Original research

First in-human modified atrial septostomy combining radiofrequency ablation and balloon dilation

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ABSTRACT

Objective Preclinical research suggests that the combined use of radiofrequency ablation and balloon dilation (CURB) could create stable interatrial communications without device implantation. This study examined the first in-human use of CURB for modified atrial septostomy in patients with severe pulmonary arterial hypertension (PAH).

Methods Between July 2018 and October 2021, CURB was performed in 19 patients with severe PAH (age: 31.5±9.1 years; mean pulmonary artery pressure: 73 mm Hg (IQR: 66–92); pulmonary vascular resistance: 18.7 Wood units (IQR: 17.8–23.3)). Under guidance of intracardiac echocardiography and three-dimensional location system, (1) fossae ovalis was reconstructed and ablated point-by-point with radiofrequency; (2) then graded balloon dilation was performed after transseptal puncture and the optimal size was determined according to the level of arterial oxygen saturation (SatO₂); (3) radiofrequency ablation was repeated around the rims of the created fenestration. The interatrial communications were followed-up serially.

Results After CURB, the immediate fenestration size was 4.4 mm (IQR: 4.1–5.1) with intracardiac echocardiography, systolic aortic pressure increased by 10.2±6.9 mm Hg, cardiac index increased by 0.7±0.3 L/min/m² and room-air resting SatO₂ decreased by 6.2±1.9% (p<0.001). One patient experienced increased pericardiac effusion postoperatively; the others had no complications. On follow-up (median: 15.5 months), all interatrial communications were patent with stable size (intraclass correlation coefficient=0.96, 95%CI:0.89 to 0.99). The WHO functional class increased by 1 (IQR: 1–2) (p<0.001) with improvement of exercise capacity (+159.5 m, P<0.001).

Conclusion The interatrial communications created with CURB in patients with severe PAH were stable and the mid-term outcomes were satisfactory.

Trial registration number NCT03554330.

INTRODUCTION

Atrial septostomy is an important palliative therapy for patients with refractory pulmonary arterial hypertension (PAH), heart failure with preserved ejection fraction and multiple forms of other cardiovascular diseases.1–14 Although graded balloon atrial septostomy is widely used, the frequency of spontaneous closure is high, thus limiting its clinical utilisation.2–5 13 14 To reduce spontaneous closure, the applications of different specialty devices have been reported; however, the usefulness of these approaches remains to be proven.15–23 Additionally, potential complications secondary to device implantation might occur, and their long-term safety is still unknown.16–24

Our preclinical study suggested that the combined use of radiofrequency ablation and balloon dilation (CURB) could create stable interatrial communications without device implantation.26 Radiofrequency catheter ablation (RFA) on the fossae ovalis can reduce the elastic recoil of local tissue, thereby contributing to a transseptal puncture and creating the desired interatrial fenestration with balloon dilation. Around the rims of the fenestration created with balloon dilation, additionally, RFA has the potential to cause irreversible damage, which prevents the re-adhesion of the septal remnants. This study was performed to investigate the first in-human use of CURB for modified atrial septostomy in patients with severe PAH.

METHODS

Study design and Participants

This prospective single-centre study was conducted to evaluate the feasibility of modified atrial septostomy with CURB, and the primary outcome
measures included the stability of created fenestration (patency and size change of communication) and the exercise tolerance (6min walk distance). Between July 2018 and October 2021, a total of 19 patients (age: 31.5±9.1 years; 3 male patients and 16 female patients) fulfilled the inclusion criteria and were referred for atrial septostomy with CURB. All patients were part of the study group registered at clinicaltrials.gov and had right heart failure refractory to medical therapy. All patients underwent chest radiography, electrocardiography and transsthoracic Doppler echocardiography (TTE). Furthermore, multi-slice CT was performed preoperatively to evaluate the morphology and exclude cardiovascular malformations and coronary artery disease. The level of N-terminal pro-brain natriuretic peptide was measured, and the exercise capacity was evaluated using the 6 min walk distance.

