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Balloon Type Elasticity Sensing for Left Ventricle of Small Laboratory Animal

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***Abstract*— This paper describes an elasticity sensing system for left ventricle of small laboratory animal. We first show the basic concept of the proposed method, where a ring shaped specimen is dilated by a balloon type probe using a pressure based control, and the elasticity of the specimen is estimated by using the stress and strain information. We introduce a dual cylinder model for approximating the strengths of the specimen's material and the balloon. Based on this model, we can derive Young's modulus of the specimen. After explaining the developed experimental system, we show a couple of experimental results using rats and mice, where HFPEF (Heart Failure Preserved Ejection Fraction) group can be distinguished from a normal group.**

I. INTRODUCTION

Various works to clarify the disease mechanism of the heart failure and to establish the recovery strategy including the disease condition diagnosis have been studied [1], [2]. Experimentally, small laboratory animals such as cats, rats, and mice have been used. In general, it is known that the left ventricle of heart with failure stiffens [4], and the Sugawara method [5] and the Langendorff method [6] are employed to evaluate the ventricular stiffness and the diastolic/systolic function of the laboratory animals. In the Sugawara method, Myocardial Stiffness Constant (MSC) is calculated by the combination of the internal pressure measured by inserting a catheter in a left ventricle in vivo and the diastolic/systolic information of the left ventricle by using an echo device. In the Langendorff method, a balloon is inserted and expanded in a removed left ventricle, and the evaluation index of stiffness is calculated from the relationship between the volume of the lumen and the internal pressure. It is relatively easy to apply the two above methods to cat (internal diameter of left ventricle : 35mm$\sim$) and rat (9mm$\sim$). In contrast, due to the extremely small left ventricle, it is difficult to handle the catheter or the balloon in mouse (2$\sim$3mm). Thus it requires considerable trainings to become possible to collect data of mouse with a high reproducibility. However, the demand for the left ventricle evaluation of the mouse as a disease model is very high from the viewpoints of the low cost and convenience on controlling the disease condition. This work is motivated by the aforementioned background and the demand on the development of an elasticity sensing system that can be applied to the left ventricle of mouse.

In this work, we develop a sensing system to obtain the left ventricle elasticity of small laboratory animal. The basic concept of the proposed method is as follows. A ring-shaped specimen removed from the left ventricle is dilated by a balloon type probe whose internal pressure is controlled, and the elasticity of the specimen is acquired by measuring the pressure in the balloon and the strain of the specimen. In the Sugawara method and the Langendorff method, the left ventricle in vivo or that immediately after the removal is used. Therefore, the stiffness of tissue and the effect of myocardial systolic function are evaluated inclusively. On the other hand, the proposed method takes a standpoint where a pure stiffness of the left ventricle tissue is evaluated, as one of the material property examinations applied to the removed heart. Next, we introduce a dual cylinder model to approximate the statics characteristics of the balloon and the specimen. Here, by combining a thick cylinder model and a thin one for the specimen and the balloon, respectively, we derive the formula for computing the Young's modulus of the specimen. By using the internal pressure of the balloon and the deformation information of the specimen in a cross section, we can obtain the Young's modulus. After explaining the developed experimental system, we show experimental results for confirming the validity of the proposed method. In the experiment using rats, we show the correlation between the Young's modulus obtained by the proposed method and the MSC, as well as the possibility to distinguish a group with heart failure from a normal group. It is further shown that the proposed method has a potential to be applied to the mouse's left ventricle.

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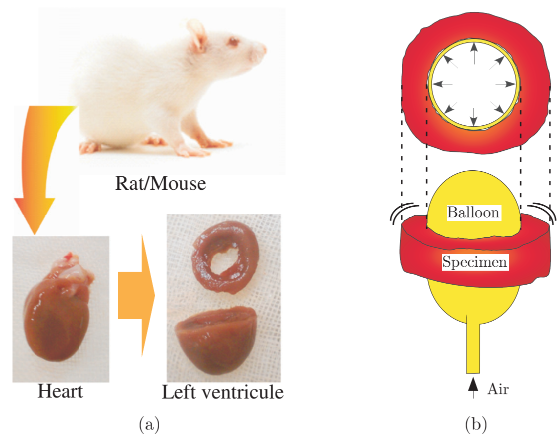


Fig. 1. Balloon type sensing for a ring-shaped specimen of the left ventricle of Rat/Mouse

