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RAPID FIRE ABSTRACT SESSION: NEW INSIGHTS IN CARDIOMYOPTHIES

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The role of 4D echocardiography and cardiac biomarkers for early detection of chemotherapy induced cardiotoxicity in nonHodgkin lymphoma patients

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CHOP regimen is standard chemotherapy in patients with non-Hodgkin's lymphoma (NHL), but its use is limited by the risk of cardiotoxicity. Aim. To define new parameters, such as 4D echo (4DE) LV deformation or biomarkers, to diagnose early cardiac dysfunction and predict cardiotoxicity.

Methods. 37 patients (13 men, 62 $\pm$ 12 years) with NHL, without cardiac disease, with EF$>$53%, scheduled to receive CHOP, were assessed at baseline, after the 2nd and 4th cycle. 4DE was used to assess EF and LV systolic deformation: longitudinal, radial, circumferential, area strain (LS, RS, CS, AS). Troponin I was measured. Cardiotoxicity was defined as a decrease of EF $<$53%, with $>$10% from the baseline.

Results. After the 4th cycle of CHOP, 10 patients (27%) (group I) developed cardiotoxicity, while 27 patients (group II) didn't. There was a significant reduction of all LV systolic deformation parameters starting with the 2nd cycle, but group I had lower values than group II (Table). The reduction of the LS after the 2nd cycle was the best independent predictor for the decrease of EF after the 4th cycle (R2=0.44, p=0.0001); a decrease of LS with $>$30% after the 2nd cycle predicted the development of cardiotoxicity after the 4th cycle (sb 100%, sp 85%).

Conclusion. Assessment of 4DE myocardial deformation parameters are able to detect early chemotherapy-induced cardiotoxicity and to predict further changes in the EF of patients with NHL.

Abstract 434 Table. 4D deformation parameters

	CHOP	Group I	Group II	p value (Anova)
LS (-%)	Baseline	22 $\pm$ 2	22 $\pm$ 2	0.0001
	2nd cycle	10 $\pm$ 1	16 $\pm$ 2*	0.0001
	4th cycle	8 $\pm$ 1*	12 $\pm$ 2*	0.0001
CS (-%)	Baseline	21 $\pm$ 2*	21 $\pm$ 2*	0.0001
	2nd cycle	15 $\pm$ 1*	17 $\pm$ 2*	0.05
	4th cycle	12 $\pm$ 3*	15 $\pm$ 1*	0.0001
RS (%)	Baseline	56 $\pm$ 5*	56 $\pm$ 5*	0.0001
	2nd cycle	40 $\pm$ 5*	46 $\pm$ 6*	0.05
	4th cycle	33 $\pm$ 6*	39 $\pm$ 6*	0.0001
AS(%)	Baseline	35 $\pm$ 4*	36 $\pm$ 4*	0.0001
	2nd cycle	22 $\pm$ 5	28 $\pm$ 4*	0.0001
	4th cycle	17 $\pm$ 5*	23 $\pm$ 4	0.01

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Identification of proto-oncogenes and genes responsible for myocardial fibrosis and diastolic dysfunction after anticancer treatment under experimental conditions

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Background: We have previously shown that liposomal encapsulation of the anthracycline doxorubicin-citrate complex (myocet, MYO) results in less cardiotoxic effect with increased left and right ventricular ejection fraction, and less myocardial fibrosis as compared with doxorubicin (DOX). The present gene expression profiling combined with predicted protein-protein interaction analysis aimed to search genes and transcriptomes responsible for myocardial fibrosis and development of heart failure induced by anticancer treatment.

Methods: Domestic pigs were treated with either DOX (n=6) or MYO (n=9) in 3 cycles of cytostatic human dose. Control animals received physiologic saline infusions (CO, n=6). Cardiac magnetic resonance imaging (cMRI) with gadolinium late enhancement were performed at baseline and after the last cycle, as well as echocardiography. LV and RV EF were assessed and myocardial fibrosis by cMRI. Myocardial samples from the LV and RV, and left atrium were isolated for mRNAs determination. The gene expression profile was analyzed by next generation sequencing (NGS). Predicted protein-protein interaction were constructed from significantly over-or down-regulated genes and displayed using the String Database.

