ポスター
：2P-091

Creation of TAC model rats according to stenosis diameter
--Changes in cardiac function due to stenosis intensity--
狭窄径別TACモデルラット作製
--狭窄強度による心機能の変化--

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Introduction

The Transverse Aortic Constriction (TAC) model is predominantly used in the study of heart failure with preserved ejection fraction (HFpEF), primarily in mice. Initially, it induces cardiac hypertrophy, which over time progresses to dilated heart failure. However, studies using TAC rats are not commonly seen. In this study, we grouped TAC rats based on the size of the constriction, and measured the changes in cardiac function that resulted from these differences over a period of 24 weeks post-operation.

Methods

This study was conducted as approved by the Institutional Animal Care and Use Committee of NISSEI BILIS Co., Ltd., Shiga Laboratory.

Animals & Group

- Animals

Slc:Wistar rats(Japan SLC,Inc.)
Gender: Male, Age: 4 weeks, Weight: 46.5-70.9 g

Group

Group	Stenosis diameter	n
1	0.80 mm	9
2	0.60 mm	13
3	0.55 mm	13
4	0.50 mm	11

TAC(Transverse Aortic Constriction) surgery

1. Rats were anesthetized with a triple combination (MMB) (medetomidine: 0.15 mg/kg, midazolam: 2.0 mg/kg, butorphanol: 2.5 mg/kg s.c.).
2. The transverse aorta was ligated with 6-0 silk to create stenoses with diameters of 0.8, 0.6, 0.55, and 0.5 mm.
3. The rib cage and skin were closed using 5-0 silk sutures. An antagonist was administered to recover from anesthesia (atipamezole: 0.15 mg/kg s.c).
4. Rats were then transferred to a box filled with oxygen, and rested in it until moving voluntarily.

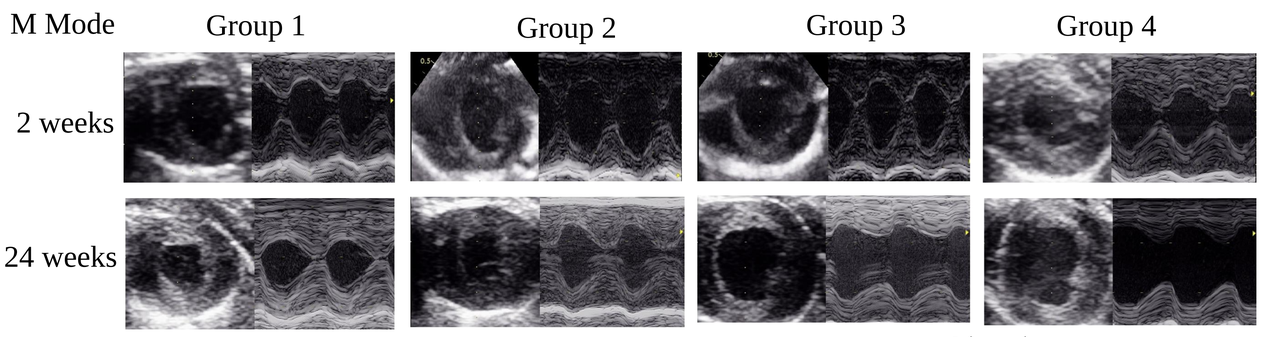
Autopsy and histopathological examination

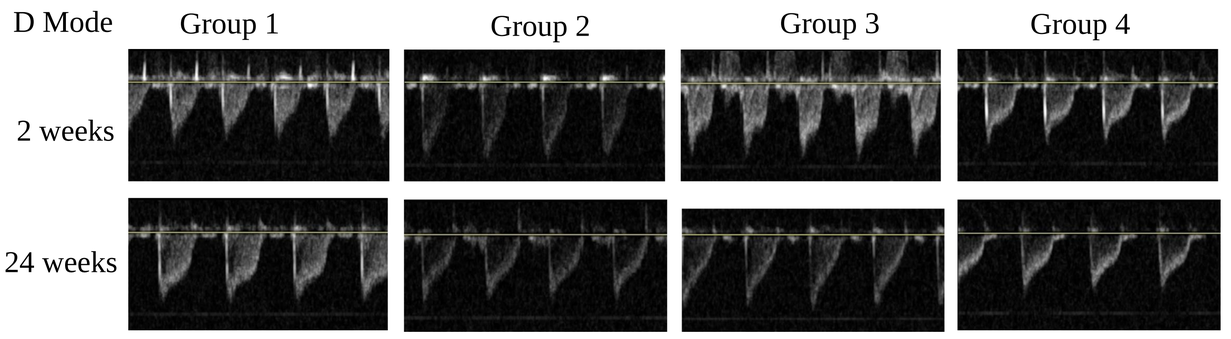
1. Rats were euthanized 24 weeks after surgery with 5% isoflurane excessive anesthesia, and the organ weights were measured.
2. Heart tissues were processed using standard procedures for Masson trichrome (MT) staining.

