissue Tei's index 0.80. Six patients had an Em velocity < 8 cm/s and 7 patients had Em / Am ratio < 1.

Overall 13.8% (n = 5) of cases fulfilled two out of three criteria as a pre-requisite for definition of baseline diastolic dysfunction.

FOLLOW-UP

Echocardiographic and clinical data from thirty- six patients were available for analysis. These patients underwent echocardiography on 3 additional occasions (in addition to the baseline echocardiography) – after receiving 100, 200 and 300 mg/m2 BSA of doxorubicin. One patient – with acute lymphatic leukemia - died due to infection during a period of neutropenia following chemotherapy. 18 patients were lost to follow up – 9 after the baseline evaluation, 7 after the 1st follow – up and 2 after the 2nd follow-up. Echocardiographic variables from these patients were not included in the overall follow up analysis.

CLINICAL EVALUATION

No patient in the study developed new onset cardiac symptoms. Nineteen patients (52.7%) complained of fatigue after commencement of chemotherapy, but they all had associated anemia, which could have accounted for the symptom. No patient developed cardiomegaly, features of cardiac failure or features suggestive of coronary insufficiency during the study. The mean (SD) dosage of doxorubicin at the time of performance of the 1st, 2nd and 3rd follow up echocardiogram was 121.54 (18.3), 248.65 (20.54) and 368.92 (18.65) mg / m2 BSA.

A repeat ECG or chest X ray examination due to cardiac symptoms was not necessitated in any patient.

ECHOCARDIOGRAPHY

M MODE AND 2 DIMENSIONAL ECHOCARDIOGRAPHY

Follow-up echocardiographic findings of 36 patients (along-with baseline) are depicted in Table 7.

Table 7: Follow up M mode indices at 1st, 2nd and 3rd review (n = 36)

	Baseline Mean (SD)	1st review Mean (SD)	2nd review Mean (SD)	3rd review Mean (SD)
LVEDD (mm)	42.78 (4.81)	44.50 (4.24)	45.92 (4.18)	46.67 (3.63)
LVESD (mm)	25.03 (3.89)	29.19 (4.36)	29.31 (3.28)	30.17 (3.67)
EF (%)	71.53 (7.04)	69.91 (7.62)	70.58 (6.86)	71.25 (6.58)

There was a mild increase in the mean LV dimensions over follow up echocardiograms. This achieved statistical significance only in the case of LVEDD ($p = 0.04$) whereas the LVESD and the EF did not change significantly ($p = 0.053$ and 0.34 respectively). No patient fulfilled the criteria for LV systolic dysfunction or left atrial enlargement during the study. No patient developed significant mitral regurgitation (> 2+ by colour Doppler) or pulmonary artery hypertension (right ventricular systolic pressure by tricuspid regurgitation jet $\geq$ 35 mmHg – 25 + right atrial mean) during follow up. No regional wall motion abnormalities were noted in any patient.

PULSE WAVE DOPPLER INDICES

Mitral Valve and Pulmonary Vein Doppler

Mean Doppler indices of mitral valve inflow and pulmonary vein at follow – up are shown in Table 8.

Table 8: Baseline and follow up indices of mitral valve Doppler study (n = 36)

	Baseline Mean (SD)	1st review Mean (SD)	2nd review Mean (SD)	3rd review Mean (SD)
E velocity (m/s)	.88(.16)	.83 (.16)	.76 (.15)	.68 (.14)
E VTI (m)	12.52(3.47)	9.7 (2.9)	10.09 (2.69)	9.36 (1.95)
A velocity (m/s)	.75 (.20)	.76 (.19)	.78 (.23)	.761 (.24)
A VTI (m)	9.32 (3.55)	8.32 (3.06)	7.51 (2.58)	8.18 (2.14)
E/A ratio	1.22 (.30)	1.17(.41)	1.05 (.32)	.94 (.26)
EdT (ms)	172.73 (46.45)	178.55 (55.6)	163.26 (37.42)	163.11 (36.70)
PV S (m/s)	.64 (.16)	2.1 (8.9)	.65 (.16)	.58 (.11)
PV D (m/s)	.54 (.16)	.54 (.14)	.53 (.13)	.54 (.14)
AR (m/s)	.34 (0.07)	.38 (.14)	.36 (0.06)	.34 (0.05)

There was a tendency for a reduction in mitral valve E velocity and E VTI and an increase in the corresponding A velocity and AVTI as cumulatively higher doses of doxorubicin was administered. On comparing the indices at baseline and at the end of the study, these changes were statistically significant for mitral valve E velocity ($p = 0.034$), A velocity ($p = 0.009$) and A VTI ($p = 0.024$). There was no significant change in the E VTI or EdT during follow up. None of the pulmonary vein doppler indices showed a statistically significant change from baseline during the study.

