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# Validation of highly human-extrapolatable cardiotoxicity assessment using an ultrasound imaging system: Evaluation of doxorubicin-induced cardiotoxicity model mice

## 超音波イメージングシステムを用いたヒト外挿性の高い心毒性評価の検証 ードキソルビシン誘発心毒性モデルマウスの評価ー

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## Summary in Japanese

本研究では，8週齢雄性C57BL/6Jマウスにドキソルビシン（5 mg/kg，腹腔内）を週1回，5週間投与して，ドキソルビシン誘発性心筋症モデルを作製し，心機能を超音波高解像度イメージングシステム（Vevo F2）を用いた心エコー検査により縦断的に評価した．
ドキソルビシン投与マウスでは，正常群と比較して収縮機能および拡張機能低下，心筋壁厚の菲薄化が認められ，心不全の進行が確認された．
さらに，左室ストレイン解析およびTei indexは，心機能障害を裏付けた．
以上より，本研究で示した心エコーによる評価は，ドキソルビシン誘発性心筋症を定量的かつ長期的に評価する有用な手法であることが示された．
また，SomaScan®による血漿中タンパク質発現の網羅的な解析を行った．

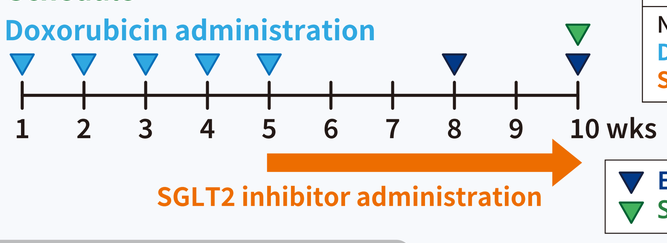
## Objective

The present study aimed to evaluate the utility of echocardiography in small animals. A cardiomyopathy model was created in mice by administering doxorubicin. Cardiac function was longitudinally assessed using echocardiography with a high-resolution ultrasound imaging system.

## Materials and Methods

Vevo F2
Fujifilm VisualSonics, Inc.

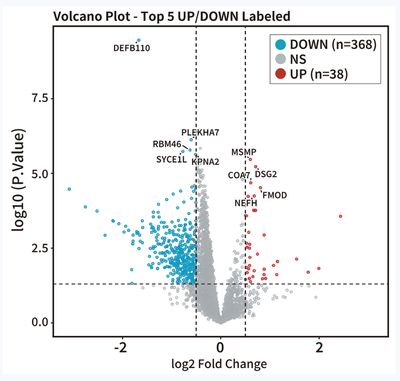
- **Animal**
  Male mouse, C57BL/6J, 8 weeks old
- **Model preparation**
  Repeated DOX (5 mg/kg),
  Intraperitoneal administration, 5 times at one a week intervals
- **SGLT2 inhibitor administration**
  Dapagliflozin (1 mg/kg), oral administration, once daily
- **Echocardiography**
  30MHz probe connected to Vevo F2 (FUJIFILM VisualSonics, Inc.)
  Mice were anesthetized by a 1.5% inspiratory concentration of isoflurane (1 L/min of air) on a heated pad.
- **SomaScan®**
  SomaScan® analysis was conducted by Fones Life (https://foneslife.com) using plasma from cardiomyopathy mice.
- **Schedule**




| Group | Route | Dose (mg/kg) | n |
|---|---|---|---|
| Normal | p.o. | 0 | 5 |
| DOX | p.o. | 0 | 7 |
| SGLT2i | p.o. | 1 | 7 |

## SomaScan®

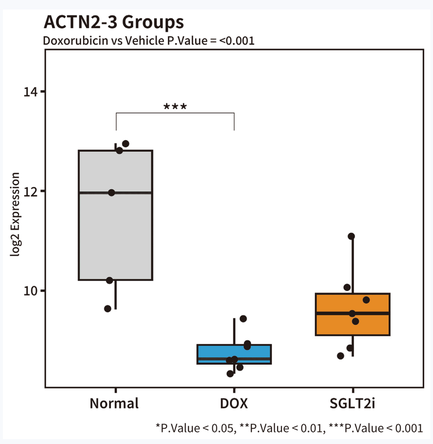
### Fig. 9 Changes in plasma protein expression induced by doxorubicin administration



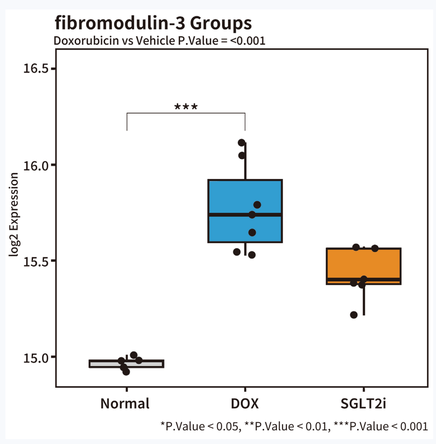

SomaScan®

- ACTN2 is an important protein that supports the structure of the sarcomere.
- Fibromodulin is a type of proteoglycan found in connective tissue and is particularly involved in the structure and function of collagen.
- More detailed data will be presented by Fones Life at JPrOS2026 (Kumamoto-jo Hall, July 21–23: https://www.j-pros.org/event/2026/).