Results: Decreased LV and RV EF was found in both DOX and MYO groups, but the MYO group showed significantly ($p<0.05$) better LV EF (56.4 $\pm$ 5.6 vs 41.9 $\pm$ 13.5%) and RV EF (42.1 $\pm$ 2.8 vs 28.9 $\pm$ 8.9%) as with DOX. A trend to smaller LV end-systolic diameter was found in MYO. The diastolic average E/E' ratio was significantly lower in MYO (6.1 $\pm$ 1.3 vs 8.6 $\pm$ 1.6, p=0.02) versus DOX, indicating better diastolic function. Trend towards less myocardial fibrosis was observed in MYO animals vs DOX, confirmed by cMRI (LV: 5.8+/-4.1 vs 6.6+/-2.9%; RV: 6.2+/-1.9 vs 8.6+/-3.9%). LV myocardial samples showed significantly activated Ras- and inhibited p53-signaling pathways in the MYO group, which play a role in cell growth regulation, proliferation and apoptosis. Functional protein association network revealed overregulation of EMILIN and SERPHIN genes both in LV and RV samples of both MYO and DOX groups, genes involved in biosynthetic pathway of collagen.

Conclusions: Liposomal-encapsulated doxorubicin (myocet) proved to be less cardiotoxic as compared with regular doxorubicin, resulting in better LV and RV systolic and diastolic function. However, both cytostatic treatments resulted in overexpression of tissue collagen-associated genes and proto-oncogenes. Therapeutic modalities targeting at these genes during anticancer treatment might be help to prevent myocardial fibrosis and cardiotoxicity.

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Wild type transthyretin cardiac amyloidosis: clinical characteristics, echocardiographic findings, and predictors of outcome

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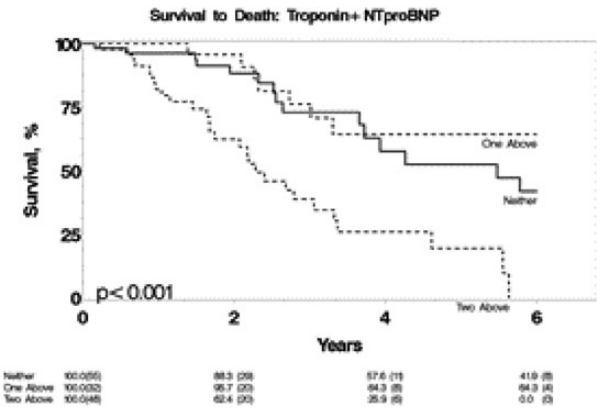
Background: Wild type transthyretin cardiac amyloidosis (ATTRwt) is increasingly recognized as a cause of heart failure, Recognition of the clinical characteristics and natural history of this disease is important due to emerging treatment options.

Purpose: To identify the clinical features, echocardiographic findings, predictors of prognosis, and survival ATTRwt.

Methods: The clinical records of all patients seen at our institution from 1965 to 2013 with a diagnosis of ATTRwt were reviewed.

Results: 428 patients (88% male, mean age 77 years) were identified with ATTRwt, 254 with a positive endomyocardial biopsy, 51 autopsy, the remainder with a positive biopsy of extracardiac tissue and typical echo findings. Dyspnea in 52%, edema 39%. The mean septal thickness: 17.3 mm, left ventricular mass index: 173.4, and EF: 48.9%. 98% had LA dilation (mean LA volume =50.2 m/m2) and 55% pericardial effusion. Mean deceleration time (DT):185.9 and estimated PASP: 43.6 mmHg. Median troponin was .04 ng/ml (n=173) and NT proBNP 5108 pg/ml (n=174) The median age at diagnosis fell from 87.5 prior to 1985 to 75 after 2010. The median survival was 3.5 years. Univariate predictors of survival included EF, DT, PASP, pericardial effusion, troponin, and NT-proBNP. On multivariate analysis, only troponin and NT-proBNP were predictive of survival. Survival according to biomarker elevation (neither, one, or both) are shown in Figure 1 (thresholds: troponin $\leq$0.035 ng/ml, NT-pro BNP $\leq$3320 pg/ml).

Conclusions: Patients with ATTRwt are almost exclusively men presenting with heart failure, markedly increased wall thickness, restrictive hemodynamics and atrial dilation. The age at diagnosis has decreased over time. Survival from diagnosis is poor and is predicted by elevated troponin and NT-proBNP.