TISSUE DOPPLER ANALYSIS

The various tissue Doppler parameters studied in the study at baseline and follow up are shown in Table 9.

Table 9: Tissue Doppler indices at baseline and follow-up (n=36)

	Baseline	**1st review**	**2nd review**	**3rd review**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Em (m/s)	10.17 (1.98)	8.42 (2.52)	7.86 (1.53)	6.89 (1.09)
Am (m/s)	7.89 (2.16)	8.22 (2.86)	8.73 (1.91)	9.36 (1.29)
S1 (m/s)	5.61 (1.95)	4.21 (1.44)	4.58 (2.09)	4.53 (1.73)
Sm (m/s)	8.19 (1.82)	7.37 (2.00)	8.69 (1.49)	9.25 (1.32)
Em / Sm ratio	1.45 (.7)	1.26 (.99)	.95 (.31)	.74 (.15)
EAT (ms)	68.61 (18.85)	69.44 (23.29)	75.00 (22.87)	71.11 (17.9)
EDT (ms)	74.17 (16.63)	73.88 (16.95)	69.86 (14.32)	68.75 (12.03)
Q– Sm Peak (ms)	114.72 (33.93)	123.61(31.90)	143.33 (32.25)	169.58 (23.92)
A-E (ms)	468.89 (54.55)	478.89 (51.81)	481.39 (36.97)	496.39 (20.02)
Sm duration (ms)	262.22 (30.34)	252.50 (39.52)	243.06 (26.17)	228.33 (22.61)
Tei's index	0.8 (.18)	0.99 (.27)	1.00 (.28)	1.19 (.21)

On comparing various tissue Doppler indcies at final review with the parameters at baseline, a statistically significant decrease in Em velocity ($p = 0.006$), increase in Am velocity ($p = 0.01$), reduction in the S1 velocity ($p = 0.03$), prolongation of A to E duration ($p = 0.01$) and a reduction in the Sm duration ($p = 0.03$) was noted. E wave acceleration and deceleration times did not show a significant change and there was a tendency for prolongation of the Q – Sm peak that was not statistically significant.

DEVELOPMENT OF DIASTOLIC DYSFUNCTION

The number of patient who developed abnormal indices of diastolic function at various stages of follow-up is depicted in Table 7.

Table 10: Number of patients who developed abnormal indices of diastolic function at baseline and follow-up (n=36)

	Number of patients (%)			
Criteria	**Baseline**	**1st review**	**2nd review**	**3rd review**
E/ A ratio < 1	6 (16.6)	13 (36.1)	18 (50)	23 (63.9)
Em velocity < 8 m/s	6 (16.6)	19 (52.7)	24 (66.7)	35 (97.2)
Em / Am < 1	7 (19.4)	21 58.3)	26 (72.2)	36 (100)

On applying the criteria of presence of 2 out of 3 parameters to define diastolic dysfunction, impaired diastolic function was present in 5 patients at baseline and 12, 23 and 35 patients at 1st, 2nd and 3rd review respectively. However almost all these patients fulfilled the 2 tissue Doppler criteria rather than a combination of pulse wave Doppler and tissue doppler.

Comparison of Different Criteria for defining diastolic dysfunction

When tissue Doppler criteria that were used to define diastolic dysfunction were compared with pulse wave Doppler criteria (MV E/A < 1), a higher number of patients were found to have diastolic dysfunction. The results of the comparison are shown in Table 8. However, a significant percentage of patients who had diastolic dysfunction as defimed by pulse wave Doppler criteria had normal tissue Doppler indices.

