Chapter

Cardiac Reshaping Net for Dilated Cardiomyopathy

Toshiaki Akita, Sho Akita, Hideki Ito, Masato Mutsuga and Toshiya Sasaki

Abstract

Dilated cardiomyopathy (DCM) is an intractable disease that progressively worsens with cardiac enlargement and heart failure. There are approximately 20,000 patients designated with intractable disease who have moderate or severe heart failure symptoms even with appropriate medical treatment, making it the most common target disease for heart transplantation in Japan. Sixty percent of designated DCM patients are over the age of 60. If we can extend their healthy life expectancy by 5 to 10 years, we can reduce the number of patients who are candidates for heart transplantation. We have developed a patient-specific cardiac reshaping net (PS-CRN) to prevent progressive cardiac enlargement (=cardiac remodeling), which is the major factor in worsening heart failure. We have conducted three first-in-human clinical trials. The past and present of the "cardiac support net therapy" will be reviewed.

Keywords: dilated cardiomyopathy, cardiac remodeling, cardiac remodeling, heart failure with reduced ejection fraction (HFrEF), left ventricular end-diastolic pressure-volume relationship, right ventricular diastolic function, functional mitral regurgitation, precision medicine

1. Introduction

1.1 General treatment of advanced heart failure

The number of heart failure patients is rapidly increasing worldwide, creating a heart failure pandemic. Heart transplantation is the only radical treatment for patients with end-stage heart failure, but the shortage of donors severely limits its use. Although survival rates with continuous-flow ventricular assist devices have improved dramatically in recent years, they are not widely available because they are extremely expensive, require significant medical resources, and are associated with a high rate of serious complications. Effective and widely available treatments are urgently needed.

1.2 Dilated cardiomyopathy and cardiac remodeling

Regardless of the underlying disease, heart failure is further compromised by progressive enlargement of the heart. The decline in cardiac function and the

progressive enlargement of the heart are linked, a phenomenon known as cardiac remodeling. Cardiac remodeling, after myocardial infarction, correlates with worse life outcomes, and prevention of cardiac remodeling has become a therapeutic goal [1].

1.3 Problems with previous cardiac support net therapy (Acorn CorCap, Paracor)

Devices to prevent cardiac remodeling by physical means, such as covering the ventricles with polyester mesh bags (Acorn CorCap) or shape memory alloy (Paracor), have been developed and used in humans since about 2000 [2–5].

The Acorn CorCap is the most extensively studied of these devices and received CE mark approval in 2001. Randomized clinical trials of 300 cases have been performed in the United States [2, 3, 6, 7]. Although it demonstrated reverse cardiac remodeling, it did not demonstrate prognostic value and was not approved by the FDA. There was a lot of missing data on the primary endpoint (NYHA), and Acorn Cardiovascular, the company developing the device, did not comply with the FDA's request for corrections. On the other hand, the FDA reviewers agreed with the need for this type of device.

The Acorn CorCap wraps the right and left ventricles equally, so applying the necessary pressure (>5 mmHg) to the left ventricle would impair right ventricular dilation and reduce cardiac output (**Figure 1** left panel) [8, 9]. At a contact pressure of 3 mmHg or higher on the ventricle, transmural myocardial pressure (Ptm) decreased in the left ventricle, while no change occurred in the right ventricle. At pressures of 5 mmHg or higher, RVEDP and CVP increased, and mean blood pressure decreased [9]. On the other hand, in the device that pressurized only the left ventricle, there

