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Echocardiographic evaluation of therapeutic effects of dapagliflozin in a doxorubicin-induced mouse model of cardiomyopathy

エコー測定によるドキソルビシン誘発心筋症モデルマウスに対するダパグリフロジンの薬効検証

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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、ドキソルビシン誘発性心筋症モデルを作製した。最終投与後より、SGLT2阻害薬ダパグリフロジン（1 mg/kg/日）を5週間経口投与し、その治療効果を検討した。心機能は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。一方、ダパグリフロジン投与により収縮機能は改善し、心筋症の進行が抑制された。さらに、左室ストレイン解析およびTei indexは、心機能障害およびその改善を裏付けた。

以上より、本研究で示した心エコーによる評価は、心エコーによる評価は、ドキソルビシン誘発性心筋症におけるダパグリフロジンの治療効果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。

Objective

The present study aimed to evaluate the utility of echocardiography in small animals. A cardiomyopathy model was created in mice by administering doxorubicin. Therapeutic effects were examined by administering SGLT inhibitor-dapagliflozin to these model mice. Cardiac function was assessed longitudinally 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

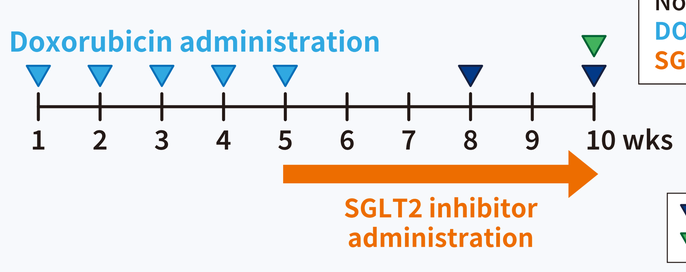
SGLT2i administration

Dapagliflozin (1 mg/kg), oral adminisitration, 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.

Schedule



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

Results

Fig. 1 Body weight change rate

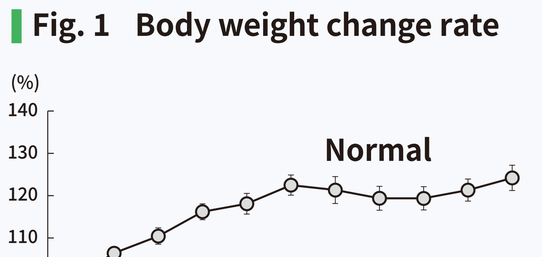
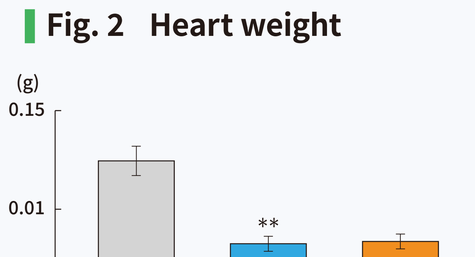