Table 11: Comparison of prevalence of tissue Doppler defined parameters of diastolic dysfunction with pulse wave Doppler based criterion (E/A < 1)

	Em / Sm <1		Em < 8 m/s	
	Additional numbers Detected N (%)	**Numbers missed N (%)**	**Additional numbers Detected N (%)**	**Numbers missed N (%)**
Baseline	3	2	2	2
1st Follow up	10	4	9	4
2nd Follow up	10	3	6	4
3rd Follow up	11	0	11	1

DISCUSSION

This study was a prospective follow up echocardiography study of patients planned for anthracycline-based chemotherapy for various types of malignancies. The mean age of patients was around 52 years. Carcinoma breast, which is one of the commonest malignancies for which anthracycline based chemotherapy is administered, constituted the commonest malignancy in this study (81.8%). This also resulted in an overwhelming female preponderance in the study.

The study was designed to sequentially follow patients receiving anthracycline-based chemotherapy with echocardiography and tissue Doppler study to determine the prevalence and onset of left ventricular diastolic impairment. A large number of exclusion criteria mentioned above were aimed at excluding co-existent diastolic dysfunction due to an unrelated cause, which may have confounded the results.

Baseline clinical and echocardiographic features

Baseline clinical characteristics of the study population were within normal limits. 55 patients were recruited into the study – however only 36 patients underwent 4 echocardiographic assessments as planned. No patients had baseline ECG or echocardiographic features of co-existent cardiac disease. Left ventricular size and systolic function was normal in all patients. The prevalence of baseline diastolic impairment of the impaired relaxation type was 16.6%. This incidence was slightly higher when tissue Doppler criterion of Em / Am ratio < 1 was used (19.4%). A high prevalence of diastolic impairment at baseline may have been a result of the relatively elderly population included in the study. None of the clinical variables (including sex or presence of coronary risk factors) had a significant co-relation with the presence of diastolic impairment at baseline.

No patient developed clinical features of anthracycline induced cardiotoxicity or congestive cardiac failure during the follow-up period of about 6 months.

ANTHRACYCLINE INDUCED DIASTOLIC DYSFUNCTION – DOES IT PRECEDE SYSTOLIC DYSFUNCTION?

Recommendations for cardiac monitoring during anthracycline chemotherapy have, till now, laid emphasis on monitoring for systolic dysfunction. Cardiac systolic dysfunction, except for a mild increase in LVIDD, was not demonstrable in this study.

Several studies, now indicate that diastolic dysfunction is common during anthracycline administration. The overall clinical significance of such diastolic dysfunction, however, is uncertain. Whereas a few studies have suggested that diastolic dysfunction may precede systolic dysfunction, [21] and may be a precursor of frank cardiac failure, others have shown that occurrence of diastolic dysfunction prior to systolic dysfunction is uncommon in anthracycline treated patients. [22]

The cause of diastolic dysfunction, though not clear, is postulated to be due to impaired calcium handling in cardiac myocytes. [19] Similar occurrence of diastolic dysfunction has been previously reported. In a study of 236 children with various types of malignancies, significant abnormalities of diastolic function were associated with anthracycline induced cardiac damage. [20] Another study of 101 children showed a reduced diastolic performance among children treated with anthracyclines. [21] This was not linearly related to anthracycline dose and appeared to reflect the underlying myocardial pathophysiology due to anthracycline toxicity.

The present study found a significantly high incidence of diastolic dysfunction in patients treated with doxorubicin. Moreover, we noted that the incidence, as defined by a reversal of E/A ratio, increased as cumulatively higher doses of doxorubicin were administered. The incidence after > 300 mg / m2 of doxorubicin had been administered was 63.9%. This high incidence may have resulted from the higher age group of our patients – which is a known risk factor for development of diastolic impairment.