II. BALLOON TYPE ELASTICITY SENSING FOR RING-SHAPED SPECIMEN

The Dahl salt-sensitive rat [7] and the mouse [8] are used as a model with HFPEF (Heart Failure Preserved Ejection Fraction). The Dahl salt-sensitive rats can be separated into normal rats grown with a normal feed and HFPEF rats grown with a high salty feed. The mice with the symptom of HFPEF can be also generated by controlling feed and hormone. The heart of rat/mouse is removed for a specimen of the disease model, as shown in Fig.1(a). The material property examinations, such as the amount of the gene expression

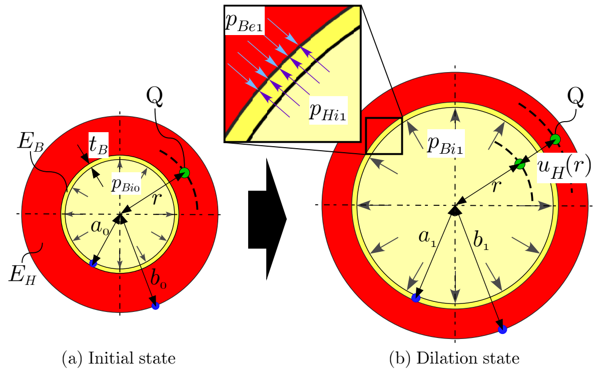


Fig. 2. Dual cylinder model for balloon and specimen

by the PCR method, the histological stain, and the amount of the protein appearance by the Western Blotting method, etc, are applied to the specimen. In this work, as part of such evaluation tests, we develop the sensing method that can evaluate the elasticity of the removed left ventricle. We aim to evaluate the average elasticity when the left ventricle is evenly pressurized. We develop the balloon type sensing system for the specimen cut in a ring shape, as shown in Fig.1(b), considering the convenience in measuring the two dimensional strain. The average Young's modulus of the whole specimen is obtained from the relationship between the internal pressure of the balloon and the strain of the specimen.

III. DUAL CYLINDER MODEL

Fig.1(b) shows the dilation behavior of the balloon and the ring-shaped specimen. We introduce the statics model by approximating the shapes of the balloon and the ring-shaped specimen in a cross section by circular shapes, as shown in Fig.2. Fig.2(a) and (b) correspond to the initial state and the dilation state, respectively. The meanings of symbols are defined as follows.

- E_H : Young's modulus of specimen
- ν_H : Poisson's ratio of specimen
- E_B : Young's modulus of balloon
- t_B : Thickness of balloon
- p_{Hi0} : Internal pressure of specimen in the initial state (IS)
- p_{Hi1} : Internal pressure of specimen in the dilation state (DS)
- p_{Bi0} : Internal pressure of balloon in the IS
- p_{Bi1} : Internal pressure of balloon in the DS
- p_{Be0} : External pressure of balloon in the IS
- p_{Be1} : External pressure of balloon in the DS
- a_0 : Internal radius of specimen, given by the length from the center to the inner wall in the IS
- a_1 : Internal radius of specimen in the DS
- b_0 : External radius of specimen, given by the length from the center to the outer wall in the IS
- b_1 : External radius of specimen in the DS

As for the internal and external pressure and the internal and external radius, the subscripts of 0 and 1 denote the initial state and the dilation state, respectively. The above symbols without the subscript of 0 and 1 express those in an arbitrary state. The external pressure of the specimen and the friction between the specimen and the balloon are assumed to be negligible small. Also, the balloon and the specimen make contact with each other without any space.

For simplicity, let us now suppose that in the initial state in Fig.2(a) the internal and external pressure of the balloon and the specimen are 0, namely $p_{Hi0} = p_{Bi0} = p_{Be0} = 0$. From such a initial state, an internal pressure p_{Bi1} is applied to the balloon as shown in Fig.2(b), and as a result the balloon and the specimen have moved to the dilation state. First, the ring-shaped specimen is modeled as a thick-walled cylinder. Suppose that a point Q on the specimen exists at the position with the distance of r from the center of the cylinder at the initial state, as shown in Fig.2(a). Based on the theory of the strength of materials [9], the displacement of Q from the initial state to the dilation one is given by

$$u_H(r) = \frac{p_{Hi1}}{E_H}\frac{(1-\nu_H)+(1+\nu_H)(b_0/r)^2}{(b_0/a_0)^2-1}r. \tag{1}$$

