

Echocardiographic evaluation of cardiotoxicity in mice treated with doxorubicin, an anticancer drug

- Utilization of echocardiography for cardio-oncology -

Axcelead Drug Discovery Partners, Inc.
Integrated & Translational Science

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Anti cancer drug-induced cardiotoxicity in clinical setting

Incidence of left ventricular dysfunction associated with anti cancer drugs

Anti cancer drugs		Incidence (%)
Anthracyclines	Doxorubicin (550 mg/m ²)	7~26
	Idarubicin (>90 mg//m ²)	5~18
	Epirubicin (>900 mg//m ²)	0.9~11.4
Alkylating agents	Cyclophosphamide	7~28
	Ifosfamide	0.5~17
Antimetabolites	Clofarabine	27
Antimicrotubule agents	Docetaxel	2.3~13
Monoclonal antibody	Trastuzumab	1.7~20.1
	Bevacizumab	1.6~4
	Pertuzumab	0.7~1.2
Proteasome inhibitor	Carfilzomib	11~25
	Bortezomib	2~5
Small molecule tyrosine kinase inhibitors	Sunitinib	2.7~19
	Pazopanib	7~11
	Sorafenib	4-8
	Dasatinib	2~4
	Imatinib	0.2~2.7
	Lapatinib	0.2~1.5

European Heart Journal (2016) 37, 2768–2801 (modification)

Guidelines regarding to cancer therapeutic related cardiac dysfunction

- ASCO: American Society of Clinical Oncology
- ESMO: European Society for Medical Oncology
- EACVI: European Association of Cardiovascular Imaging
- ASE: American Society of Echocardiography
- ESC: European Society of Cardiology
- JSE: Japanese Society of Echocardiography
- JCS: Japanese Circulation Society



Echocardiography is useful diagnostic tool

Recommended echocardiographic parameters in guidelines

Classes of recommendations and level of evidence in cardiac evaluation during treatment with cardiotoxicity inducing drugs

Parameters	Criteria	Classes of recommendations	Level of evidence
LVEF	↓ > 10% (CTRCD)	I	C
GLS	↓ > 15%* (Sub-clinical LV dysfunction)	IIa	C
Diastolic function/ LV filling pressure	—	IIb	C

CTRCD: cancer therapeutics-related cardiac dysfunction

*: relative percentage from baseline

JCS 2021 Guideline on the Clinical Application of Echocardiography (modification)

European Heart Journal (2016) 37, 2768–2801 (modification)

Doxorubicin-induced cardiac dysfunction in clinical setting

Systolic dysfunction: LVEF↓, GLS↓

Diastolic dysfunction: E wave↓, E/A↓, e' ↓, IVRT↑, etc.

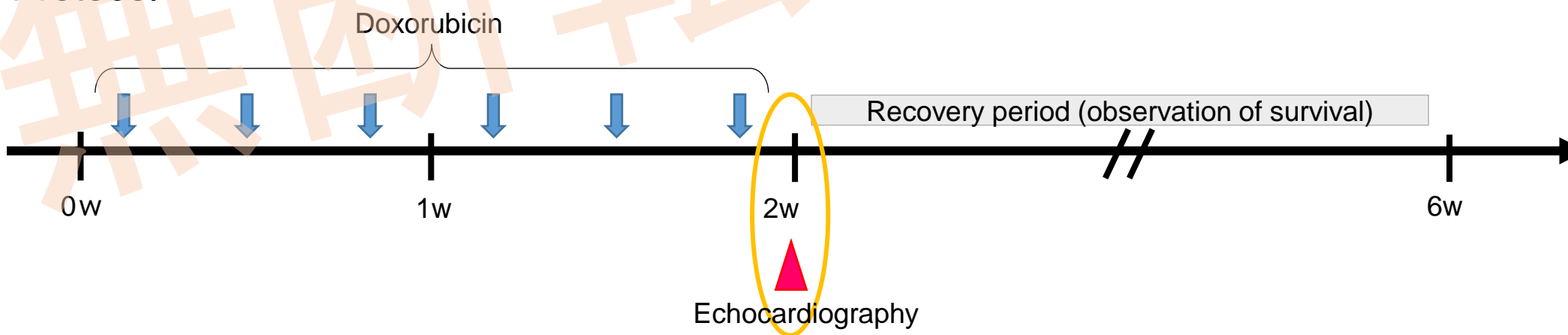
Study design

- Animal: Male C57BL/6J mice (8 weeks old)

- Groups

Drug	Dose	Route	Duration	N
Vehicle (saline)	-	i.p.	2 weeks	6
Doxorubicin	4 mg/kg x 6			8

- Protocol



Echocardiographic evaluation

■ Equipment: Vevo2100 (FUJIFILM VisualSonics, Inc.)