ROLE OF TISSUE DOPPLER IN ASSESSMENT OF DIASTOLIC DYSFUNCTION

Tissue Doppler analysis, which implies measurement of myocardial motion using pulse wave Doppler has many advantages in assessment of ventricular dysfunction. The technique holds particular promise is evaluation of diastolic performance of the heart. In contrast to conventional Doppler, it can be used to assess both global and regional diastolic dysfunction and permits differentiation of restrictive from constrictive physiology. It also enables diastolic function assessment in patients with a poor echo window and in patients with atrial fibrillation. [23]

Though no strict recommended diagnostic criteria for definition of diastolic dysfunction as assessed by tissue Doppler analysis have been made, most studies have relied on the reduction in early mitral annulus velocity (Em) in the presence of a normal systolic function as being indicative of diastolic impairment. Farias et al in a study of 51 patients with diastolic dysfunction as compared to 27 controls concluded that myocardial velocities assessed by Doppler tissue echocardiography was useful in differentiating patients with normal from those with abnormal diastolic function. Moreover, myocardial velocity remains reduced even in those stages of diastolic dysfunction characterized by increased preload compensation.[24] The usual definition of diastolic dysfunction in most studies has been an Em / Am ratio of less than 1 or an absolute Em velocity of < 8 cm/s. These definitions were also used in the present study.

Tissue Doppler evaluation of diastolic dysfunction has been used in many clinical conditions including hypertension [25], sub-clinical coronary artery disease [26], postmenopausal women on estrogen replacement therapy [27] and hypertrophic cardiomyopathy [28]. Literature on evaluation of this technique in assessing anthracycline induced diastolic dysfunction is only beginning to emerge. In a study from Netherlands, Kapusta et al studied 63 survivors of childhood malignancy treated with doxorubicin with tissue Doppler analysis.[29] The authors concluded that tissue Doppler imaging has the potential to become a useful noninvasive method for detecting subclinical myocardial damage in apparently healthy patients who received moderate doses of anthracyclines for treatment of childhood malignancy. In another study, Takenaka et al showed tissue

Doppler assessment of anthracycline induced diastolic dysfunction methods to be a highly sensitive tool for monitoring anthracycline cardiotoxicity.[29] In a study similar to the present study by Kapusta et al, tissue Doppler was found to be an effective modality for discrimination between healthy controls and patients with sub clinical diastolic dysfunction.[30]

In the present study, we analyzed the efficacy of tissue Doppler in evaluation of diastolic dysfunction as defined by standard criteria. We found a significantly high incidence of diastolic impairment by this method. The near complete prevalence of diastolic abnormalities on tissue Doppler study is hard to explain. We reason that the high incidence may be due to a cumulative effect of age and coronary risk factors in addition to doxorubicin toxicity. Additionally, this impairment may represent an acute form of cardiotoxicity – since echocardiography was performed in between and immediately following chemotherapy courses. Such a protocol has rarely been followed in the past as most authors have studied diastolic dysfunction only after completion of chemotherapy courses. Whether the acutely induced diastolic dysfunction is partly reversible or not will have to be addressed in future long-term follow-up trials.

TEI'S INDEX IN DIASTOLIC DYSFUNCTION

Since its first description in1995, Tei's index has rapidly emerged as a composite echocardiographic parameter for assessment of ventricular dysfunction.[31] This parameter, which is calculated by dividing the sum of isovolumetric contraction time and isovolumetric relaxation time by the ventricular ejection time is relatively easy to determine and is preload independent. This index has been evaluated in patients with myocardial infarction, [32] left ventricular dysfunction, [33, 34] and even in anthracycline induced cardiac toxicity – where it was found to be useful.[19] This index was found to correlate well with other parameters of left ventricular dysfunction such as evidence of cardiac falure on cardiac catheterization[35,36] and levels of brain natriuretic peptide. [37.]

Tei's index can also be calculated using tissue Doppler techniques. This is done by measuring the A wave to E wave duration (A to E) and duration of Sm (which is the

myocardial equivalent of systolic ejection time), and calculating using the formula {(A-E)- Sm} ÷ Sm.

Tissue Tei's index was calculated as a part of the present study even though it was not used as a defining criterion for diastolic dysfunction. We noted a consistent increase in tissue Tie's index as higher doses of doxorubicin were administered. This was due to a combination of prolongation of the A to E interval and an abbreviation of the Sm duration. Both these parameters had shown significant changes from their baseline values at the end of the study.

Though desirable, one cannot assign specific values of Tei's index to define diastolic dysfunction on the basis of this study. This is because the present study included only 36 patients with a mean age was 51.9 years. Establishment of such a diagnostic criterion requires population-based studies with a large number of patients.