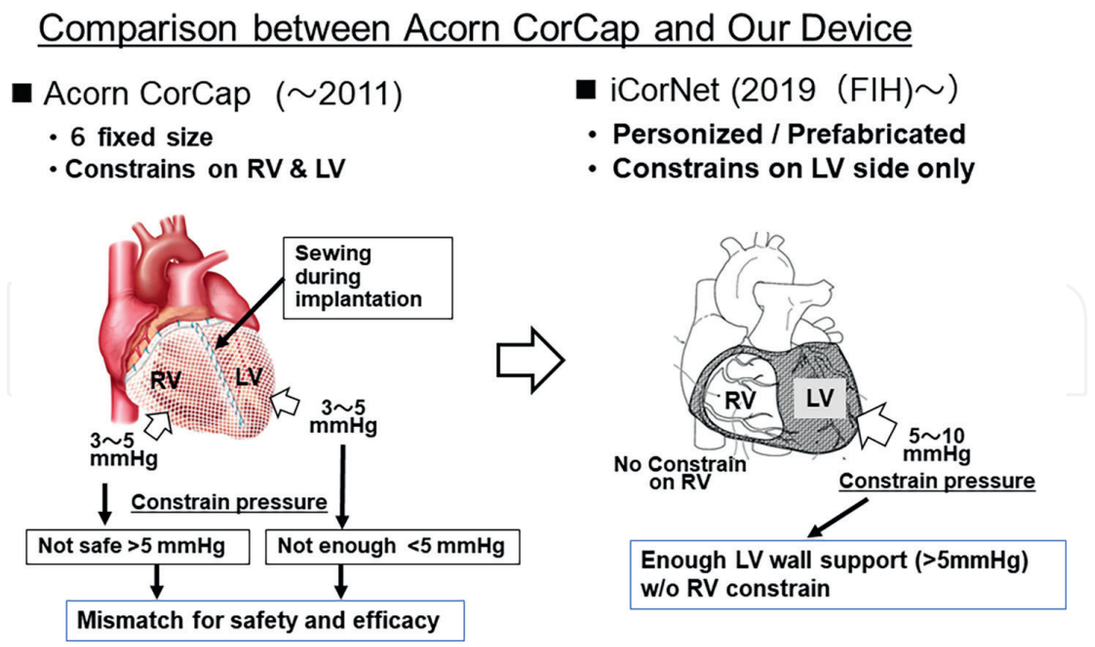


Figure 1.
Comparison between Acorn CorCap and our device. (Left panel) Acorn CorCap has six sizes. The surgeon had to adjust the size to fit. Acorn described that the contact pressure should be 3-5 mmHg. More than 5 mmHg contact pressure on the right ventricular side depresses right ventricular diastolic function. Less than 5 mmHg on the left ventricular side is not sufficient to achieve a meaningful improvement in left ventricular systolic function. (Right panel) iCorNet patient-specific cardiac reshaping net with a hole on the right ventricular side. It is a personalized/prefabricated product that constrains only on the LV side. It can provide sufficient LV wall support (>5 mmHg) without RV constraint.

was no increase in CVP and no decrease in mean blood pressure [8], even when the pressure on the left ventricle was increased up to 14 mmHg. Pressure-volume area and stroke work, which are indirect measures of oxygen consumption, were significantly reduced, and energy efficiency was improved [8].

2. Method and results of experimental study

2.1 Cardiac support net with patient-specific design

In 2005, I read a newspaper article introducing a computer-controlled three-dimensional (3D) knitting machine (Shimaseiki Co. Ltd., Wakayama, Japan). This machine can produce 3D knitted product without sewing "WHOLEGARMENT". I came up with an idea that if we prefabricate patient-specific cardiac support net with this computer-controlled 3D knitting machine using the patient's heart images, then we do not need to adjust the net size (**Figure 1**. right panel). It will eliminate the surgeon's arbitrary adjustment and shorten the operation time.

2.2 Experimental study to determine the suitable size and shape of cardiac support net

In order to eliminate the arbitrary adjustment of the cardiac support net, we need to determine the most appropriate size before the operation. For this purpose, we investigated the systolic and diastolic functions of the right and left ventricles with different sizes of the cardiac support net in a porcine model of chronic heart failure (HF). The HF model was established by rapid atrial pacing (200 bpm for 3 weeks) using a commercial intravenous pacing leadwire and an experimental pacing system (Taishoikakikai Co, Osaka, Japan).