All patients underwent routine right and left heart catheterisation to assess the haemodynamics without discontinuation of targeted medical therapy. Then, CURB was performed. Based on the levels of resting arterial oxygen saturation (SatO₂) and left ventricular end diastolic pressure, the optimal size of inter-atrial communication was achieved with graded balloon dilation. After CURB, the immediate haemodynamic parameters were measured, and the created fenestration was evaluated with intracardiac echocardiography (ICE) and TTE. Anticoagulation was commenced postoperatively, and the size of the interatrial fenestration was followed-up serially with TTE.

### Patient and public involvement
Patients or the public were not involved in the design, conduct, reporting or dissemination plans of the research.

### Inclusion and exclusion criteria
The inclusion criteria were: (1) severe idiopathic PAH or severe PAH related to repaired congenital heart diseases; (2) WHO functional class III or IV with right heart failure refractory to medical therapy; (3) mean pulmonary artery pressure (MPAP) >50 mm Hg and pulmonary vascular resistance (PVR) >12 Wood units/m² with targeted medical therapy.

The exclusion criteria were: (1) severe right heart failure with cardiorespiratory support; (2) presence of deep vein thrombosis or pulmonary embolism; (3) presence of cardiovascular malformations, patent foramen ovale or coronary artery disease; (4) presence of implanted cardiac devices; (5) echocardiographic evidence of intracardiac thrombus, mass, tumour or vegetation; (6) mean right atrial pressure >20 mm Hg; (7) room-air resting SatO₂ <88%; (8) left ventricular end diastolic pressure ≥18 mm Hg; (9) indexed PVR>55 Wood units/m².

### CURB Procedure
**Preparation**
Under local anaesthesia, percutaneous punctures of the femoral vein were performed and two intravenous introducers were inserted (one 8F introducer and one 11F introducer; Cordis, Cashel, Ireland) (online supplemental figure 1). All patients underwent right heart catheterisation using a 6F multipurpose diagnostic catheter (Cordis, Miami, Florida, USA). After percutaneous puncture of the right femoral artery or radial artery, a 5F pigtail catheter (Terumo Medical, Somerset, New Jersey, USA) was introduced to perform left heart catheterisation. Complete haemodynamic data and blood samples were obtained. Haemodynamic parameters included right atrial pressure, right ventricular pressure, pulmonary artery pressure (PAP), aortic pressure and left ventricular pressure (online supplemental figure 2).

Cardiac output (systemic blood flow), cardiac index (cardiac output/body surface area) and PVR (IMPAP—left ventricular end diastolic pressure/cardiac output) were calculated using Fick’s oximetric principle.

### Reconstruction of fossae ovalis
Under fluoroscopic guidance, a ThermoCool SmartTouch SF Bi-Directional Navigation catheter (Biosense Webster, Diamond Bar, California, USA) was introduced into the right atrium, and

### Table 1 Baseline characteristics of patients with severe PAH (n=19)

| Characteristic                          | Value                |
|----------------------------------------|----------------------|
| **Age (years)**                        | 31.5±9.1             |
| **Female, No (%)**                     | 16 (84.2)            |
| **Body mass index, kg/m²**             | 21.5±3.0             |
| **Aetiology of PAH, No (%)**           |                      |
| **Idiopathic PAH**                     | 10 (52.6)            |
| **PAH related to repaired CHD**        | 9 (47.4)             |
| **Symptoms, No (%)**                   |                      |
| **Exertional dyspnoea**                | 19 (100)             |
| **Syncope**                            | 11 (57.9)            |
| **Lower limb oedema**                  | 14 (73.7)            |
| **WHO functional class, median (IQR)** | 3 (3, 4)             |
| **III, No (%)**                        | 11 (57.9)            |
| **IV, No (%)**                         | 8 (42.1)             |
| **6MWD (metre)**                       | 252.9±98.3           |
| **NT-proBNP (pg/mL), median (IQR)**    | 1478 (859, 2331)     |
| **Haemoglobin (g/dL)**                 | 14.9±2.0             |
| **Cardiothoracic ratio (%)**           | 56.4±4.4             |
| **Electrocardiography**                |                      |
| **Heart rate (beats/min)**             | 84.9±12.3            |
| **Atrial tachycardia, No (%)**         | 2 (10.5)             |
| **Paroxysmal atrial flutter, No (%)**  | 1 (5.3)              |
| **First-degree atrioventricular block, No (%)** | 1 (5.3) |
| **TTE**                                |                      |
| **RAD (mm)**                           | 56.0±7.9             |
| **RVD (mm)**                           | 43.4±6.4             |
| **LAD (mm)**                           | 28.1±4.0             |
| **LVD (mm)**                           | 33.2±4.7             |
| **LVEF (%)**                           | 65.4±4.2             |
| **TAPSE (mm)**                         | 17.3±3.1             |
| **Tricuspid regurgitation (moderate/severe), No (%)** | 14 (73.7) |
| **Pericardial effusion, No (%)**       | 8 (42.1)             |
| **Targeted medical therapy, No (%)**   |                      |
| **Ambrisentan**                        | 14 (73.7)            |
| **Tadalafil**                          | 16 (82.1)            |
| **Bosentan**                           | 3 (15.8)             |
| **Sildenafil**                         | 3 (15.8)             |
| **Macitentan**                         | 2 (10.5)             |
| **Subcutaneous treprostinil**          | 5 (26.3)             |
| **History of balloon atrial septostomy, No (%)** | 3 (15.8) |