As shown in Table 11, diastolic dysfunction – as defined by tissue Doppler based criteria (in contrast to pulse wave Doppler criteria) - was present in a significantly higher number of cases at follow-up. Additionally, this difference was noticeable from the first follow-up onwards and persisted till the end of the study. Whether the higher prevalence of diastolic dysfunction, thus defined, constitutes a high sensitivity of tissue Doppler or a high incidence of false positives will need to be addressed in future long term comparative studies. Of concern however, was the observation that a high percentage of patients diagnosed to have diastolic dysfunction by conventional Doppler definition were deemed to have normal diastolic function by tissue Doppler based definitions. This could either imply a low negative predictive value of this modality or a need to further refine the diagnostic criteria for diastolic dysfunction as assessed by tissue Doppler.

The other parameters studied (but not included in the definition of diastolic dysfunction) included Em acceleration and deceleration times (which did not change significantly during follow-up) and Q to Sm peak duration, which showed a tendency towards prolongation with higher doses of the drug.

Limitations of the study

Though designed as a prospective follow-up study, it was felt that the following drawbacks were present in this study:

- The study conducted only a short-term follow-up of patients receiving anthracycline-based chemotherapy. A high incidence of diastolic dysfunction – as already highlighted – may have been due to the acute effects of the drug on cardiac diastolic function. It is not certain whether these diastolic indices will remain deranged over a longer period of time or will be reversible. This aspect will need to be studied in a longer follow up studies.
- The importance of anthracycline induced diastolic dysfunction itself needs accreditation. Though a large number of studies (as mentioned previously) do suggest its clinical relevance, there are a few studies which have suggested that indices of diastolic dysfunction do not seem to add additional information over the information provided by presence of systolic dysfunction .[3]
- The study did not include a definite cardiac catheterization based criterion as a gold standard for defining diastolic dysfunction. This, though ideal, is relevant only in experimental settings. No future study is likely to rely on repeated cardiac catheterizations for diagnosis of cardiac dysfunction. More reliance will hence have to be placed on non – invasive tests such as echocardiography, which are reproducible and easy to perform.
- An age matched control arm, which was not included in the present study, may have been a useful strategy to adopt.

CONCLUSION

This study, which included patients receiving anthracycline based chemotherapy regimes for various malignancies, found a high incidence of clinically occult diastolic dysfunction, at higher cumulative doses of the drug. The incidence of diastolic dysfunction was higher in this study than previously reported – probably due to the relatively older age of patients. The performance of echocardiography while patients were receiving chemotherapy or soon thereafter may also have contributed to the high incidence.

This study also found a much higher incidence of diastolic dysfunction when tissue Doppler based criteria as compared to conventional pulse wave Doppler criteria were applied. This may have been due to a relatively high sensitivity of this investigation modality. This study also suggests a low negative predictive value of tissue Doppler in diagnosis of diastolic dysfunction.

Finally, the present study also attempted to describe a few parameters – which are not yet included in the definition of diastolic dysfunction – to highlight their changes with progressive diastolic impairment. Further long term and larger studies are needed to establish their clinical relevance.

REFERENCES

1. Richard M Stone, Kenneth R Bridges, Peter Libby.Hematological – Oncological Disorders and Cardiovascular Disease. In Heart Disease. Ed:Eugene Braunwald, Doughlas P Zipes, Peter Libby. Harcourt, 6th edition2233-2243.
2. Bristow MR. Anthracycline cardiotoxicity. In: Bristow MR edDrug induced heart disease. New York: Elsevier, 1980:191-215. Pawan K Singal, Natasha Iliskovic. Doxorubicin induced cardiomyopathy. N Eng J Med 1998;339:900-905
3. Ritchie JL, Singer JW, Thorning D, Sorenson SG, Hamilton GW. Anthracycline cardiotoxicity:clinical and pathological outcomes assessed by radionuclide ejection fraction. Cancer 1980;46:1109-16
4. Piver MS, Marchetti DL, Parathasarathy KL, Bakshi S, Reese P. Doxorubicin hydrochloride (adriamycin) cardiotoxicity evaluated by sequesntial radionuclide angiography. Cancer 1985;56:76-80
5. Mason JW, Bristow MR, Billingam ME, Daniels JR. Invasive and non invasive methods of assessing Adriamycin cardiotoxicity in man: superiority of histopathological assessment using endomyocardial biopsy Cancer Treat rep 1978; 62:857 – 64
6. Lipshultz SE, Rifai N, Sallan SE et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation 1997; 96:2641 – 8
7. Ono M, Tanabe K, Asanuma T, Yoshitomi H, Shimizu H, Ohta Y, ShimadaT.