After 3 weeks of rapid pacing, LVDd increased from 34.2 ± 7.0 to 51.0 ± 4.5 mm, and LVDs increased from 24.0 ± 7.1 mm to 46.3 ± 5.2 mm5., respectively. LVEF decreased from 60.6 ± 12.5 to 20.8 ± 8.5% (**Table 1**). We then examined the effects on right and left ventricular pressure-volume relations. The Sigma5 system (CardioDynamics, Zoetermeer, The Netherlands) was used. End-systolic and end-diastolic pressure-volume relations were measured by rapid volume loading with 500 ml of lactated Ringer's solution. The solution was equilibrated with blood before infusion.

We found that the slope of Emax (= end-systolic pressure-volume ratio), which is the most reliable systolic function independent of preload and afterload conditions, became steeper in both right and left ventricles when smaller nets were applied

Atrial Pacing 200 bpm for 3 weeks		
	Before	**After 3 weeks**
LVDd(mm)	34.2 ± 7.0	51.0 ± 4.5
LVDs(mm)	24.0 ± 7.1	46.3 ± 5.2
LVEF(%)	60.6 ± 12.5	20.8 ± 8.5

Table 1.
Change in UCG parameters before and after rapid pacing.

(**Figures 2** and **3a**: Improvement in Contractility). However, the end-diastolic pressure-volume relation (EDPVR) also shifted to the left and upward, indicating a worsening of diastolic function (**Figures 2** and **3b**) [10]. The deterioration of the right ventricular diastolic function was more pronounced than that of the left ventricle, especially at 85% of the original heart size (**Figure 3b**). There was a point at which RVEDV stopped increasing in response to rapid volume loading, and from that point only RVEDP increased (**Figure 2b**). This phenomenon was speculated to be due to compression of the right ventricle by the left ventricle and the cardiac support net, which prevented right ventricular dilation. The cardiac support net lowers Ptm, thereby improving left ventricular contractility. However, the positive effect of the cardiac support net on systolic function is offset by the decrease in stroke volume due to the worsening of right ventricular diastolic function [8].

2.3 Patient-specific cardiac reshaping net (PS-CRN) with less constraint on RV side

Based on the above experimental results, we developed a patient-specific cardiac reshaping net (PS-CRN) with less constraint on the right ventricle (RV) by making a hole on the right ventricle side (**Figure 1**) [11]. PS-CRN is made of polyester fiber thread and is prefabricated using computer-controlled knitting machine. The size and shape are designed base on the patient's cardiac images (MRI or contrasted CT) and left ventricular end-diastolic pressure. The relationship between left ventricular end-diastolic pressure and volume is calculated using the Klotz equation [12], The PS-CRN is then designed to achieve 5 to 10 mmHg contact pressure on the LV.

1. The design and manufacturing process is as follows (**Figure 4**)

    i. Cardiac imaging (MRI T2 Whole Heart or Contrast CT).

    ii. Cardiac catheterization: Measurement of LVEDP.

    iii. 3D modeling of LV & RV cavity, whole ventricle surface from cardiac images

    iv. (Converted to STL data).