### Fig. 10 Changes in ACTN2 expression




### Fig. 11 Changes in fibromodulin expression



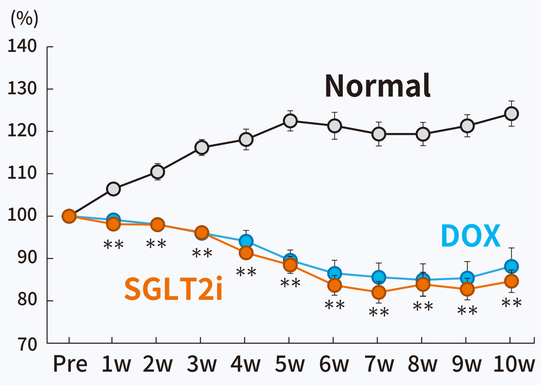

## Results and Conclusion

- Myocardial atrophy was induced by reduction of the heart weight and LVAWs (Fig. 2 and Fig. 4)
- The decreased LVEF was induced by systolic dysfunction (Fig. 3).
- Elevation of the E/e' ratio and DecT induced by diastolic dysfunction (Fig. 5 and Fig. 6).
- Elevation of the Tei index indicated left ventricular systolic and diastolic dysfunction (Fig. 7).
- Myocardial strains were strongly associated with alterations in left ventricular function parameters (Fig. 8).
- Comprehensive protein expression analysis by SomaScan® revealed changes in protein expression related to the myocardium (Fig. 9, Fig. 10 and Fig. 11).

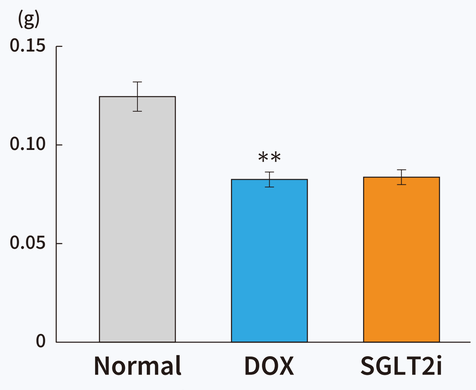
**The present study showed quantitative assessment of both left ventricular systolic and diastolic function, even in mice with small hearts and high heart rates. This approach enabled the acquisition of cardiac functional data with translational relevance to humans.**

## Body and Heart Weight

### Fig. 1 Body weight change rate



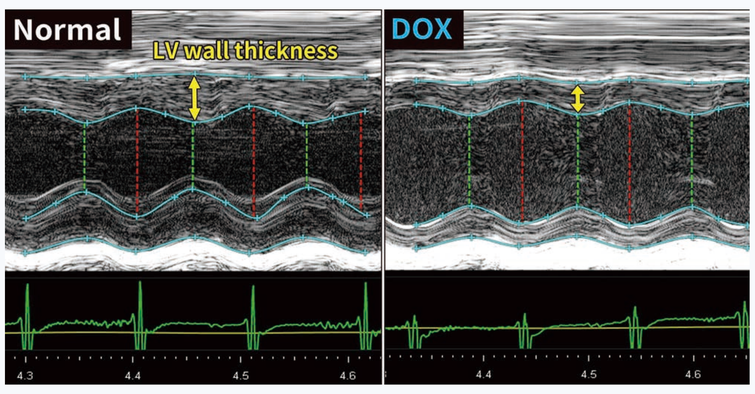

### Fig. 2 Heart weight



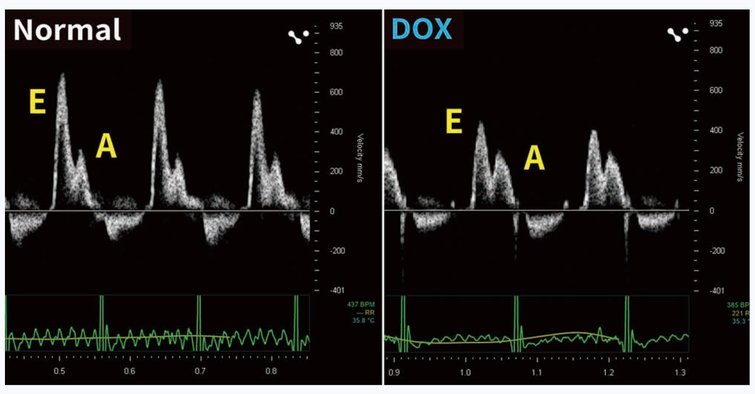

Mean±S.E.
**: P<0.01, vs Normal (Student's *t*-test)