   Doppler echocardiography-derived index of myocardial performance (TEI index): comparison with brain natriuretic peptide levels in various heart disease. Jpn Circ J. 2001 Jul;65(7):637-42.
8. Ganz WI, Sridhar KS, Ganz SS, Gonzalez R, Chakko S, Serafinin A. Reiew of of tests for monitoring doxorubicin induced cardiomyopathy. Oncology 1996; 53: 461 – 70.
9. McKillop JH, Bristow MR, Goris ML, Billingham ME, Bockemuehl K. Sensitivity and specificity of radionuclide ejection fractions in doxorubicin cardiotoxicity. Am Heart J 1983 ; 106:1048-56.

10. Alexander J, Dainiak N, Berger HJ et al Serial assessment of doxorubicin toxicitywith quantitative radionuclide angiography N Eng J Med1979;300:278-83
11. Schwartz RG et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy : seven year experience using radionucleotide ventriculography. Am J Med. 82:1112, 1987.
12. Marchandise B, Schroeder E, Bosly A et al. Early detection of doxorubicin toxicity: intrest of Doppler echocardiographic analysis of left ventricular filling dynamics Am Heart J1989; 118: 92-8
13. Stoddard MF, Ruffmann K, Schaefer E et al. Prologation of isovolumetric relaxation time as assessed by Doppler echocardiography predicts doxorubicin induced systolic dysfunction in humans. J Am Coll cardiol 1992; 20: 62-69
14. G Tjeerdsma, MT Meinardi, WTA van der Graaf et al. Early detection of anthracycline induced cardiotoxicity in asymptomatic patients with normal left ventricular systolic function: autonomic versus echocardiographic variables. Heart 1999; 81:419-23.
15. DJA Price, DR Wallbridge, MJ Stewart. Tissue Doppler imaging: current and potential clinical applications. Heart 2000; 84(Suppl II): ii 11 – ii 18
16. B Ocal, D Oguz, S Karademir, D Birgen, N Yuksek, U Ertem, F Cabuk. Myocardial performance index combining systolic and diastolic myocardial performance in doxorubicin treated patients and its correlation to conventiona echo / Doppler indices. Pediatr Cardiol 2002; 23: 522 – 7.
17. Schwartz RG et al.: Congestive heart failuer and left ventricular dysfunction complicating doxorubicin therapy: seven years experinec using serial radionucleotide angiocardiography. Am J Med 87; 82: 1112.
18. Maeda A, Honda M, Kuramochi T, Takabatake T. Doxorubicin cardiotoxicity: diastolic cardiac myocyte dysfunction as a result of impaired calcium handling in isolated cardiac myocytes. Jpn Circ J. 1998 Jul;62(7):505-11.
19. Bu'Lock FA, Mott MG, Oakhill A, Martin RP. Left ventricular diastolic function after anthracycline chemotherapy in

childhood: relation with systolic function, symptoms, and pathophysiology. Br Heart J. 1995 Apr;73(4):340-50