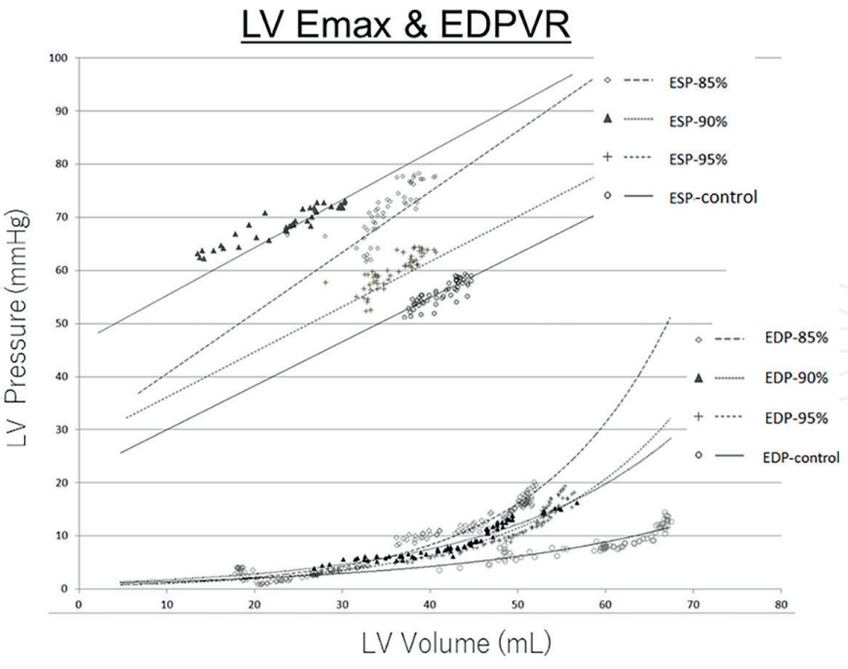
    v. Create design paper for computer-controlled knitting machine from 3D cardiac model (custom software), setting contact pressure 5 to 10 mmHg on LV surface at LVEDP 30 mmHg).

    vi. Prefabrication of the PS-CRN by computer-controlled knitting machine.

    vii. Washing and packaging with insertion tool and sterilization.

2. What are the important aspects of cardiac assist device therapy?

In heart failure patients, cardiac output decreases above a certain LVEDP point (usually LVEDP >30 mmHg), known as the descending slope of the Frank-Starling curve. Therefore, it is reasonable to set sufficient compression pressure (close to 10 mmHg) above the point of the descending slope of the Frank-Starling curve to



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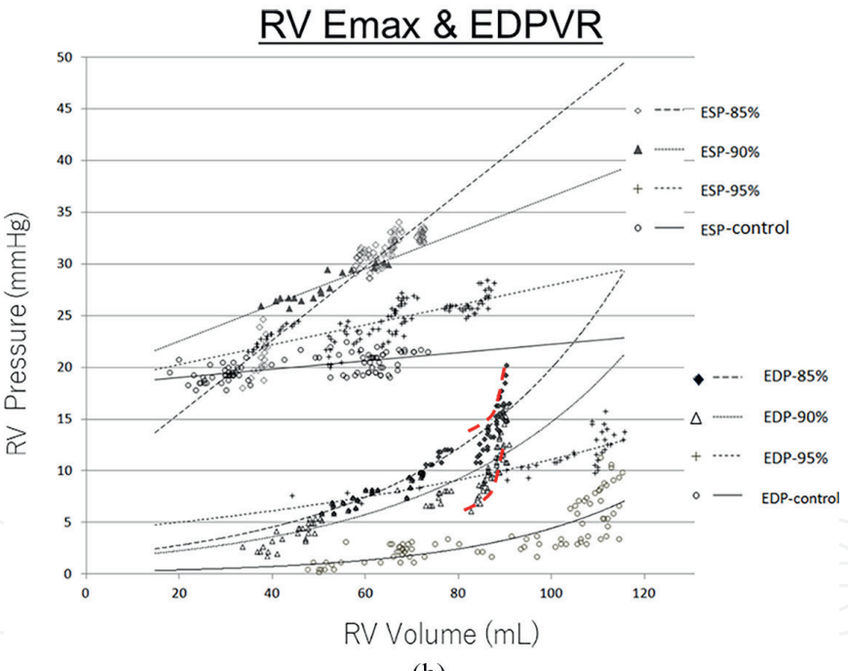
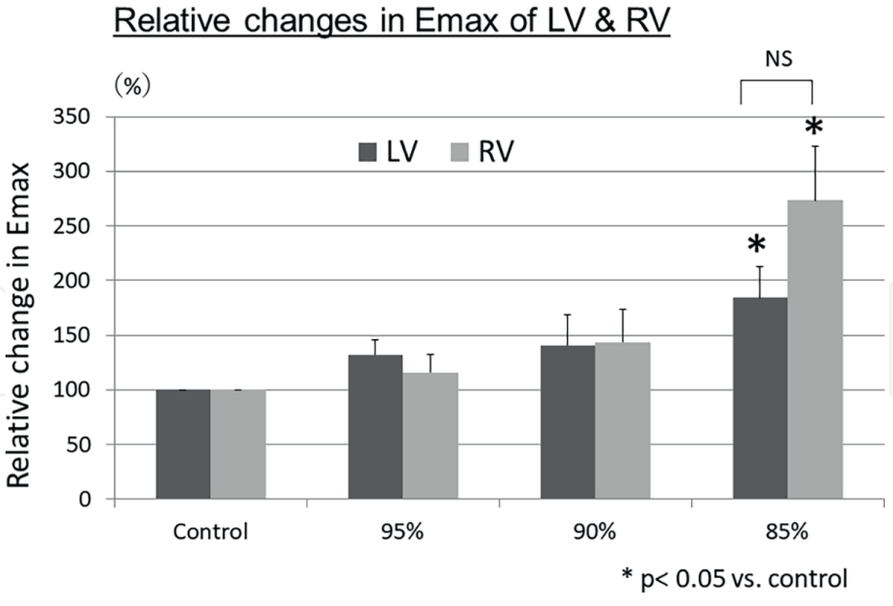