Abstract 436 Figure 1. Survival according to biomarkers

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A novel echocardiographic index for detection of cardiac amyloidosis.

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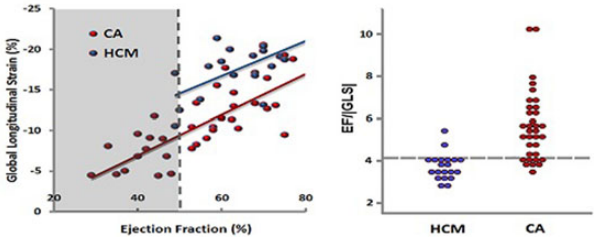
Purpose: This study aimed at investigating the relationship between ejection fraction (EF) and various strain components in cardiac amyloidosis (CA) and to determine if this EF to strain relationship is specific to CA, differentiating it from other increased left ventricular (LV) wall thickness substrates such as hypertrophic cardiomyopathy (HCM).
Methods: We included 75 subjects of which 35 were patients with biopsy-proven CA (65.9 ± 11.1 years, 65.7% male, 60% AL type), 20 HCM patients matched for maximum LV wall thickness (51 ± 17 years, 70% male) and 20 healthy volunteers. Apart from EF and speckle tracking derived global longitudinal strain (GLS), regional and global circumferential (CGS) and radial (GRS) strain indices along with LV twist were analyzed.
Results: Only patient group and GLS were found to be significant regressors of EF with a linear equation: EF=19.3-2.5*GLS+10.8*GROUP (0 for HCM and 1 for CA), (model R^2=0.82, GLS p<0.0005 and Group p=0.008). A graphical representation of this equation (figure) revealed a novel index, EF strain ratio (EFSR=EF/|GLS|) which was significantly higher among CA patients compared to other groups (5.7 ± 1.7 in CA vs 3.7 ± 0.6 in HCM vs 3.2 ± 0.3 in controls, p<0.0005) (figure). ROC analysis showed an optimal cut off value of EFSR=4.1 to differentiate CA from HCM [AUC=0.913, 95%CI(0.884-0.973), p<0.00005)].
Conclusions: Our study demonstrated that in patients with thickened hearts, the relation between EF and GLS is dependent on the underlying pathology. A novel index EFSR has shown an excellent differentiating capacity between HCM and CA.



Abstract 437 Figure.

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Left ventricular outflow obstruction is a treatable feature rather than a risk marker in patients with hypertrophic cardiomyopathy

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Purpose and Methods: In 513 patients (pts., mean age: 55.3 + 14.3 years) treated with percutaneous septal ablation (PTSMA) for symptomatic hypertrophic obstructive cardiomyopathy (HOCM) we analyzed predictors of long-term outcome.
Results: Hospital mortality was 1% (5 pts.) Mean CK rise was 513 ± 249 U/l (reference: <80). A DDD-pacemaker (DDD-PM) had to be implanted in 45 pts. (9%) for PTSMA-induced AV conduction problems. During follow-up (66 ± 54 months [range: 0.1-207.0] 2820 pt.-years), 56 pts. (11%) died, of these 22 (4%) from non-cardiac, and 34 (7%) from cardiovascular causes. Overall survival was 93% at 5 years, and 90% at 10 years.
On multivariable analysis the following parameters (hazard ratio/p value) were predictive for overall mortality: Baseline LV end-diastolic diameter (1.06/0.03), baseline age (1.07/0.0001), baseline septal thickness (1.12/0.004), ethanol dose (1.37/0.00), and syncope during follow-up after PTSMA (2.73/0.02).
The cumulative end point of cardiovascular mortality and appropiate discharge in ICD carriers was predicted by: Baseline septal thickness (1.10/0.01), ethanol dose (1.32/0.03), NYHA class during follow-up (1.84/0.01), and syncope during follow-up (3.56/0.0005).
Conclusions: As compared to the new ESC risk stratification in HCM in this post-PTSMA cohort different risk predictors were identified. Elimination of the outflow gradient in symptomatic HOCM pts. may thus also modify the risk profile. A multi-center initiative to aggregate additional pt.-years is warranted.