■ Echocardiographic parameters

Systolic function

Diastolic function

Combined systolic and diastolic function

Morphology

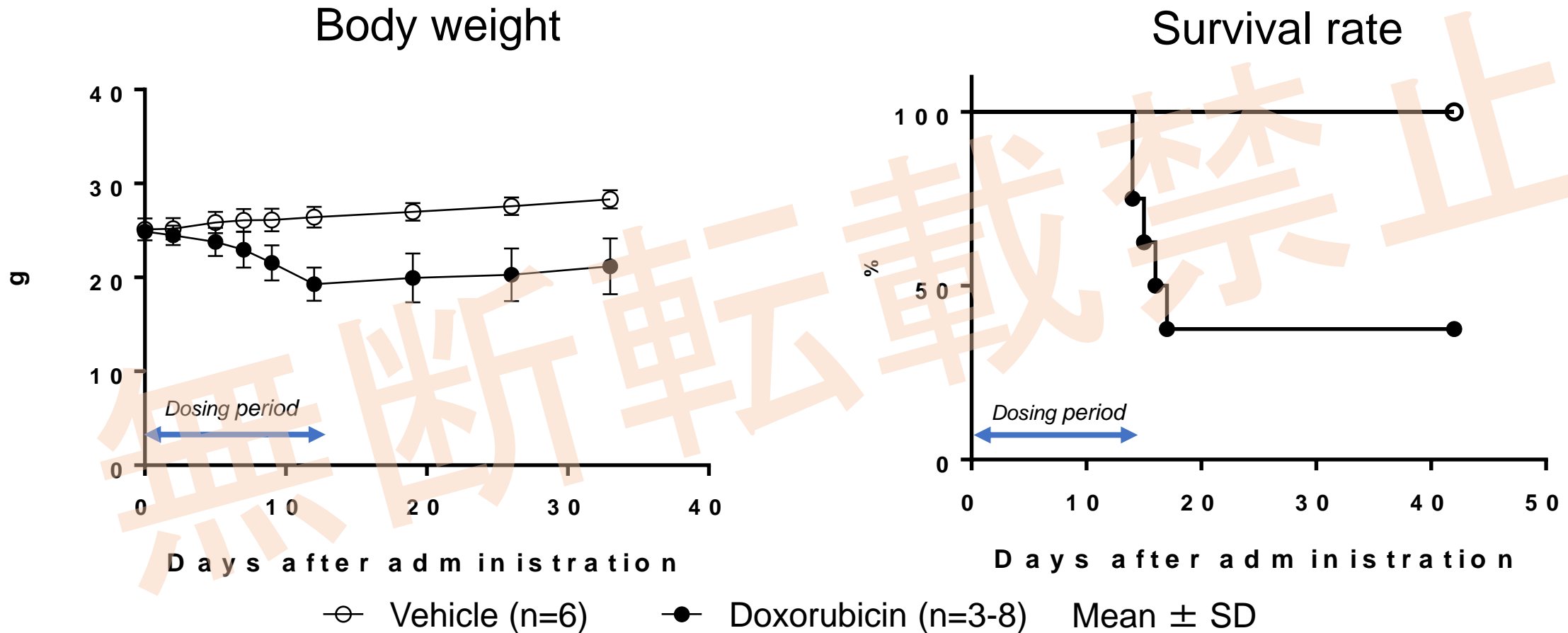
Long axis B-mode	Short axis M-mode	Pulsed-wave doppler/ Tissue doppler	Strain
LVEF EDV ESV	FS LVID LVAW LVPW	IVCT/ET IVRT/ET E wave e' E/e' Tei index	GLS GCS GRS

,EF: ejection fraction, EDV: end diastolic volume, ESV: end-systolic volume, FS: fractional shortening, LVID: left ventricle internal diameter, LVAW: left ventricle anterior wall, LVPW: left ventricle posterior wall thickness, IVCT: Isovolumetric contraction time, IVRT: isovolumetric relaxation time, ET: ejection time, E wave: early mitral filling velocity, e': early diastolic mitral annular tissue velocity, GLS: global longitudinal strain, GCS: global circumferential strain, GRS: global radial strain.