(b)

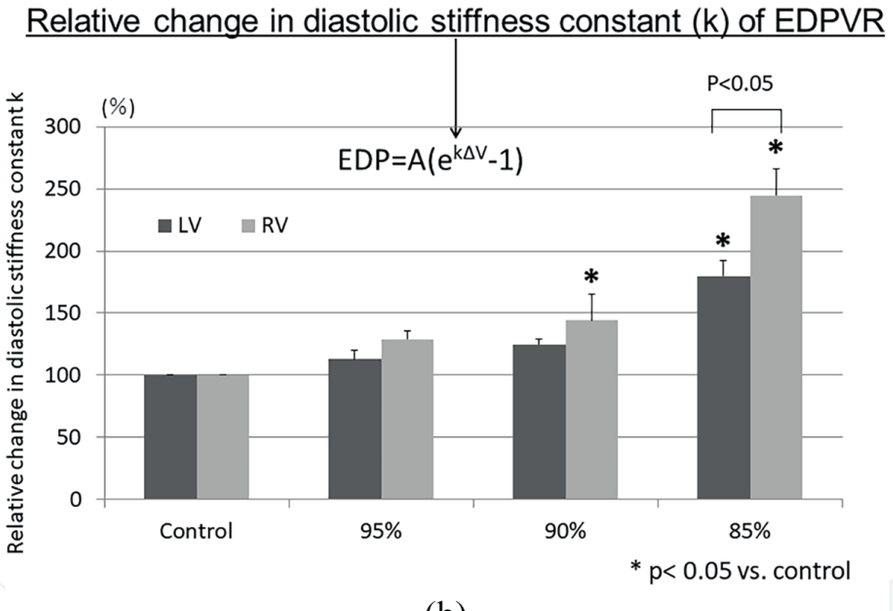
Figure 2.
a. LV ESPVR & EDPVR. Typical recordings of LV Emax (ESPVR) and EDPVR. Wearing a smaller cardiac net tended to increase Emax. LV EDPVR shifted upward and to the left by wearing a smaller cardiac net. b. RV Emax & EDPVR. Typical recordings of RV Emax (ESPVR) and EDPVR. Wearing a smaller cardiac net tended to increase Emax. RV EDPVR shifted upward and to the left by wearing a smaller cardiac net. Under the 90% size of the cardiac net, RVEDP increased sharply (red dotted line), which meant that RVEDV did not increase further by rapid fluid infusion.

prevent further dilation. This is another important consideration in the design of the PS-CRN in addition to less right ventricular constraint.