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The international stress echo registry in hypertrophic cardiomyopathy

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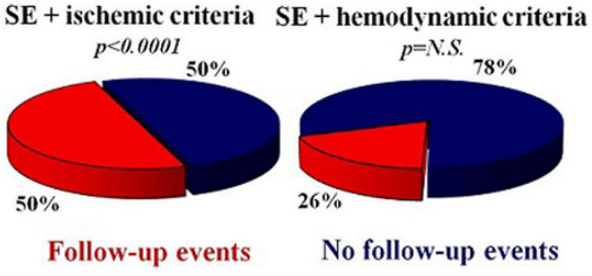
Background: Stress echo (SE) in hypertrophic cardiomyopathy (HCM) is limited by lack of standardization and prospective data.
Aim: To retrospectively assess the feasibility and prognostic value of SE in HCM
Methods: We enrolled 702 patients (age 49 ± 16 years; maximal wall thickness 21 ± 5 mm; 15% with resting LV outflow tract obstruction, LVOTO). The employed stress was exercise (n=609) or dipyridamole (n= 93). We defined SE positivity for ischemic criteria as: new wall motion abnormalities (WMA, all stresses) and/or coronary flow velocity reserve (CFR) in left anterior descending artery <2.0 (with dipyridamole) and/or ST-segment depression >2 mm. (all stresses). We defined SE positivity for hemodynamic criteria as: exercise-induced LVOTO (> 50 mmHg) and/or exercise hypotension (fails to increase > 20 mmHg).
Results: 242 patients (34%) had SE positivity for hemodynamic criteria: LVOTO in 196/595 (32%), exercise hypotension in 146/603 (24%), whereas 102 patients (14%) had SE positivity for ischemic criteria: ST segment depression in 76/380 (20%), WMA in 18/299 (6%), reduction in CFR in 31/68 (46%), with 26 patients showing > 1 positivity criteria. During median follow-up of 49 months, 164 patients (23%) showed events: 33 died, 56 had acute heart failure, 13 sustained ventricular tachycardia, 78 atrial fibrillation, 52 internal defibrillator implantation. Events occurred more frequently in patients with compared to those without SE positivity for ischemic criteria (50% vs 19%, p<.0001), whereas no difference was observed in patients with versus those without positivity by hemodynamic criteria (26% vs 24%, p=NS, Figure).
Conclusion: SE is feasible in HCM patients. SE positivity for ischemic — but not hemodynamic — criteria was associated to higher risk.



Abstract 439 Figure.

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Value of left atrial size and function to risk stratify for new onset atrial fibrillation in hypertrophic cardiomyopathy

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Purpose: Atrial fibrillation (AF) affects at least 20% of hypertrophic cardiomyopathy (HCM) patients, yielding significant morbidity and mortality. Left atrial (LA) diameter is a strong AF predictor and, according to current guidelines, patients with LA diameter (<45 mm) are considered to be at low risk for AF. We aimed to explore the additional value of LA volume and function to risk stratify HCM patients for new onset AF.
Methods: HCM patients without AF history were evaluated by 2-dimensional conventional and speckle tracking echocardiography to assess LA diameter, volume (biplane assessment) and strain (peak systolic strain during reservoir phase). The study endpoint was defined as new onset AF during follow-up, detected on ECG, Holter and/or intracardiac device readings.
Results: 243 HCM patients comprised the study population and were followed for a mean of 4.8 ± 3.7 years. The median LA diameter, volume and strain was 40 mm (36-44), 36 ml/m2 (28-46) and 23.4% (16.9-29.1) respectively. A total of 40 patients (16%) developed AF. Multivariable analysis showed LA diameter (HR 1.07, 95% CI 1.02-1.13, p=0.011), LA volume (HR 1.03, 95% CI 1.01-1.06, p=0.007) and LA strain (HR 0.91, 95% CI 0.86-0.96, p<0.001) as independent correlates of AF after correcting for age, diabetes, diastolic function and mitral regurgitation. Importantly, 23/40 AF events (58%) occurred in the subgroup of 186 patients with relatively preserved baseline LA diameter <45 mm. In this subgroup receiver operating curve (ROC) analysis indicated that LA strain (AUC 0.73, p<0.001) provided greater predictive value for new onset AF compared to LA volume (AUC 0.70, p=0.004). Moreover, patients with LA volume <36 versus ≥36 mL/m^2 and LA strain >23.4 versus ≤23.4% had better cumulative 5-year AF free survival of 92% versus 80% (p=0.013) and 98% versus 74% (p=0.001), respectively. LA volume <36 mL/m^2 and strain >23.4% showed high negative predictive values of 93% and 94% for new onset AF in this HCM sub-population. Furthermore, in this subgroup of HCM patients with LA diameter <45 mm likelihood ratio test indicated significant incremental value of LA volume assessment (p <0.001) on top of LA diameter to predict new onset AF. Addition of LA strain evaluation further increased predictive value of the model (p =0.042).
Conclusions: LA diameter, volume and strain are independently related to new onset AF in HCM patients. In patients with preserved LA diameter (<45 mm), however, both LA volume and strain further refine risk stratification for new onset AF, beyond current recommendations.