| Value expressed as mean±SD for normally distributed variables, median (IQR) for non-normally distributed variables and No (%) for categorical variable. |
|---|---|
| *Calculated as weight in kilograms divided by height in meters squared. | |
| †Non-normally distributed variables. | |
| ‡Thirteen patients performed the 6-minute walk test before the procedure. | |

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Modified atrial septostomy with combined use of radiofrequency ablation and balloon dilation (CURB). Under the guidance of intracardiac echocardiography (left panel) and a three-dimensional location system (right panel), the fossae ovalis was delineated and reconstructed. On the region of the fossae ovalis, radiofrequency catheter ablation (RFA) was conducted point-by-point to reduce the elastic recoil of local tissue and facilitate transseptal puncture and balloon dilation. After transseptal puncture, graded balloon dilation was performed. RFA was repeated around the rims of the created fenestration to cause irreversible damage and prevent spontaneous closure. Finally, the interatrial created fenestration was evaluated with intracardiac echocardiography.
fast anatomic mapping was performed to reconstruct the right atrium. Then, an ICE Catheter (SoundStar; Biosense Webster) was advanced intravenously into the right atrium, and images of the atrial septum were obtained using the GE Vivid i System. Under the guidance of ICE, the fossae ovalis was delineated and reconstructed (online supplemental video 1), and the thickness of fossae ovalis was measured.

RFA on fossae ovalis
The SmartTouch SF catheter was introduced into the right atrium. Calibration of the contact force and respiratory gating were performed in the right atrium. Then, the steerable SmartTouch SF catheter was deflected and advanced until it touched the region of the fossae ovalis. Under the guidance of ICE and a three-dimensional location system (Carto3 system; Biosense Webster), point-by-point RFA was performed on the fossae ovalis (online supplemental video 2) using a compatible SmartAblate RFA generator (Biosense Webster) in the power-controlled mode (without ramping). The maximum interlesion distance between two neighbouring lesions was ≤6 mm to ensure the contiguity of the lesion undergoing RFA. The following parameters were used: RFA power, 40 W; cut-off temperature, 43°C; heparin saline irrigation flow rate, 17 mL/min; contact force, 5–25 g; and application time, 20 s.

Transseptal puncture and balloon dilation
Under the guidance of fluoroscopy and ICE, transseptal puncture of the central area of the fossae ovalis was performed using the Brockenbrough transseptal needle, a Mullins transseptal dilator and an 8.5F sheath (Medtronic, Minneapolis, Minnesota, USA); the transseptal needle was preshaped to facilitate puncture. Then, the needle and dilator were slowly withdrawn and blood was aspirated from the sheath. After transseptal puncture, all patients were administered 100 units/kg of intravenous heparin. The positioning of the sheath was confirmed to be in the left atrium with manual contrast injection. Using the sheath, a 6F multipurpose diagnostic catheter was introduced and manipulated deep into a left superior pulmonary vein with the aid of a 0.035-inch, 150 cm hydrophilic guidewire (Terumo Medical). Then, it was exchanged for a 0.035-inch, 260 cm guidewire (Cordis). Over the fixed guidewire, the catheter was withdrawn and graded dilation of the atrial septum was performed using