The PS-CRN is designed to set the surface pressure on the left ventricular side to 5 to 10 mmHg at LVEDP 30 mmHg. This requires prediction of the LV end-diastolic



(a)



(b)

Figure 3.
a. Relative changes in Emax (end-systolic pressure-volume relation) of LV & RV. The CHF swine model was created by rapid atrial pacing at 200 bpm for 3 weeks. LVEF decreased from 60.6 ± 12.5 to 20.8 ± 8.5% after 3 weeks of rapid pacing. Conductance and pressure catheters were placed in both ventricles and pressure and volume were recorded using the Sigma5 system. A venous cannula was inserted into the right atrium and connected to a bag filled with 1 L of lactated Ringer's solution. Blood and lactated Ringer's solution were equilibrated by infusing and draining the bag fluid. Emax and end-diastolic pressure-volume relation (EDPVR) were measured by rapid fluid infusion. Each Emax value without cardiac net (control) was set at 100% and compared with Emax data with cardiac net. Emax tended to increase with decreasing cardiac mesh size. In both LV and RV, statistical significance was reached at 85% of the cardiac net size. b. Relative change in diastolic stiffness constant (k) of EDPVR. Each EDPVR data point was fitted to the curve with the equation: EDP = a(ekEDV-1). Each diastolic constant k value without cardiac net (control) was set to 100% and compared to the k value with cardiac net. Diastolic constant k value tended to increase with decreasing cardiac net size. RV k-value reached statistical significance at 90% size, while LV k-value reached statistical significance at 85% size. The increase of k value in RV was greater than that in LV at 85% cardiac net size.

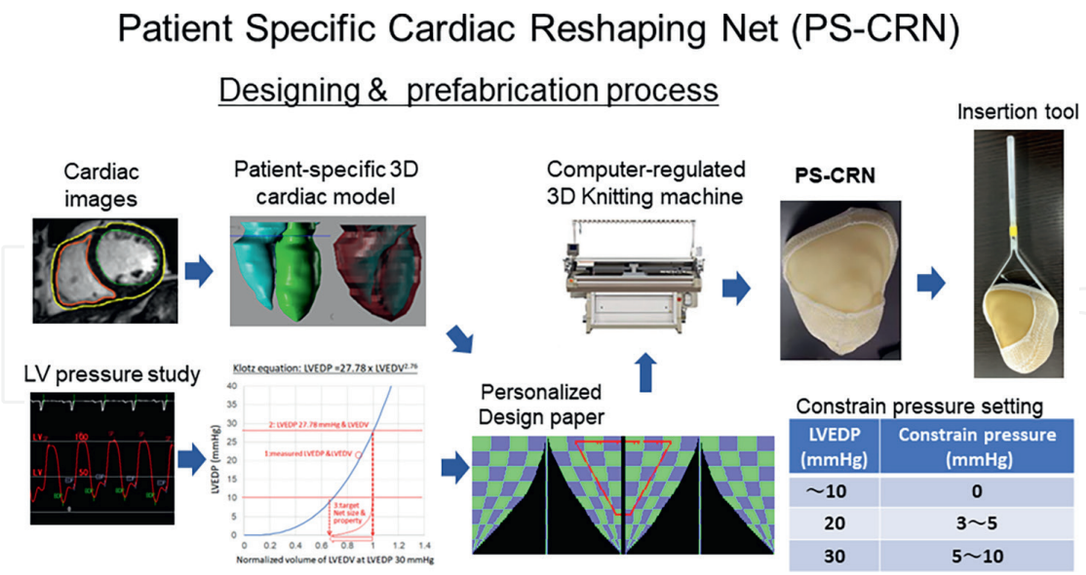


Figure 4.
Design and prefabrication process of patient- specific cardiac reshaping net (PS-CRN). (1) cardiac imaging (MRI T2 whole heart or contrast CT). (2) cardiac catheterization: Measurement of LVEDP. (3) 3D modeling of LV & RV cavity, whole ventricle surface from cardiac images (converted to STL data). (4) create design paper for computer-controlled knitting machine from 3D heart. Model (custom software: Set contact pressure 5 to 10 mmHg between LV surface and heart mesh at LVEDP 30 mmHg). (5) prefabrication of PS-CRN by computerized knitting machine.