## Echocardiography

### M-mode of parasternal long-axis view

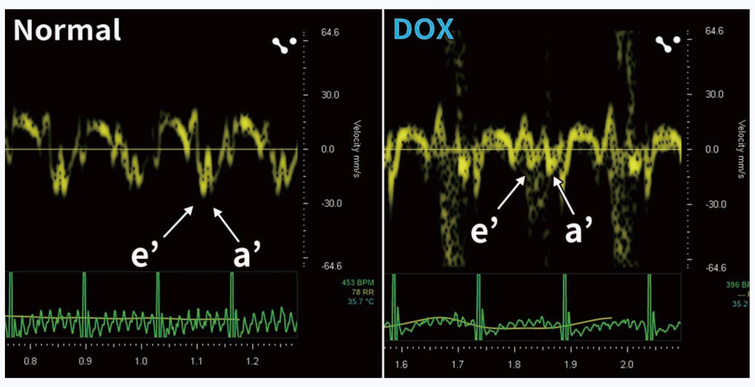



### Transmitral inflow velocity waveform



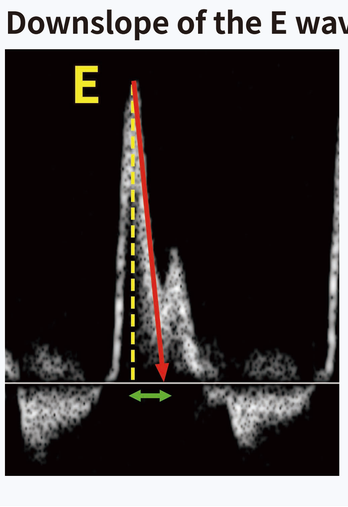

E: Early diastolic mitral inflow velocity
A: Atrial contraction mitral inflow velocity

### Mitral annular motion velocity



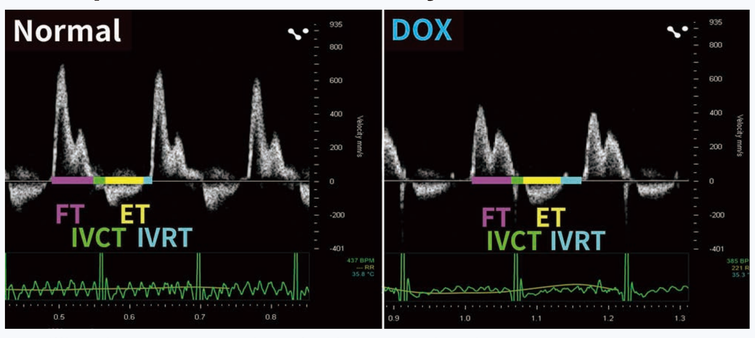

e': Early diastolic mitral annular velocity
a': Atrial contraction mitral annular velocity

### Downslope of the E wave




- **DecT (Deceleration Time):**
  Time interval from peak early diastolic mitral inflow (E wave) to baseline, reflecting left ventricular diastolic function.

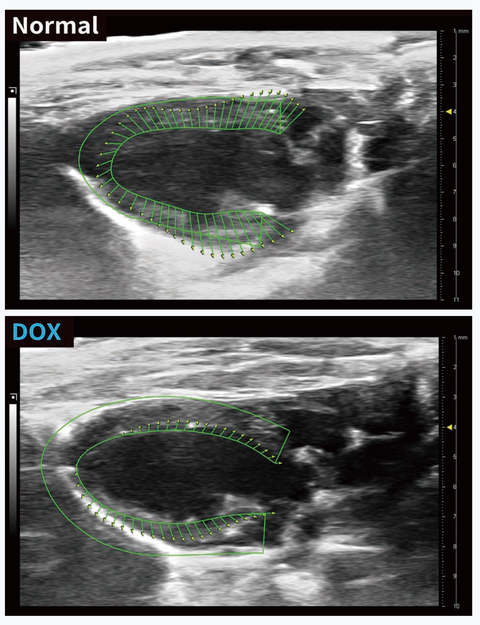
### The 4 phases of the cardiac cycle



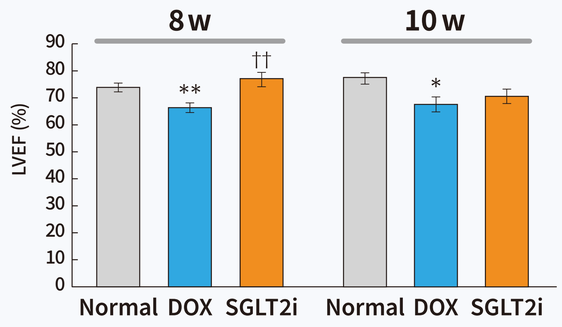

FT: Filling time
ET: Ejection time
IVCT: isovolumic contraction time
IVRT: isovolumic relaxation time