Fig. 2 Heart weight



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

Echocardiography

M-mode of parasternal long-axis view

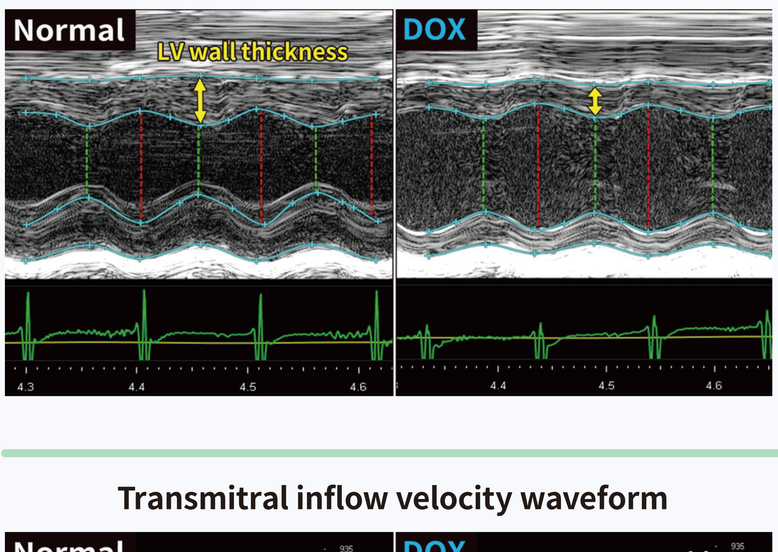


Fig. 3 LVEF
systolic function

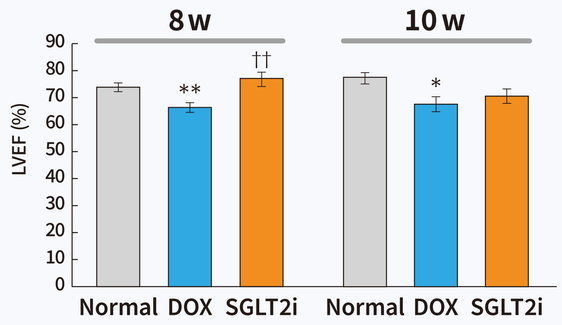
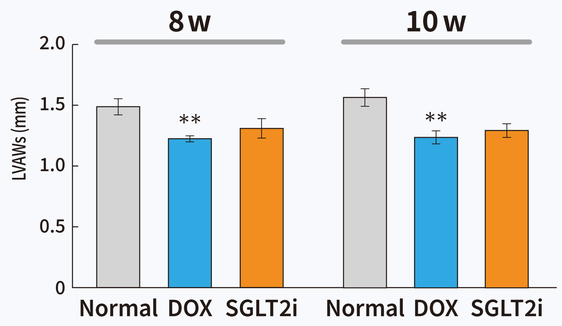
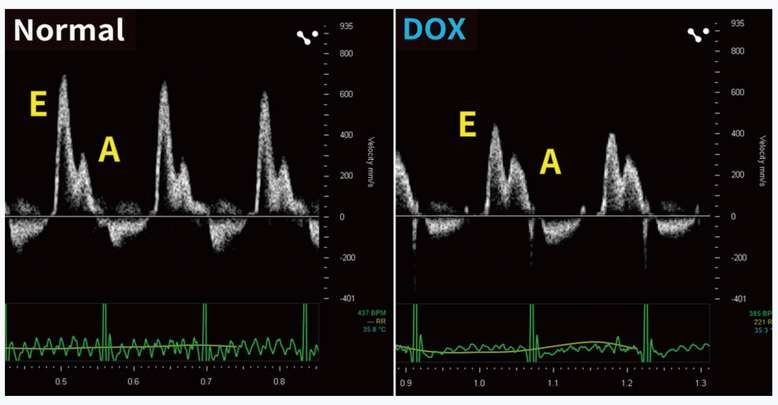


Fig. 4 LVAWs
morphological changes of the myocardiumystolic



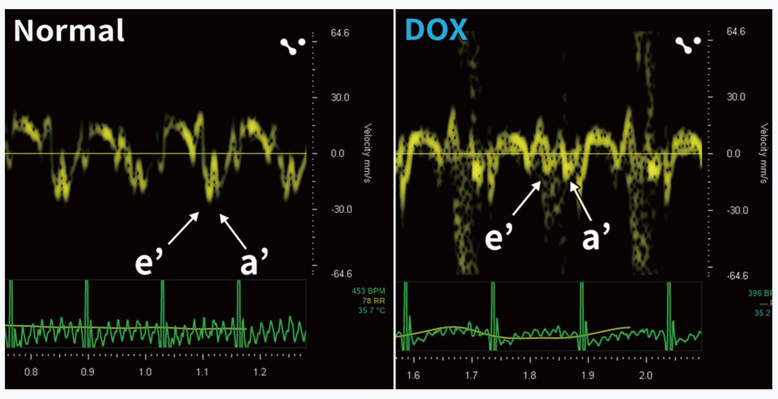
Mean±S.E.
*: P<0.05, vs Normal
**: P<0.01, vs Normal
††: P<0.01 vs DOX
(Student's *t*-test)

Transmitral inflow velocity waveform



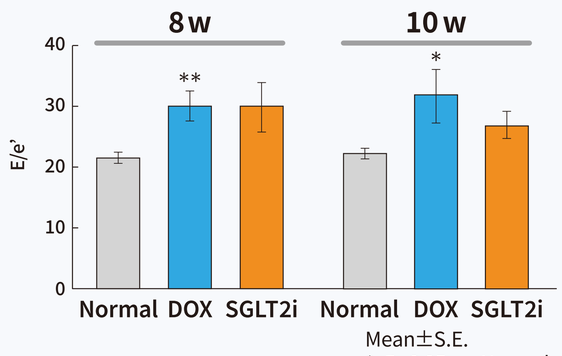
E: Early diastolic mitral inflow velocity
A: Atrial contraction mitral inflow velocity

Mitral annular motion velocity



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

Fig. 5 E/e'
diastolic function



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

Downslope of the E wave

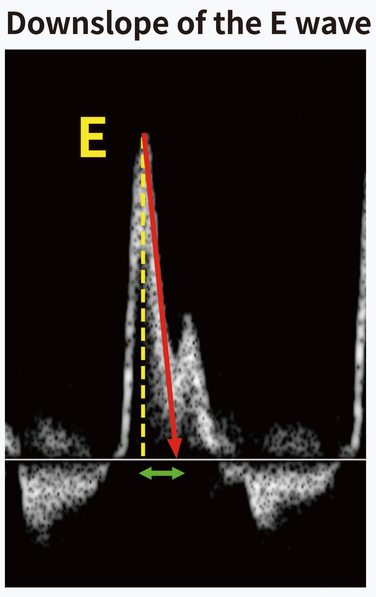
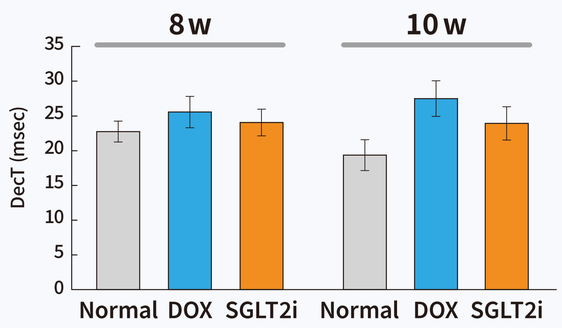