pressure-volume ratio (LVEDPVR) in individual cases. We use the LVEDPVR estimation formula reported by Klotz et al. [12]. The concept is based on studies showing that the LVEDPVR of the human heart is almost identical when LVEDV at LVEDP 30 mmHg is normalized to 1 (normalized volume), regardless of whether the heart is normal or diseased (DCM, ICM, and HCM).

$$\begin{aligned}&\text{LVEDPVR is expressed as LVEDP} = \alpha \text{x EDV}^{\beta}\\&\left(\alpha = 27.78\,\text{mmHg}, \beta = 2.76\,(\text{unitless})\right),\\&\text{LVEDV is normalized to 1 at LVEDP 30 mmHg.}\end{aligned} \tag{1}$$

In other words, if LVEDV is set to 100% at LVEDP 30 mmHg (more precisely, at 27.78 mmHg), then LVEDP 10 mmHg is approximately 70%, 20 mmHg is approximately 80%, and 25 mmHg is 95% of the size of LVEDV at LVEDP 30 mmHg. With respect to LVEDV, the LVEDP/LVEDV ratio increases sharply as LVEDP approaches 30 mmHg. Similarly, because the PS-CRN is a knitted product, the pressure remains low just above near-unloaded sizes, but when the mesh is fully stretched, the pressure increases rapidly relative to the change in volume. The PS-CRN can be designed to prevent the heart from expanding beyond the LVEDV at LVEDP 30 mmHg by designing the mesh to be nearly fully stretched at the LVEDV size at LVEDP 30 mmHg.

Using a computer-controlled knitting machine that can produce 3D-shaped knitted products without sewing (Shima-Seiki Co. Ltd.), PS-CRN is designed and manufactured in advance for each heart failure patient according to the above concept. It is possible to safely exert sufficient pressure (>5 mmHg) on the left ventricle to improve cardiac function while avoiding right ventricular dilatation failure by making a hole in the right ventricular part.

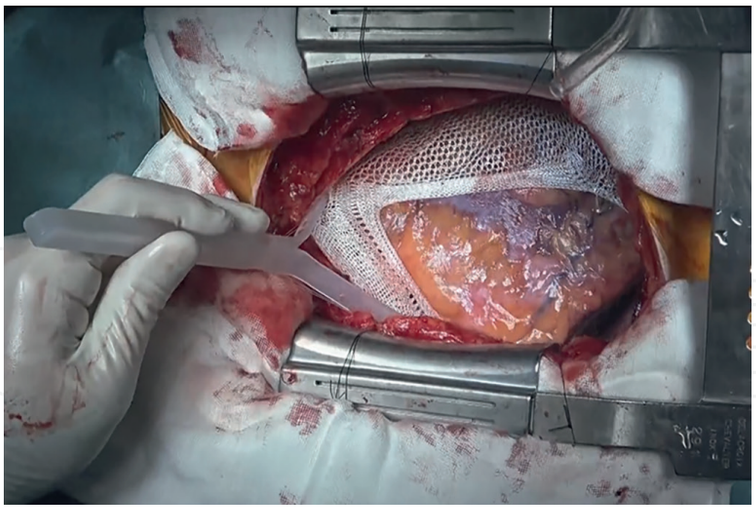


Figure 5.
Operative image of PS-CRN implantation with insertion tool. Insertion of the PS-CRN took approximately 1 minute.

	Case 1	Case 2	Case 3
gender	Male	Male	Male
Age	65	69	70
NYHA	III	III	III
INTERMACS	7	6	5
ICD/CRT-D	CRT-D	CRT-D	—
BNP (pg/ml)	111.5	111.1	1065.9
LVEDD(mm)	73.3	70.8	70.1
LVEF(%)	24.5	26.9	29.1

Table 2.
Patient demographics.

3. Implant procedure (**Figure 5**)
   i. Median sternotomy or left anterior mini-thoracotomy.
   ii. Insert the PS-CRN without lifting the heart using the insertion tool.