By substituting $r = b_0$ into (1), the change of the external radius of the specimen $b_1 - b_0$ is expressed as follows,

$$\begin{aligned} b_1 - b_0 &= u_H(b_0) \\ &= \frac{p_{Hi1}}{E_H}\frac{2a_0^2 b_0}{b_0^2 - a_0^2}. \end{aligned} \tag{2}$$

Next, considering that the thickness of the balloon t_B is small enough compared with its radius, the balloon is modeled as a thin-walled cylinder. By supposing that the radius of the balloon in the initial state is r_B, the change of the radius $u_B(r_B)$ in the transition from the initial state to the dilation one is given by

$$u_B(r_B) = \frac{p_{Be1} - p_{Bi1}}{E_B}\frac{r_B^2}{t_B}. \tag{3}$$

It is considered that the radius of the balloon is equal to the internal radius of the specimen, since $t_B \ll r_B$. By substituting $r_B = a_0$ into (3), the change in the radius of the balloon is expressed as follows,

$$\begin{aligned} a_1 - a_0 &= u_B(a_0) \\ &= \frac{p_{Be1} - p_{Bi1}}{E_B}\frac{a_0^2}{t_B}. \end{aligned} \tag{4}$$

Since, the internal pressure of the specimen p_{Hi1} in (2) and the external pressure of the balloon p_{Be1} in (4) are the contact pressures, and they are equivalent to each other. Therefore, by removing $p_{Hi1} = p_{Be1}$ from (2) and (4), we can obtain

$$E_H = \frac{2a_0^2 b_0}{(b_1 - b_0)(b_0^2 - a_0^2)}\left\{p_{Bi1} - \frac{(a_1 - a_0)t_B}{a_0^2}E_B\right\}. \tag{5}$$

The above equation shows that the Young's modulus of the specimen E_H can be calculated by measuring the internal pressure of the balloon p_{Bi1}, the internal and external radius of the specimen at the initial state a_0 and b_0, and those at the dilation state a_1 and b_1. The thickness t_B and the Young's modulus E_B of the balloon are assumed to be already known.

In the same way, the Young's modulus of the specimen E_H in general case that the internal pressure of the balloon is given by $p_{Bi0} \geq 0$, can be calculated as follows,

$$E_H = \frac{2A^2 B}{(b_1 - b_0)(B^2 - A^2)}\left\{P - \frac{(a_1 - a_0)t_B}{A^2}E_B\right\} \tag{6}$$

where

$$\begin{aligned} A &\triangleq \frac{p_{Bi1}a_0 - p_{Bi0}a_1}{p_{Bi1} - p_{Bi0}} \\ B &\triangleq \frac{p_{Bi1}b_0 - p_{Bi0}b_1}{p_{Bi1} - p_{Bi0}} \\ P &\triangleq p_{Bi1} - p_{Bi0} \end{aligned}$$

The Young's modulus of the specimen E_H obtained by (6) is used as an elasticity evaluation index, where the strain is linearized

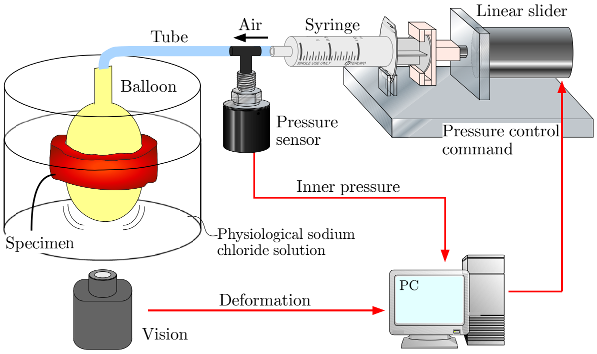
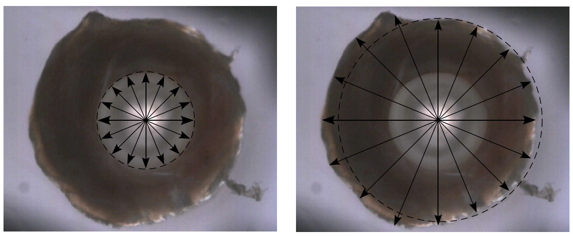


Fig. 3. Overview of the experimental system.