Figure 2  Accurate transseptal puncture assisted with intracardiac echocardiography. The accurate transseptal puncture site and position of the long sheath were confirmed with intracardiac echocardiography (upper left panel) and a three-dimensional location system (upper right panel). The exact location of the interatrial communication (arrow) was demonstrated with transthoracic Doppler echocardiography (lower panels). The fenestration size was 5.1 mm with continuous shunting from right to left (1 year after the procedure).
a 6 mm diameter balloon in increments of 2 mm until 12 mm was reached (Mustang balloon; Boston Scientific, Marlborough, Massachusetts, USA). Five minutes after each dilation of the atrial septum, room-air resting SatO₂, left ventricular pressure and aortic pressure were measured. The endpoints were a post-operative level of resting SatO₂ ranging from 85% to 88% and left ventricular end diastolic pressure <18 mmHg.

RFA around the rims of interatrial fenestration

Through the interatrial created communication, the SmartTouch SF catheter was advanced into the left atrium. Under the guidance of the three-dimensional location system, the curved SmartTouch catheter was dragged slowly from the left atrium to the right atrium until the desired contact force was recorded. The correct position of the electrode tip was determined with continuously recorded contact force (5–25 g) and ICE images, in which the electrode tip overrode and touched the fenestration rim, and the microbubbles of irritating saline from the electrode tip were identified simultaneously in both atria (online supplemental video 3). Then, RFA was performed and the related parameters were identical to those of fossae ovalis ablation. The SmartTouch catheter deflected and/or rotated slightly to change the vector of contact force to four different desired directions, upper, lower, anterior and posterior, around the fenestration rim, and RFA was conducted at the four target sites (one RFA site per quadrant). After the procedure, the interatrial fenestration was evaluated with ICE (online supplemental video 4) and TTE. Right and left heart catheterisation were repeated, and the postoperative cardiac index was calculated.

Transthoracic Doppler echocardiography

For each patient, TTE was performed before CURB (online supplemental figure 3) and during follow-up. The interatrial fenestration size was defined as the largest dimension observed.

Table 2  Haemodynamic parameters before and after CURB (n=18*)

|                      | Pre-CURB | Post-CURB | P value |
|----------------------|----------|-----------|---------|
| SAOP (mm Hg)        | 102.2±11.6 | 112.4±6.5 | <0.001 |
| SPAP (mm Hg), median (IQR)† | 116.5 (101.0–134.0) | 110.5 (98.0–127.0) | <0.001 |
| MPAP (mm Hg), median (IQR)† | 72.5 (66.0–92.0) | 71.0 (65.0–91.0) | <0.001 |
| LVEDP (mm Hg)       | 12.6±2.0 | 10.1±1.4 | <0.001 |
| CI (L/min/m²)       | 2.1±0.3 | 2.8±0.2 | <0.001 |
| PVR (Wood unit)     | 21.1±6.8 | 21.1±6.7 | 0.666 |
| Room-air resting SatO₂ (%) | 93.4±1.9 | 87.2±0.8 | <0.001 |

Values expressed as means±SD for normally distributed variables and median (IQR) for non-normally distributed variables.

*The patient who had increased pericardiac effusion postoperatively was excluded.
†Non-normally distributed variables.
CI, cardiac index; CURB, combined use of radiofrequency ablation and balloon dilation; LVEDP, left ventricular end diastolic pressure; MPAP, mean pulmonary artery pressure; MRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; SAOP, systolic aortic pressure; SatO₂, arterial oxygen saturation; SPAP, systolic pulmonary artery pressure.

Figure 3  Aortic pressure before and after combined use of radiofrequency ablation and balloon dilation (CURB). An appropriate interatrial communication was created successfully with CURB, and a right-to-left shunt was detected (left panel, before CURB; right panel, after CURB). The immediate systolic aortic pressure increased from 99 to 106 mm Hg, and there was no significant change in the mean right atrial pressure. Furthermore, the symptoms improved immediately. AO, aorta; RA, right atrium.