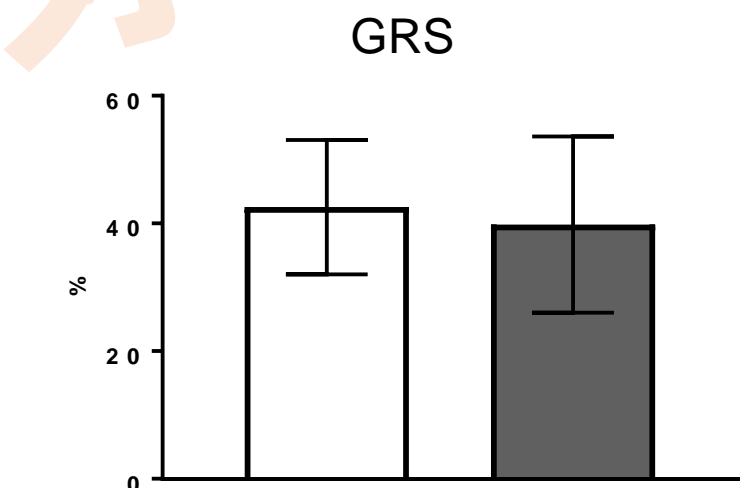
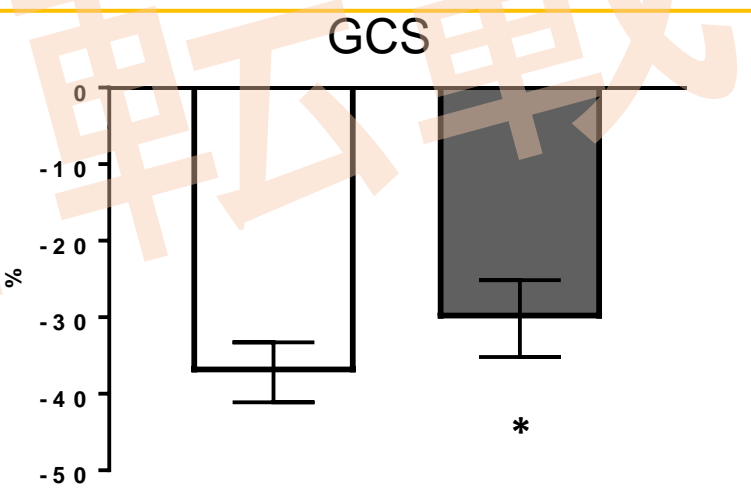
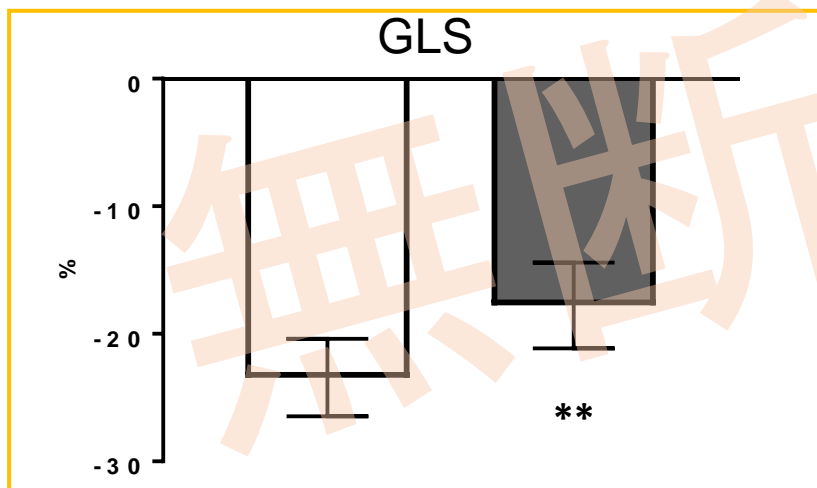
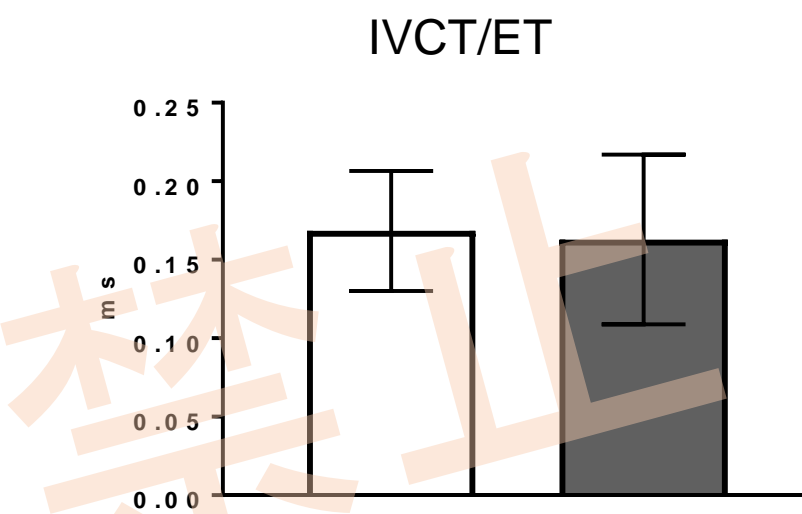
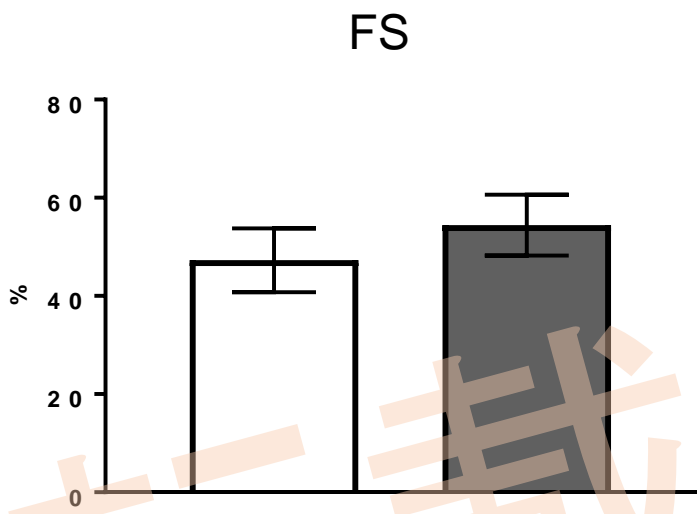