(a) Internal radius a (b) External radius b

Fig. 4. Measurement of radius of specimen.

when the internal pressure of the balloon rises from p_{Bi0} to p_{Bi1}. In biological tissues, however, the nonlinearity generally appears in the relationship between the stress and the strain. To cope with this issue, we give a small differential pressure of the balloon P to (6), and treat E_H as a local Young's modulus near the internal pressure of the balloon p_{Bi1}. For an arbitrary internal pressure of the balloon p_{Bi}, we calculate E_H by giving $p_{Bi1} = p_{Bi}$ and $p_{Bi0} = p_{Bi} - P$ to (6). Hereafter, we simply call this result the Young's modulus E_H at the internal pressure p_{Bi}.

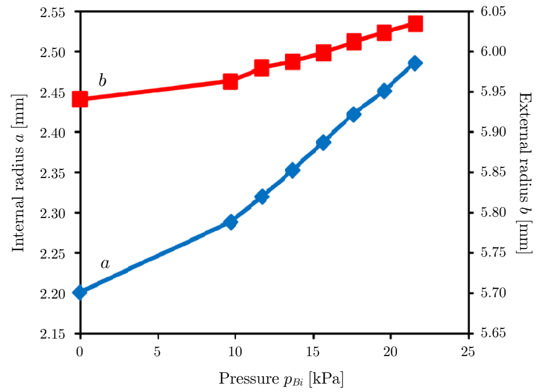
We would also like to note that the Young's modulus of the specimen in (6) corresponds to the average of the whole specimen. Therefore, it is expected that the adaptability to the disease model with high blood pressure, whose heart stiffens evenly, is high.

IV. EXPERIMENT

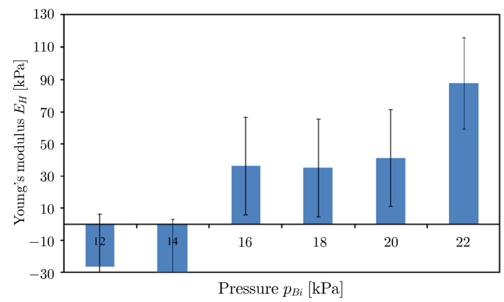
Fig.3 shows the overview of the experimental system. The balloon and the syringe are connected via the air tube, and the internal pressure of balloon p_{Bi} is measured by the pressure sensor. The syringe is attached to the linear slider, and the internal pressure of balloon p_{Bi} is controlled by the pressure feedback by using the PC. The balloon is inserted in the ring-shaped specimen, soaked into physiological sodium chloride solution, and its dilation is generated by increasing the internal pressure. Two balloons with two different sizes of LB-1 and LB-3, made by LABO SUPPORT CO., LTD, are employed for mouse and for rat, respectively. The deformation information of the balloon and the specimen is obtained by CCD camera with 640×480 pixels and 0.01 mm per pixel. Fig.4 shows photos of the specimen and the balloon taken by the camera. As shown in Fig4 (a) and (b), the average wall position in 16 directions from the balloon center is calculated as the internal and external radius a and b.

V. RESULTS

Fig.5(a) shows an example of the change in the internal and external radius a and b with respect to the internal pressure of



(a) Internal and external radius



(b) Young's modulus

Fig. 5. Experimental result with a rat specimen.

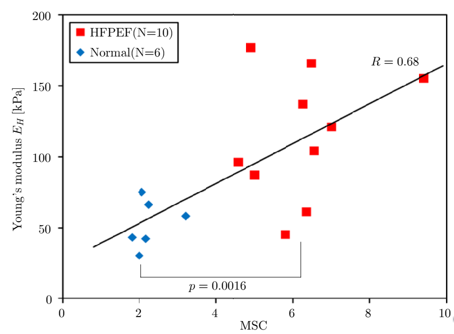
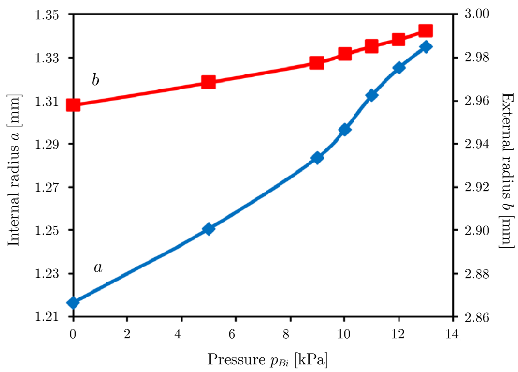