Transthoracic Doppler echocardiography

For each patient, TTE was performed before CURB (online supplemental figure 3) and during follow-up. The interatrial fenestration size was defined as the largest dimension observed.
from the parasternal short-axis view, parasternal four-chamber view or subcostal view. Additionally, the direction of shunting was determined using Doppler echocardiography. In the apical four-chamber view, the end diastolic right ventricular dimension and left ventricular dimension were measured, and tricuspid annular plane systolic excursion was measured by M-mode echocardiography with the cursor optimally aligned along the direction of the tricuspid lateral annulus. All echocardiographic data were averaged over three beats.

**Follow-up**

For each patient, chest radiography, electrocardiography and TTE were recorded serially at 1 week, 1 month and 3-month to 6-month intervals. The patency and size of the interatrial fenestration were evaluated with TTE. Additionally, clinic visits included an evaluation of the WHO functional class and 6 min walk distance. At 3 to 6 months after the procedure, repeated multi-slice CT was suggested to evaluate the interatrial fenestration and cardiac remodelling. At 1 year after the procedure, repeat right heart catheterisation was suggested to evaluate the haemodynamic parameters and patency of the interatrial fenestration.

**Statistical analysis**

Based on previous studies, the probability of spontaneous closure for balloon atrial septostomy was estimated to be 30%. For CURB, a sample size of 13 cases was required to achieve 80% power to detect a 25% reduction in spontaneous closure. The characteristics of the patients are expressed as mean±SD or median and IQR for normally distributed variables and non-normally distributed variables, respectively; categorical variables are expressed as the number and percentage. To determine the clinical efficacy of CURB, we compared the differences in aortic pressure, PAP, mean right atrial pressure, left ventricular end diastolic pressure, cardiac index, PVR, SatO₂, WHO functional class and 6 min walk distance before and after CURB using the paired t-test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed variables. Intraclass correlation coefficient (ICC) (two-way mixed absolute agreement) and its 95% CI were used to assess the concordance of fenestration size across follow-up, and ICC >0.75 was considered as good concordance. All tests were two-tailed, and p<0.05 was considered statistically significant. All analyses were performed using SAS software (V9.4; SAS Institute).

**RESULTS**

**Baseline characteristics**

Among 19 patients, 10 patients had idiopathic PAH and 9 had PAH related to repaired congenital heart disease (surgical repair of a ventricular septal defect in 5 patients and transcatheter closure of the patent ductus arteriosus in 4 patients). All patients underwent targeted medical therapy (two or more pulmonary vasodilators), and the clinical baseline characteristics of the enrolled patients are presented in Table 1. There were 11 patients with syncope and 14 patients with peripheral oedema. Six patients were unable to perform the 6 min walk test. The right atrium (56.0±7.9 mm) and right ventricle (43.4±6.4 mm) in all patients were greatly enlarged and had concurrent opposite changes in the markedly diminished left atrium (28.1±4.0 mm) and left ventricle (33.2±4.7 mm). Moderate to severe tricuspid insufficiency was identified in 14 patients, and mild pericardial effusion was observed in 8 patients. Additionally, the tricuspid annular plane systolic excursion was 17.7±3.1 mm. There were three patients with a history of balloon atrial septostomy alone who had spontaneous closure confirmed at 2 weeks, 2 weeks and 1 month, respectively.