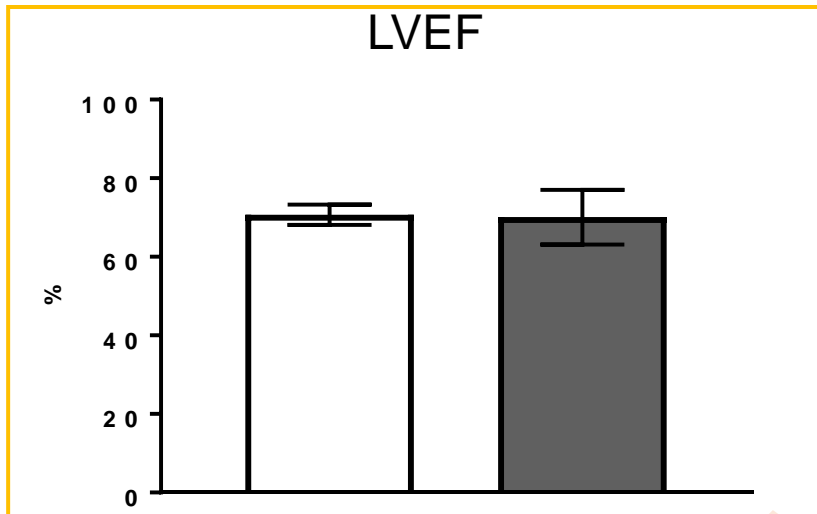
- Heart rate was adjusted to approximately 500 to 530 bpm under isoflurane anesthesia.
- Data were acquired and analyzed in a blinded manner.