The device can be inserted through either a median sternotomy (**Figure 5**) or a left anterior thoracotomy (minimally invasive approach (MICS). Since the PS-CRN is designed and prefabricated prior to surgery, no intraoperative adjustments are required.

3. Results of first-in-human study

The first-in-human study was completed in three patients with DCM (**Table 2**) (https://jrct.niph.go.jp/en-latest-detail/jRCTs042180025). All patients are over 65 years of age, NYHA-III. UCG data showed LVDD>70 mm, LVEF<30%, and moderate mitral regurgitation. Implantation of the PS-CRN reduces left ventricular volume and mitral regurgitation to trace or mild degree during surgery. Peak oxygen consumption at

24 weeks after surgery increased by 2.8 ml/kg/min (average of 3 cases). Pulmonary wedge pressure decreased drastically (20.7 → 10.3 mmHg for average in three cases). Patients maintained a better quality of life than before surgery (preparation for submission).

We proceeded to the investigator-initiated feasibility clinical trial from June 2022 (https://jrct.niph.go.jp/en-latest-detail/jRCT2042210157). The first case had severe mitral regurgitation and pulmonary hypertension above 70 mmHg in systole at the time of surgery. Immediately after implantation, mitral regurgitation was reduced to mild, and pulmonary artery pressure dropped below 30 mmHg in systole.

4. Discussion

4.1 Current status of the patient-specific cardiac reshaping net and future direction

PS-CRN is the device that compresses the primary LV surface, the annulus of the mitral, and tricuspid valves. The amount of compression is designed by the patient's LV end-diastolic pressure-volume relationship. These two key features allow the PS-CRN to apply sufficient constraining pressure on the LV surface without compromising RV diastolic function. This direct mechanical action immediately reduces LV diastolic volume (LV reverse remodeling) and the mitral and tricuspid annulus, ultimately reducing functional mitral and tricuspid regurgitation. A first-in-human study supported these hypotheses.

With the use of the insertion tool, device implantation does not require lifting of the heart, which can cause hypotension or ventricular arrhythmias. None of the four patients in the first-in-human study required IABP or cardiopulmonary support. Insertion time in the last case was only 1 minute. The minimally invasive nature of PS-CRN implantation ensures rapid recovery from surgery.

Another advantage of this device is the ease of postoperative care. No anticoagulation or immunosuppressive medications are required, as is the case with LVADs or heart transplantation.

4.2 Limitations

The lack of randomization and the small number of patients with its possibility of bias are clear limitations in drawing definitive conclusions from our first-in-human study and need to be addressed in further studies. Another limitation is the lack of long-term results.

Future randomized trials will determine whether the observed beneficial effect is significant and sustained in patients who are maintained on evidence-based heart failure therapies over the long term.

For this reason, we believe that this device should be used preferentially in older patients until long-term results demonstrate sustained beneficial effects, such as quality of life and survival. The younger patients, who are eligible for heart transplantation, should be informed that the use of PS-CRN may increase the risk of heart transplantation. Although successful heart transplantation after CorCap implantation has been reported, the procedure required longer time for dissection of the dense adhesion of CorCap and epicardium and pericardium [13, 14].

5. Conclusion

The Patient-specific cardiac reshaping net (PS-CRN) is a pathophysiological treatment for dilated cardiomyopathy, and its reverse remodeling effect was demonstrated intraoperatively because it is designed and fabricated for each heart failure patient. The procedure was safe and fast with no device-related adverse events. The first case was followed for up to 4 years postoperatively. Initial results were promising.

6. Research funding

The first-in-human study (https://jrct.niph.go.jp/en-latest-detail/jRCTs042180025) was funded by the Terumo Foundation for Life Science and Arts.

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Conflict of interest

The authors, Toshiaki Akita and Toshiya Sasaki, are co-founders, shock holders, and current board members of iCorNet Laboratory (Nagoya, Japan), the company that developed the device.

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