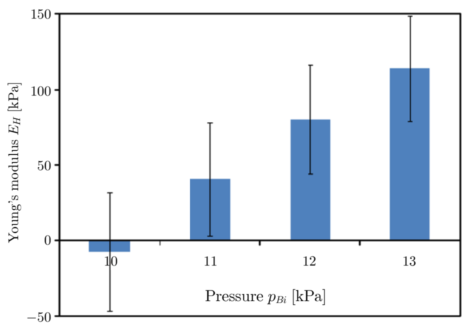
Fig. 6. Relationship between MSC and Young's modulus.

the balloon p_{Bi}, where a specimen removed from a normal rat is tested. Here, by using a balloon LB-3, we measure p_{Bi} within the range of $p_{Bi} \leq 22$ kPa with the consideration of the limit pressure for avoiding the damage of the balloon. From Fig.5(a), as the internal pressure p_{Bi} increases, we can see that the strain of the specimen wall given by $b - a$ increases. Fig.5(b) shows the Young's modulus of the specimen E_H, where we set the differential pressure of $P = 2$ kPa, and six trials are done for each p_{Bi} with changing the specimen's installed direction from top to bottom. As shown in Fig.5(b), along with the increase of the internal pressure of the balloon p_{Bi}, the Young's modulus of the specimen also increases. This is because of the nonlinearity of the specimens.

Then, we investigate the validity of the proposed method by comparing the MSC of rat measured in vivo and the Young's modulus E_H of the ring-shaped specimen removed from the same rat. Here, six normal rats and ten HFPEF rats are tested. Fig.6 shows the relationship between the MSC and the Young's modulus E_H at

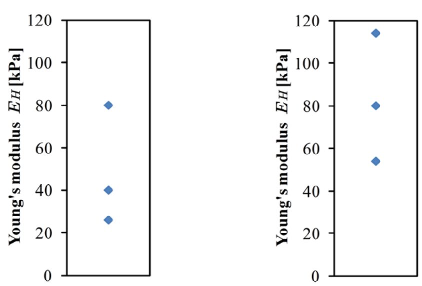


(a) Internal and external radius



(b) Young's modulus

Fig. 7. Experimental result with a mouse specimen.



(a) p_{Bi}=12kPa (b) p_{Bi}=13kPa

Fig. 8. E_H of normal mouse.

the internal pressure of the balloon $p_{Bi} = 22$ kPa. The correlation coefficient is $R = 0.68$. Also, for the comparison between normal and HFPEF rats by using E_H, it is confirmed that a significant difference with high reliability of the critical rate of 1% or less ($p < 0.01$). While two lowest Young's modulus values of the HFPEF group are close to the average of the normal group, it is possible to distinguish the HFPEF group from the normal group by using the proposed method.

Fig.7 shows the experimental results where a normal mouse is tested. The data is measured with a range of $p_{Bi} \leq 13$ kPa by using a balloon LB-1. The Young's modulus of the specimen E_H for the internal pressure of the balloon p_{Bi} is shown in Fig.7(b), where we set the differential pressure $P = 1$ kPa. We tested three normal mice, and the average value $\bar{E}_H = 48.7 \pm 28.0$ kPa and 82.6 ± 30.1 kPa are obtained at $p_{Bi} = 12$ kPa and $p_{Bi} = 13$ kPa, respectively, as shown in Fig.8. Since these values are with the same level with the Young's modulus of normal rats, we can expect that the proposed method may be applicable to mouse .

VI. CONCLUSION

This paper described the elasticity sensing system for the left ventricle of small laboratory animal. We proposed the balloon type elasticity sensing for a ring-shaped specimen of the left ventricle. In this method, the specimen is dilated by the balloon controlled by the pressure feedback, and the elasticity is obtained from the internal pressure of the balloon and the strain of the specimen. A dual cylinder model was introduced to approximate the static characteristic of the balloon and the specimen, and the Young's modulus of the specimen based on the model was derived. Through experiments using rats, we clarified the relationship between the Young's modulus obtained by the proposed method and the MSC. By the proposed method, it was shown that it is possible to evaluate the elasticity condition and also to distinguish the HFPEF group from the normal group. We further showed the applicability of the proposed method to mouse.

We would like to note that the Young's modulus of the specimen obtained by the proposed method is valid in evaluating the relative elasticity of the left ventricle. On the other hand, it is an important issue to investigate appropriate internal pressure, balloon size, and calibration method in order to improve the reliability as a material property.

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