Body weights and mortality



Systolic function

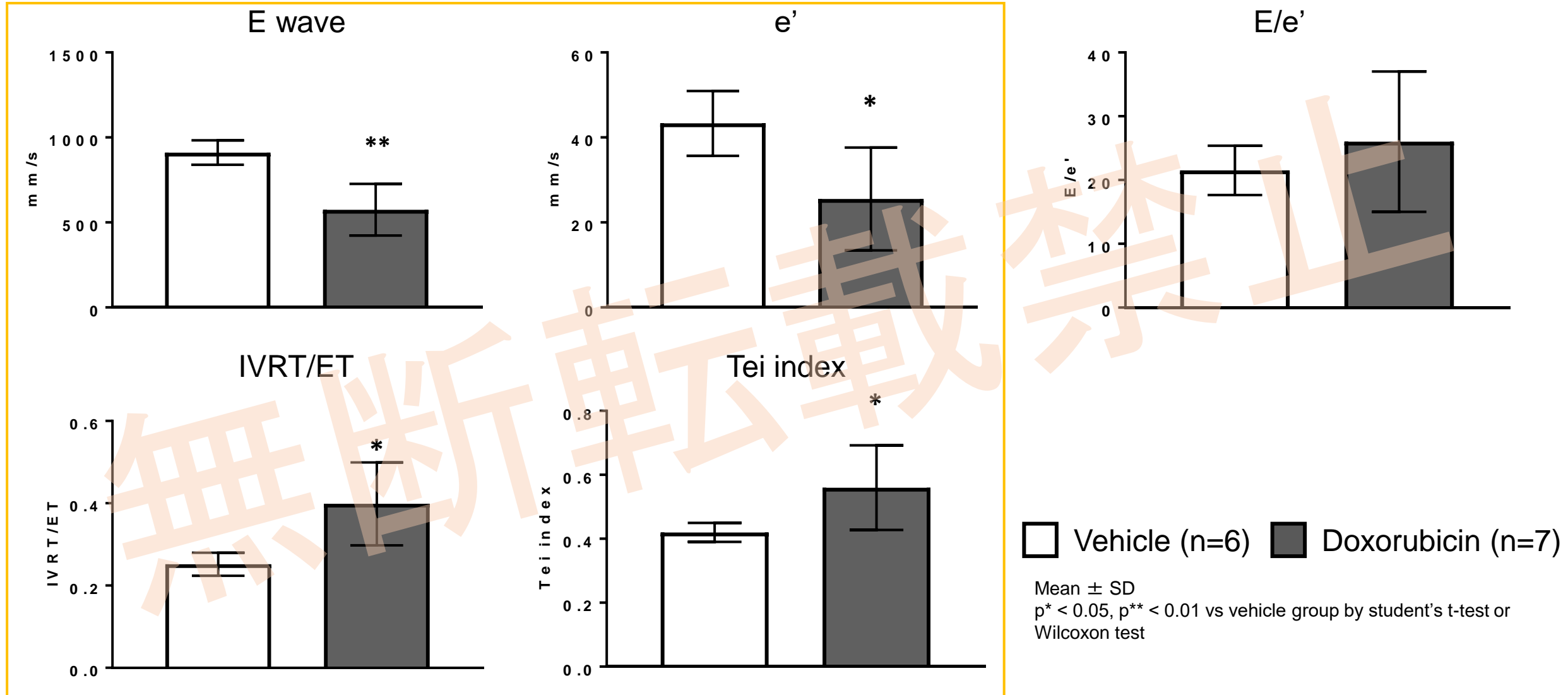


□ Vehicle (n=6) ■ Doxorubicin (n=7)