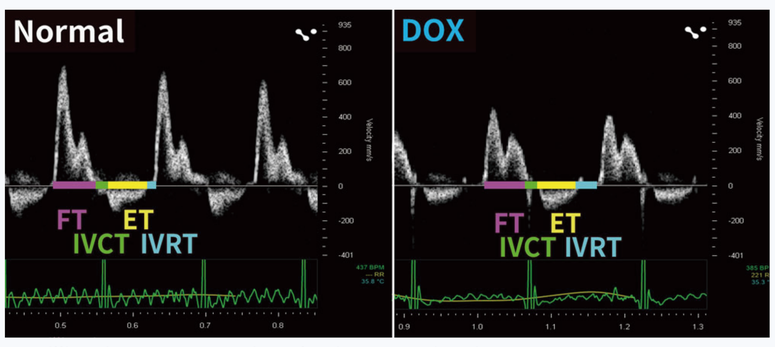
Fig. 6 DecT
diastolic function



Mean±S.E.
N.S

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

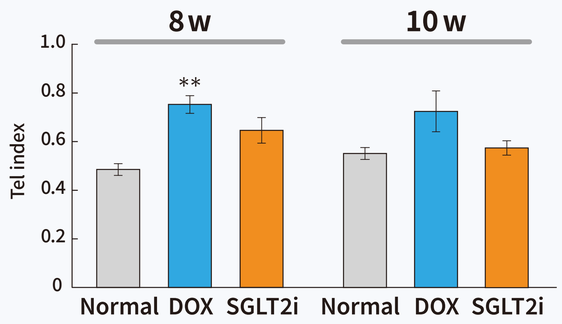
The 4 phases of the cardiac cycle



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

Tei index=(IVCT+IVRT)/ET

Fig. 7 Tei index
systolic and diastolic function



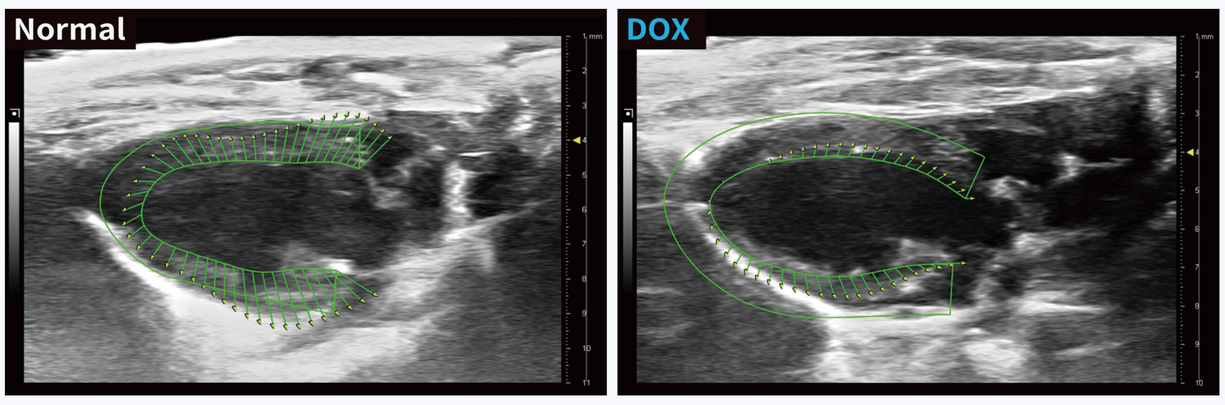
Mean±S.E.
**: P<0.01, vs Normal
(Student's *t*-test)

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).

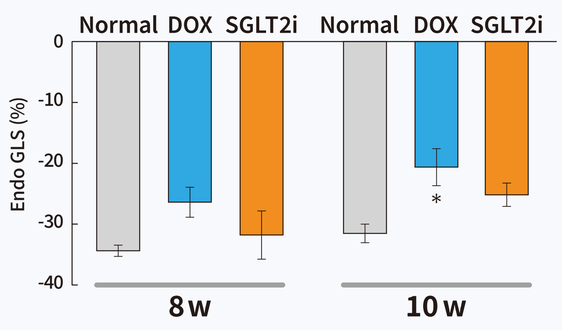
The present study showed quantitative assessment of both left ventricular systolic and diastolic function, even in mice with small hearts and high heart rates.
This approach enabled the acquisition of cardiac functional data with translational relevance to humans.

Endocardium global longitudinal strain



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.

Fig. 8 Endo GLS



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