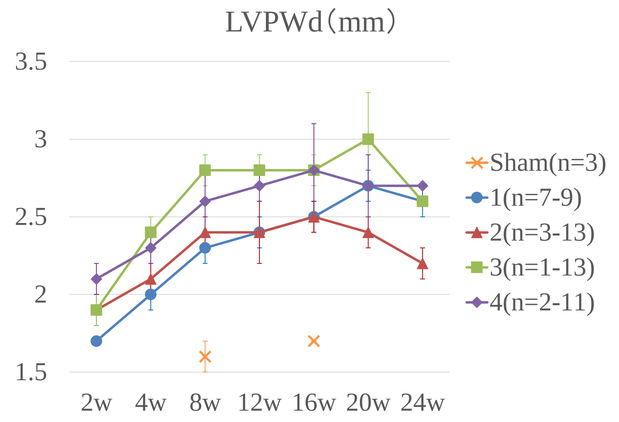
Echocardiography

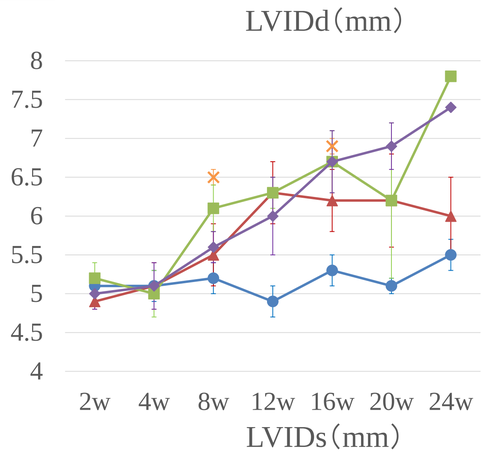
1. Rats were anesthetized with a dual anesthetic mixture (ketamine: 28 mg/kg, xylazine: 5.6 mg/kg i.p.).
2. Rats were placed in the left lateral decubitus position and scanned by an echocardiographic system (Vivids6 with a 5-to 11-MHz transducer GE Healthcare Co., Ltd.).
3. Myocardial wall thickness and the diameter of the cardiac chamber were measured in Motion mode.
4. Blood flow in the aortic and mitral valves, and aortic diameter were measured in Doppler mode.
5. Left ventricular contractility and stroke volume were calculated based on the measurement results.
6. All measurements were performed with blinding, and all data were obtained as averages of three consecutive cardiac cycles.
7. Echocardiography was performed every 2 or 4 weeks after model creation.