Mean \pm SD, $p^* < 0.05$, $p^{**} < 0.01$ vs vehicle group by student's t-test

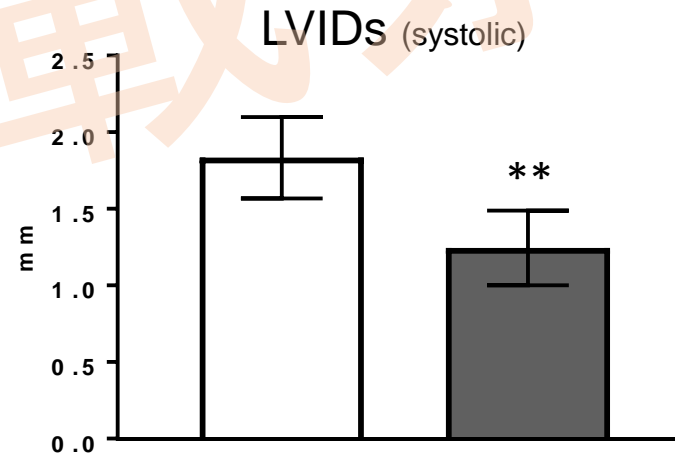
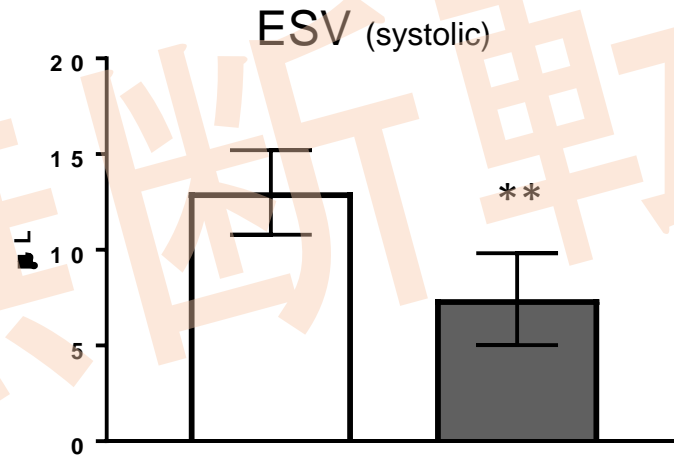
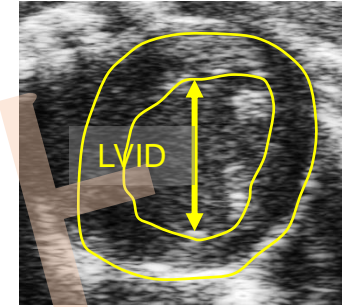
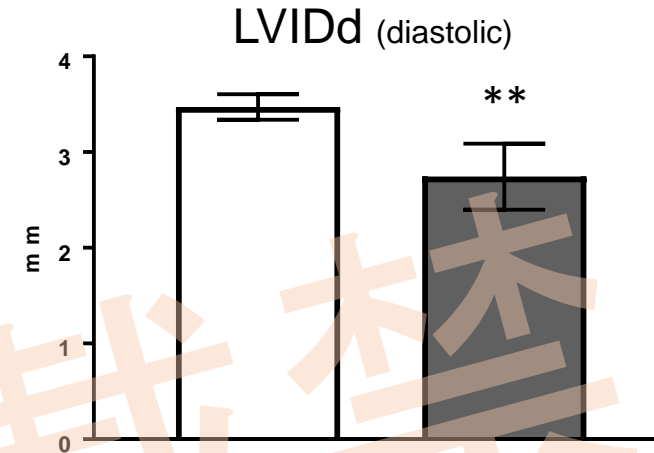
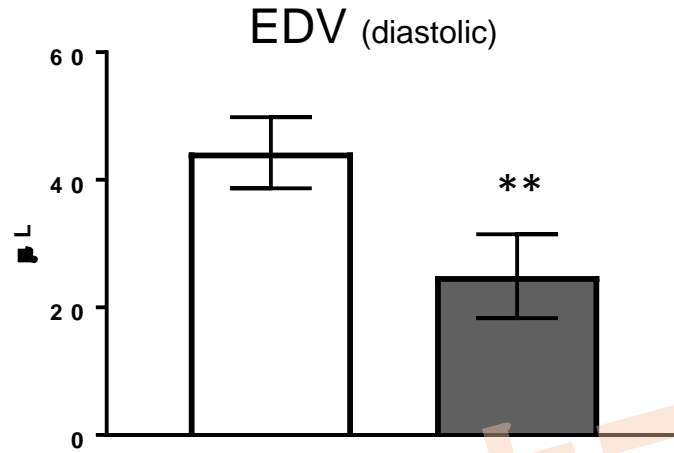
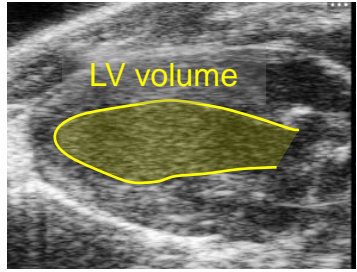
Doxorubicin did not change LVEF but decreased GLS and GCS

Diastolic function



Doxorubicin induced diastolic dysfunction

Cardiac morphology (heart chamber)



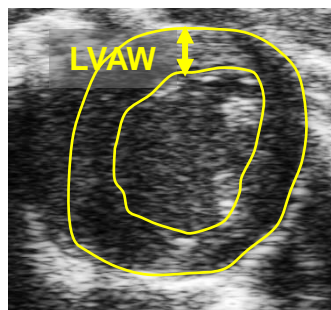
□ Vehicle (n=6)

■ Doxorubicin (n=7)

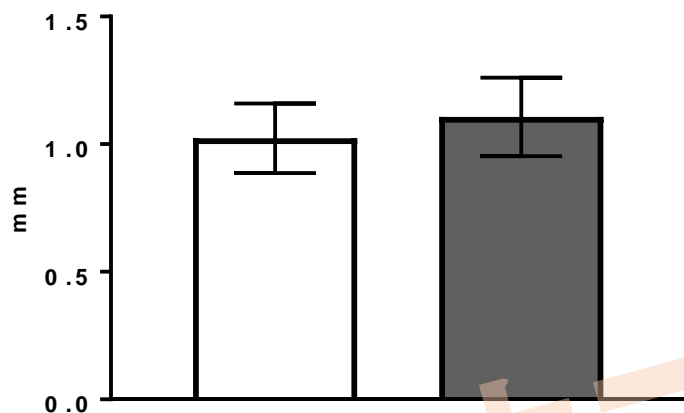
Mean \pm SD, p** < 0.01 vs vehicle group by student's t-test