**Tei index = (IVCT+IVRT)/ET**

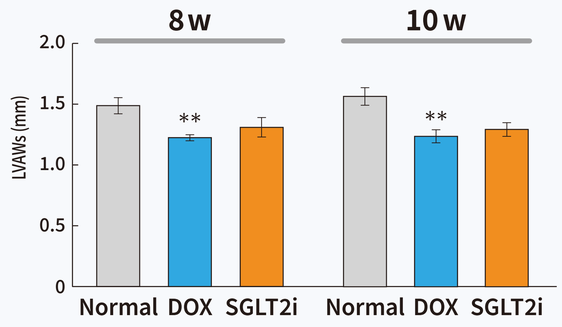
### Endocardium global longitudinal strain




### Fig. 3 LVEF: systolic function

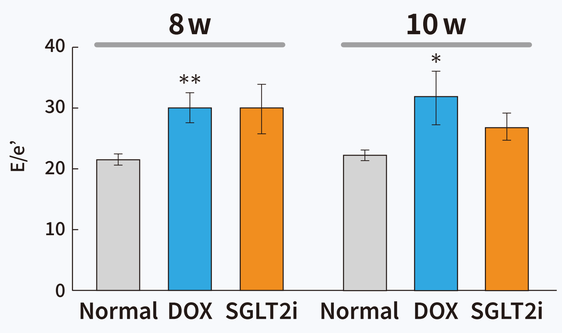



### Fig. 4 LVAWs: morphological changes of the myocardiumystolic



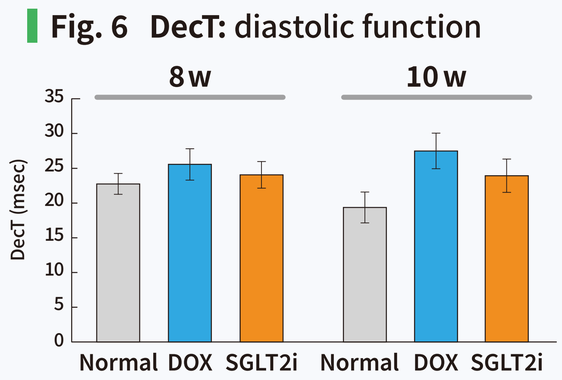

Mean±S.E.
*: P<0.05, **: P<0.01 vs Normal
††: P<0.01 vs DOX (Student's *t*-test)

### Fig. 5 E/e': diastolic function



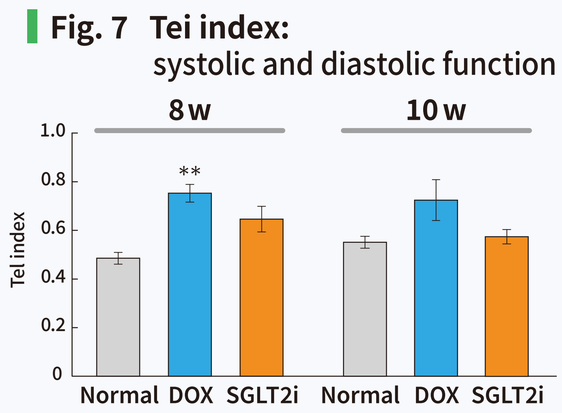

Mean±S.E.
*: P<0.05, **: P<0.01, vs Normal (Student's *t*-test)

### Fig. 6 DecT: diastolic function



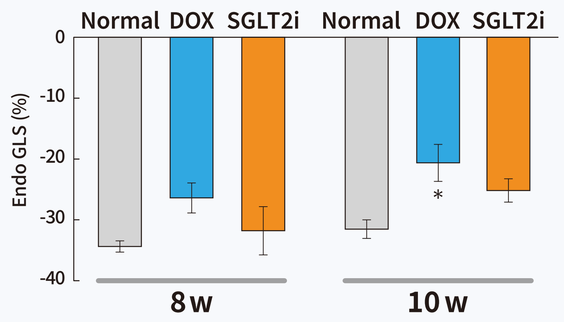

Mean±S.E.
N.S

### Fig. 7 Tei index: systolic and diastolic function




Mean±S.E.
**: P<0.01, vs Normal (Student's *t*-test)

### Fig. 8 Endo GLS




Mean±S.E.
*: P<0.01, vs Normal (Student's *t*-test)

- The green arrows in Endo GLS indicate endocardial myocardial contraction; the direction of the arrows represents longitudinal shortening of the left ventricle, and the arrow length represents the magnitude of strain.
- Endo-GLS is a sensitive marker of left ventricular systolic function and enables the detection of myocardial dysfunction.

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