**Combined use of radiofrequency ablation and balloon dilation**

Right heart catheterisation showed that MPAP was 73 mm Hg (IQR: 66–92) and PVR was 18.7 Wood units (IQR: 17.8–23.3) with targeted medical therapy. Systolic PAP at baseline was 118.7±18.7 mm Hg and systolic aortic pressure at baseline was 102.6±11.4 mm Hg. Furthermore, systolic PAP was suprasystemic in 16 patients (online supplemental figure 4) and near-systemic in three patients. CURB was performed successfully in all patients (Figure 1). The thickness of fossae ovalis was 2.1±0.7 mm (online supplemental figure 5), and the intended transseptal puncture sites of the fossae ovalis were confirmed with ICE and the three-dimensional location system (Figure 2; online supplemental figure 6). The maximum balloon diameter was 10 mm (IQR: 10–12), and the immediate fenestration size was 4.4 mm (IQR: 4.1–5.1) according to ICE. Postoperatively, the systolic aortic pressure increased by 10.2±6.9 mmHg, cardiac index increased by 0.7±0.3 L/min/m² and room-air resting SatO₂ decreased by 6.2%±1.9% (p<0.001) (Figure 3 and Table 2). Additionally, the mean right atrial pressure decreased by 2.5±1.8 mm Hg (online supplemental figure 7). After the procedure, one patient had increased pericardial effusion (effusion thickness posterior to the left ventricular posterior wall increased from 5 mm preoperatively to 11 mm postoperatively). Subsequently, pericardiocentesis was performed. The patient underwent thoracotomy exploration later and a tiny perforation of the left atrial wall was detected, which might have been secondary to the guidewire. No complications were observed in the other patients. The procedural time was 113.2±30.3 min.

During follow-up (median: 15.5 months; range: 2–39 months; n=18), all interatrial communications were patent and the fenestration size was stable (ICC=0.96, 95% CI: 0.89 to 0.99; Figures 4 and 5). Symptomatic improvement was observed in all patients. The WHO functional class increased by 1 (IQR: 1–2) (p<0.001) and the exercise capacity improved significantly (+159.5 m, p<0.001). Repeat multi-slice CT was performed...
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in nine patients, and patent fenestrations were confirmed with favourable cardiac remodelling (figure 6, online supplemental figure 8,9). Twelve patients participated in more than 1 year of follow-up. Right heart catheterisation was performed in two patients whose fenestrations were confirmed to be patent with the passage of the catheter and angiography (online supplemental video 5).

DISCUSSION

For patients with severe PAH, CURB has the potential to create stable interatrial communications without device implantation. During the follow-up, all communications were patent and there was no significant change in the fenestration size. This work describes the first in-human use of CURB for modified atrial septostomy, and the mid-term outcomes were satisfactory with improvement of symptoms and exercise capacity.

During the follow-up, the size of the fenestration created with CURB was stable. With balloon atrial septostomy alone, spontaneous closure was common (nearly 30%), which mainly occurred within 1 year.2–3 13 14 In comparison, all fenestrations created with CURB were patent on mid-term follow-up. In this study, the combination of RFA and balloon dilation exhibited complementary advantages that produced a personalised interatrial fenestration with a stable size. Because RFA and balloon dilation are mature clinical techniques with satisfactory safety,

CURB might become an alternative procedure for atrial septostomy. The stability of the created fenestration with CURB was demonstrated in patients with severe PAH. Further research is ongoing to investigate the clinical application of this approach for heart failure with preserved ejection fraction (ClinicalTrials.gov ID: NCT04573166).

Based on the levels of SatO₂ and left ventricular end diastolic pressure, CURB has the potential to produce personalised interatrial communications. To improve the shunt patency, different types of specialty devices have been designed and applied for atrial septostomy. Because of the fixed size of the fenestration with these devices, they make it difficult to create personalised interatrial communications. Additionally, their long-term safety is still unknown, and the potential risks related to such devices have to be considered, such as device embolisation, device-associated thrombus, spontaneous closure, among others.16–24 During the current study, CURB was demonstrated to be a reliable procedure for personalised atrial septostomy without device implantation. According to the haemodynamic parameters, the optimal size of the fenestration was determined with graded balloon dilation, and fenestration stability was achieved with RFA. Furthermore, the effectiveness and safety of CURB were confirmed by the improvement of symptoms and haemodynamic parameters with an acceptable level of resting SatO₂.
CONCLUSIONS

For patients with severe PAH, CURB is a reliable procedure that can create personalised and stable interatrial communications. Mid-term outcomes were satisfactory with clinical improvements. Further research is required to investigate the clinical application of CURB in a large population.

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Data availability statement Data are available upon reasonable request.

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