Doxorubicin caused cardiac atrophy

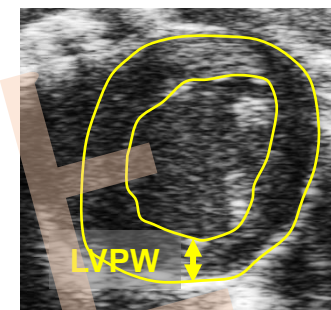
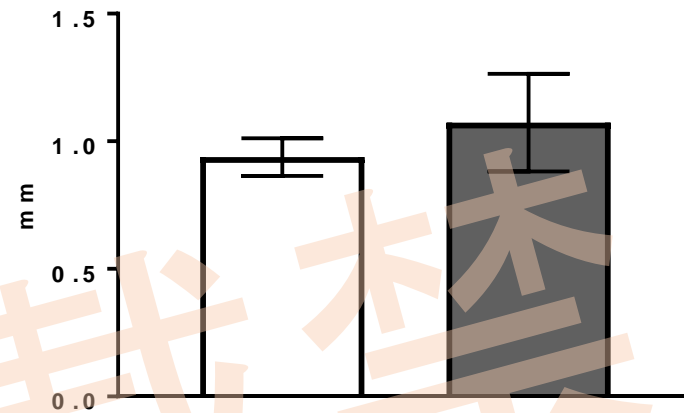
Cardiac morphology (heart wall)



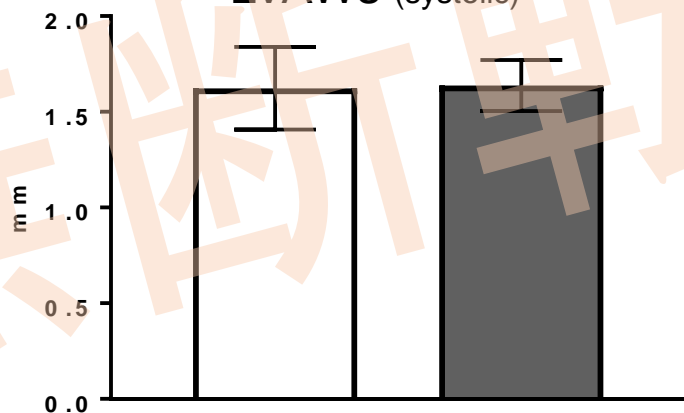
LVAWd (diastolic)



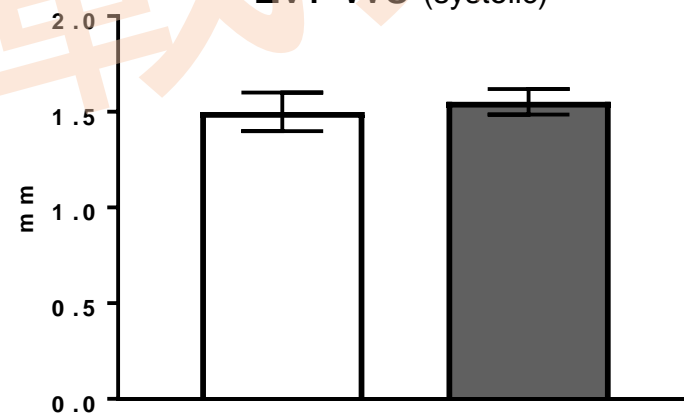
LVPWd (diastolic)



LVAWs (systolic)



LVPWs (systolic)