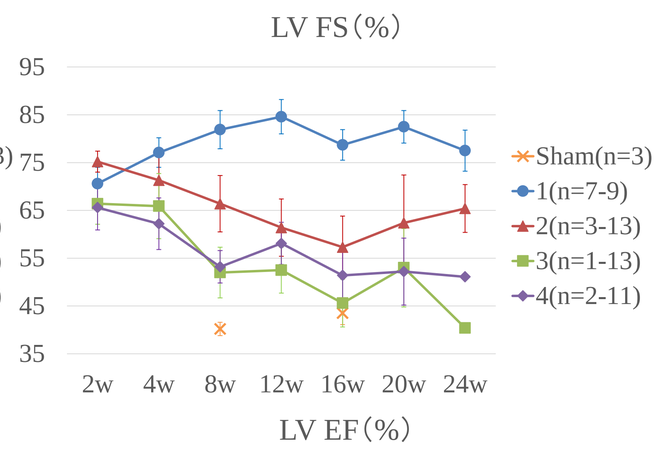
Result

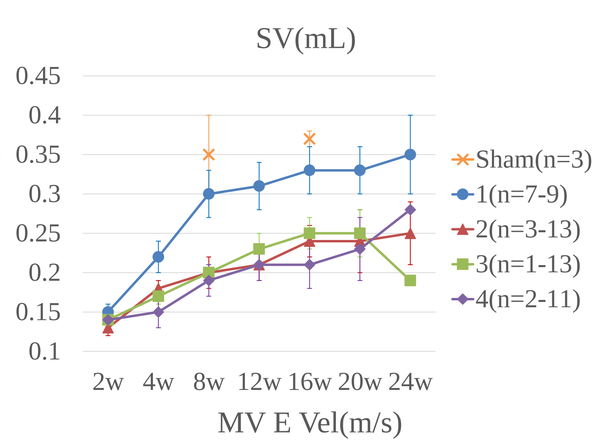


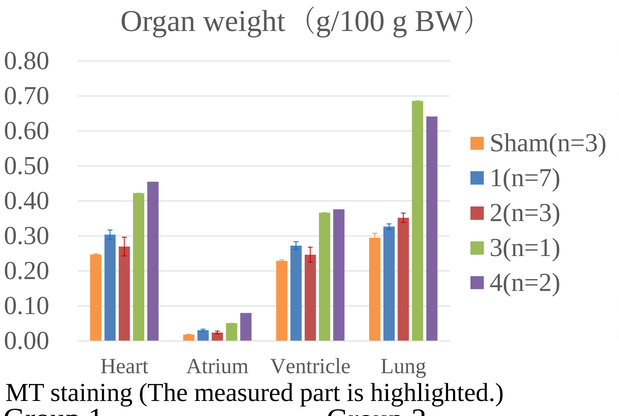


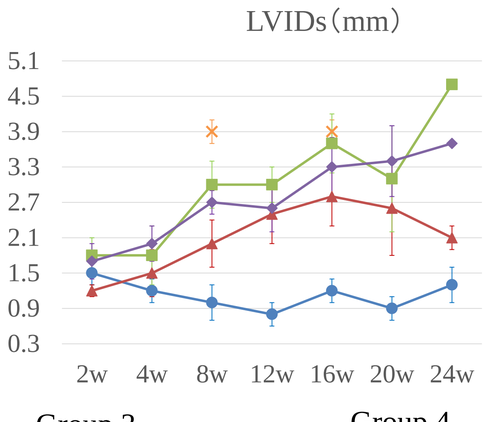


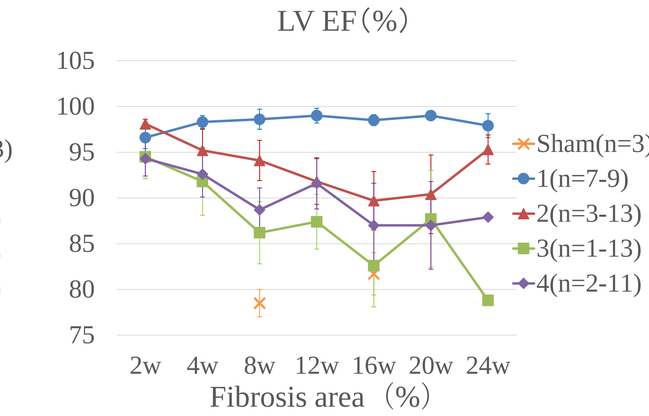


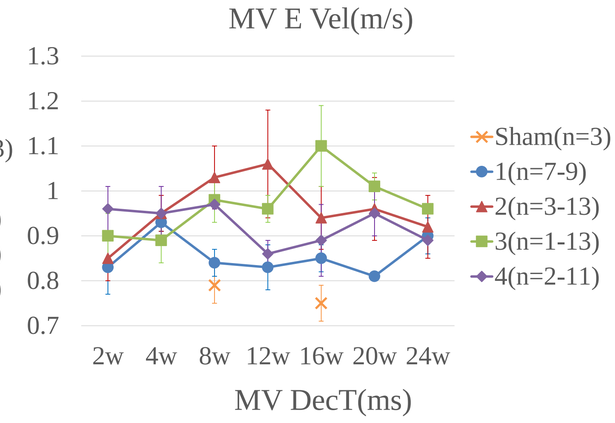




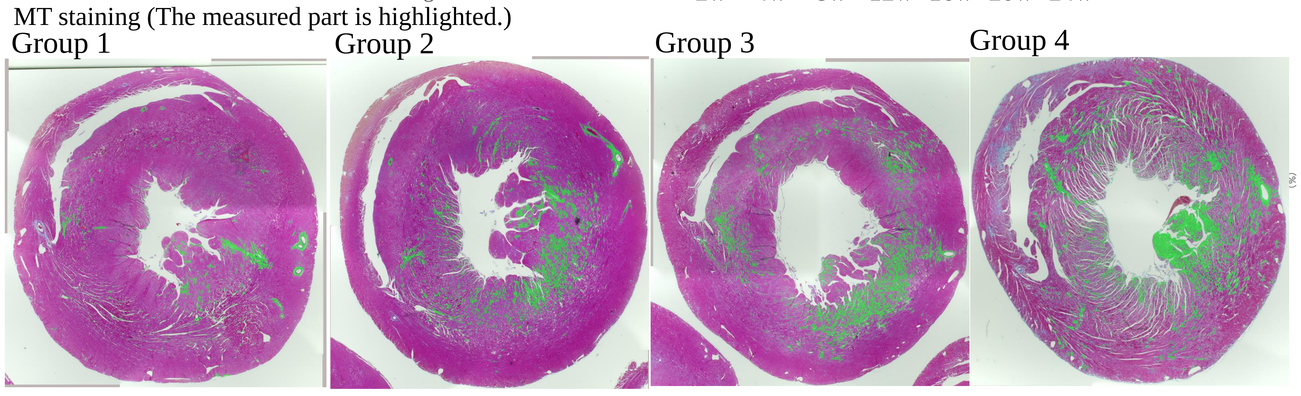


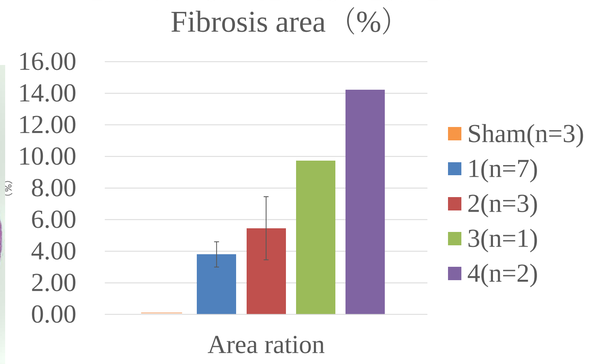


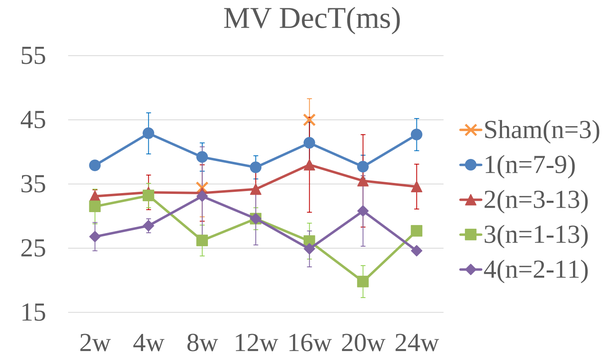




MT staining (The measured part is highlighted.)







※：The data for ‘sham’ was repurposed from a prior TAC model development experiment.

- The left ventricular diastolic posterior wall (LVPWd) of each group was thicker compared to the sham. The thickness of the wall did not thin out even 24 weeks after stenosis.
- The left ventricular end-diastolic diameter (LVIDd) and left ventricular end-systolic diameter (LVIDs) were narrower than those of the Sham group in all groups after 8 weeks of model creation. However, in Groups 2, 3, and 4, the ventricular cavity gradually expanded over time, showing a tendency to widen to a similar extent as the Sham group.
- The stroke volume (SV) was lower in groups 2, 3, and 4 compared to the sham group, but group 1 exhibited values closer to those of the sham group.
- The mitral valve E-wave velocity（MV E Vel） was higher compared to the sham. The deceleration time of the mitral valve E-wave (MV Dec T) was higher in only one group compared to the sham group 8 weeks after stenosis. However, 16 weeks after stenosis, it was lower in all groups compared to the sham.
- The left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LV FS) were within the normal range, similar to the Sham group.
- In Groups 2, 3, and 4, rats have gradually decreased due to sudden death and humane euthanasia over time.
- The percentage of fibrosis area in the left ventricle was measured. As the stenosis diameter decreased, fibrosis was observed in a wider area of the myocardium.

Conclusion

The TAC rat model was examined up to 24 weeks postoperatively and, unlike the TAC mouse model, did not show a transition from cardiac hypertrophy to dilation. However, distinct characteristics were noted due to differences in stenotic diameter. Group 1 is considered to be a mild cardiac hypertrophy model, solely based on the thickness of LVPWd and the narrowness of the left ventricular cavity. Group 2 showed tendencies of dilation in addition to the characteristics of Group 1. Moreover, the decrease in SV and the increase in MV E vel suggest it to be a strong cardiac hypertrophy model. Group 3 and 4 were considered to be HFpEF models because they had a stronger diastolic tendency, decreased MV Dec T suggesting diastolic dysfunction, and fibrosis of the myocardium. However, more conclusive evidence could not be obtained because the mitral A wave (A Vel) could not be measured in isolation. We aim to include other measures of diastolic ability in further research.

COI：disclosure information :We have no financial relationship to disclose for our presentation contents.