20. Iarussi D, Galderisi M, Ratti G, Tedesco MA, Indolfi P, Casale F, Di Tullio MT, de Divitiis O, Iacono A. Left ventricular systolic and diastolic function after anthracycline chemotherapy in childhood. Clin Cardiol. 2001Oct;24(10):663-9.
21. Parmentier S, Melin JA, Piret L, Beckers C. Assessment of left ventricular diastolic function in patients receiving anthracycline therapy. Eur J Nucl Med. 1988;13(11):563-7.
22. Price DJA, Wallbridge DR, Stewart MJ. Tissue Doppler imaging: current and potential clinical applications. Heart 2000; SupplementII: ii 11 – ii 18.
23. Farias CA, Rodriguez L, Garcia MJ, Sun JP, Klein AL, Thomas JD. Assessment of diastolic function by tissue Doppler echocardiography: comparison with standard transmitral and pulmonary venous flow. J Am Soc Echocardiogr. 1999 Aug;12(8):609-17.
24. Galderisi M, Cicala S, Caso P, De Simone L, D'Errico A, Petrocelli A, de Divitiis O. Coronary flow reserve and myocardial diastolic dysfunction in arterial hypertension. Am J Cardiol. 2002 Oct 15;90(8):860-4
25. Gokce M, Karahan B, Erdol C, Kasap H, Ozdemirci S. Left ventricular diastolic function assessment by tissue Doppler echocardiography in relation to hormonal replacement therapy in postmenopausal women with diastolic dysfunction. Am J Ther. 2003 Mar-Apr;10(2):104-11.
26. Kato T, Noda A, Izawa H, Nishizawa T, Somura F, Yamada A, Nagata K, Iwase M, Nakao A, Yokota M. Myocardial velocity gradient as a noninvasively determined index of left ventricular diastolic dysfunction in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2003 Jul 16;42(2):278-85.
27. Kapusta L, Thijssen JM, Groot-Loonen J, Antonius T, Mulder J, Daniels O. Tissue Doppler imaging in detection of myocardial dysfunction in survivors of childhood cancer treated with anthracyclines. Ultrasound Med Biol. 2000 Sep;26(7):1099-108.
28. Takenaka K, Kuwada Y, Sonoda M, Uno K, Asakawa M, Sakurai S, Takahashi T, Sasaki K, Matsuzaki M, Kikuchi A, Amagai R, Furudate N,

Nagai R. Anthracycline-induced cardiomyopathies evaluated by tissue Doppler tracking system and strain rate imaging. J Cardiol. 2001;37 Suppl 1:129-32.

29. Kapusta L, Thijssen JM, Groot-Loonen J, van Druten JA, Daniels O. Discriminative ability of conventional echocardiography and tissue Doppler imaging techniques for the detection of subclinical cardiotoxic effects of treatment with anthracyclines. Ultrasound Med Biol. 2001 Dec;27(12):1605-14.
30. Tei C, Ling LH, Hodge DO, Bailey KR, Oh JK, Rodeheffer RJ, Tajik AJ, Seward JB. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function--a study in normals and dilated cardiomyopathy. J Cardiol. 1995 Dec;26(6):357-66.
31. Hole T, Vegsundvag J, Skjaerpe T. Estimation of left ventricular ejection fraction from Doppler derived myocardial performance index in patients with acute myocardial infarction: agreement with echocardiographic and radionuclide measurements. Echocardiography. 2003 Apr;20(3):231-6.
32. Harjai KJ, Scott L, Vivekananthan K, Nunez E, Edupuganti R. The Tei index: a new prognostic index for patients with symptomatic heart failure. J Am Soc Echocardiogr. 2002 Sep;15(9):864-8.
33. Bruch C, Schmermund A, Marin D, Katz M, Bartel T, Schaar J, Erbel R. Tei-index in patients with mild-to-moderate congestive heart failure. Eur Heart J. 2000 Nov;21(22):1888-95.
34. LaCorte JC, Cabreriza SE, Rabkin DG, Printz BF, Coku L, Weinberg A, Gersony WM, Spotnitz HM. Correlation of the Tei index with invasive measurements of ventricular function in a porcine model. Am Soc Echocardiogr. 2003 May;16(5):442-7.
35. Tei C, Nishimura RA, Seward JB, Tajik AJ. Noninvasive Doppler-derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr. 1997 Mar;10(2):169-78.
36. Ono M, Tanabe K, Asanuma T, Yoshitomi H, Shimizu H, Ohta Y, Shimada T. Doppler echocardiography-derived index of myocardial

performance (TEI index): comparison with brain natriuretic peptide levels in various heart disease. Jpn Circ J. 2001 Jul;65(7):637-42.

37. Iarussi D, Galderisi M, Ratti G, Tedesco MA, Indolfi P, Casale F, Di Tullio MT, de Divitiis O, Iacono A. Left ventricular systolic and diastolic function after anthracycline chemotherapy in childhood. Clin Cardiol. 2001 Oct;24(10):663-9.