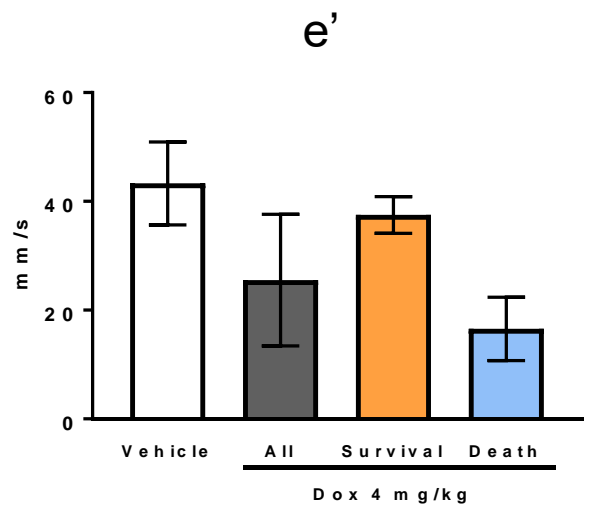
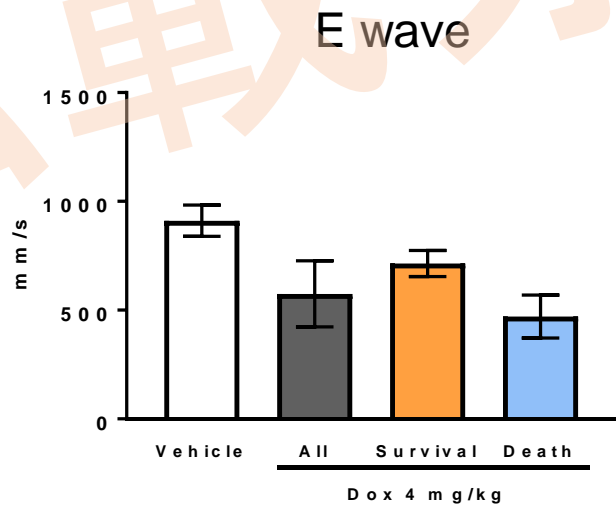
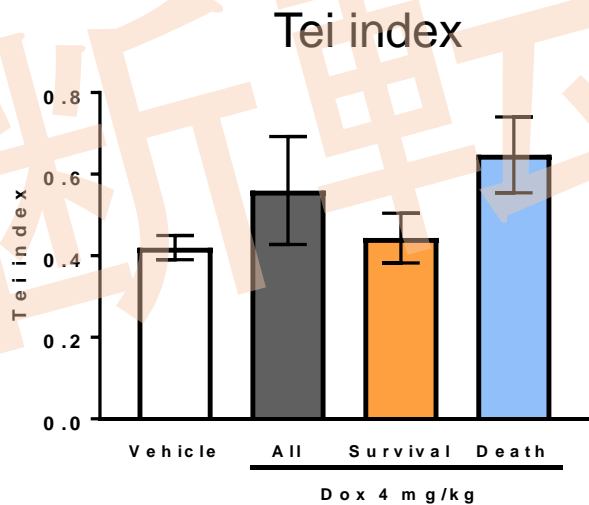
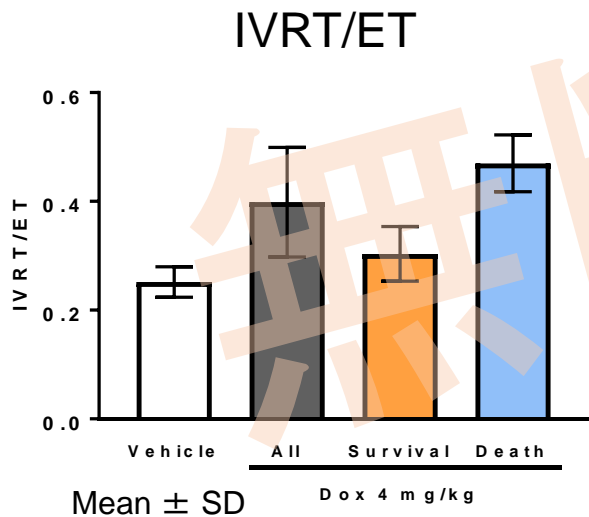
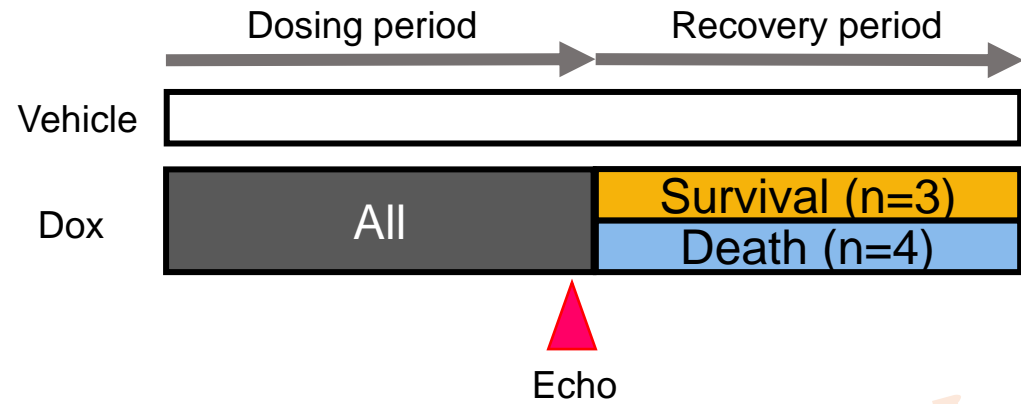


□ Vehicle (n=6)

■ Doxorubicin (n=7)

Mean \pm SD , No statistically significant changes

Diastolic dysfunction predicts subsequent death



Diastolic dysfunction might predict death

Summary

Echo parameters	Mice	Human	Abnormalities
LVEF	→	↓	(Potential) systolic dysfunction
GLS	↓	↓	
IVRT	↑	↑	Diastolic dysfunction
E wave, e'	↓	↓	
LV mass	↓	↓	Cardiac atrophy

↑: Increase/prolongation, ↓: Decrease

心エコーは非臨床でも心毒性を予測する有用なツール