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Right ventricle ejection fraction by cardiac resonance imaging is superior in discrimination between early phase ARVC and right ventricular outflow tract ventricular tachycardia

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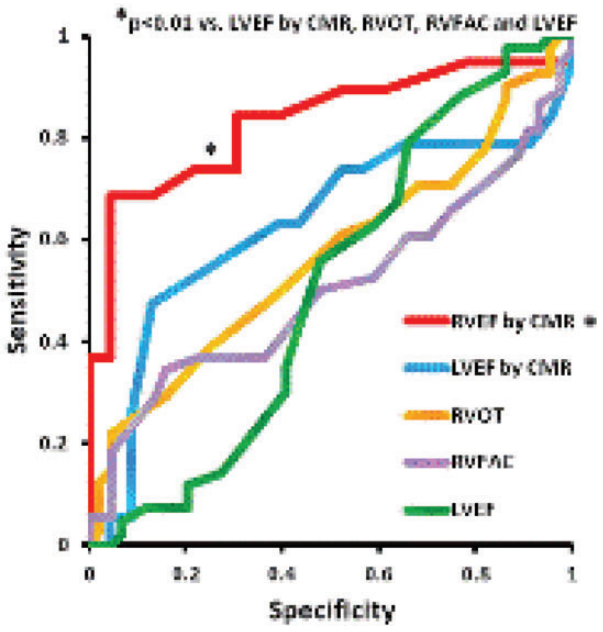
Purpose: Discrimination between life threatening early phase arrhythmogenic right ventricular cardiomyopathy (ARVC) and benign right ventricular outflow tract ventricular tachycardia (RVOT-VT) is challenging and correct diagnosis is important. We investigated if cardiac imaging parameter from the ARVC Task Force Criteria 2010 (TFC 2010) and from LV function could help to discriminate between early phase ARVC and RVOT-VT.

Methods: We included 44 RVOT-VT patients (age 47 ± 14 years) and 44 early phase ARVC patients (age 39 ± 17 years), defined as non-definite ARVC diagnosis by TFC 2010. By echocardiography, we assessed RVOT, RV fractional area change (RVFAC) and LV ejection fraction (LVEF). RV and LV ejection fractions were assessed by cardiac resonance imaging (CMR).

Results: RV function by RVEF by CMR was decreased in early phase ARVC compared to RVOT-VT patients (41 ± 8% vs. 49 ± 4%, p<0.001), while LVEF by CMR, RVOT diameters and RV and LV function by echocardiography did not differ (LVEF by CMR 52 ± 7% vs. 53 ± 6%, p=0.39; RVOT 33 ± 5mm vs. 32 ± 4mm, p=0.36; RVFAC 47 ± 7% vs. 46 ± 5%, p=0.96; LVEF 58 ± 4% vs. 57 ± 5%, p=0.85; respectively). By ROC analyses, RVEF by CMR was the superior imaging parameter to discriminate between early phase ARVC and RVOT-VT and a cut-off value of 43% showed optimal discriminative ability (AUC of 0.83, 95%CI 0.70 - 0.97)(Figure).

Conclusions: Early phase ARVC patients had reduced RVEF by CMR compared to RVOT-VT patients. RVEF by CMR from the TFC 2010 was the best cardiac imaging parameter to discriminate between early phase ARVC and RVOT-VT.



Abstract 441 Figure.