Special Report

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Left-to-right interatrial shunt percutaneously implanted devices: a new avenue in the treatment of heart failure

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Heart failure (HF) is highly prevalent with major impact on quality of life and survival, but still, has important therapeutic limitations. Elevated left atrial filling pressure has been associated to poor prognosis. In addition, previous experiences suggest that the remaining small atrial septal defects (ASD) may act in certain situations as 'outlet valves' preventing acute failure as happens during closure of large ASD, in other congenital cardiopathies and in patients under left ventricular assist devices. Shunts created by balloon-dilation at the interatrial septum have limited duration. However, recent experiences with two specific new systems (interatrial septal device system and V-Wave) have reported symptomatic improvement at mid-term. This intriguing hypothesis represents a new avenue in the treatment of HF if the impact is confirmed at long-term.

Keywords: heart failure • IASD • interatrial shunt devices • left atrial pressure • V-Wave device

Background

Heart failure (HF) is one of the fastest-growing cardiovascular diagnoses in western countries with an estimated lifetime risk of nearly 20% and a current prevalence of up to 2% of the population [1]. Despite many diagnostic and pharmacotherapeutic advances over the past decades, symptomatic HF still carries a poor prognosis [2]. In particular, progressive HF represents the main cause of death in patients with New York Heart Association (NYHA) class III or IV HF. Therefore, limiting this progression is a major target to improve, not only quality of life, but also mid-term survival [2,3].

Importantly, although there has been a large development in therapies for heart failure with reduced ejection fraction (HFREF), very few advances have occurred in the heterogeneous scenario of heart failure with preserved ejection fraction (HFPEF), which lacks of therapies that are proven to be effective despite its comparable rates of morbidity and mortality [4]. The growing prevalence of both entities (HFREF and HFPEF) each of them accounting for about 50% of the patients suffering from HF, and the limited therapeutic arsenal strongly support the fact that novel approaches are needed.

Left ventricular (LV) systolic and diastolic dysfunction are commonly characterized by elevated left atrial pressure (LAP) in most patients with chronic HF who are hospitalized due to decompensation. A strict control of LAP by invasive monitoring and a physician directed self-management has been associated with significant improvement in LV ejection fraction and NYHA class, as well as with major reduction in rehospitalizations suggesting that this may have an important impact on mortality at mid-term follow-up [2]. Recent limited series have also suggested that the reduction of LAP by creating a left-to-right interatrial shunt may limit LAP rising, thus potentially improving exercise tolerance and protecting from episodes of acute pulmonary edema. This might lead to a reduction of rehospitalizations, increase of quality of life and potentially diminish mortality [5–8]. This work aims to summa-

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rized the current knowledge concerning this novel therapeutic approach for HF, analyze the weak points of this hypothesis and depict its future indications.

Therapeutic blood shunting: origin of the hypothesis

The rationale for shunting blood between atria as a means to reduce elevated pressures is based on the medical knowledge from the 1960s (creation of atrial septostomies) to divert blood from one atrium to another in the treatment of elevated pressures (both right and left offloading). Moreover, currently the use of septostomy procedures is recommended by the pulmonary hypertension guidelines for patients with advanced pulmonary hypertension with elevated right atrial pressure [9–15].

Historically, it was recognized that patients with mitral valve stenosis who had a co-existing atrial septal defect (ASD; Lutembacher syndrome) had fewer symptoms than patients with an intact septum [16]. Also, the closure of congenital ASD has been associated with rise in LAPs and decompensated HF in some patients, often resulting in immediate pulmonary edema [17–21]. As a consequence of the latter, the medical guidelines indicate that poor LV function (systolic and diastolic) may cause pulmonary congestion after ASD closure and may require preinterventional testing (balloon occlusion with reassessment of hemodynamics) and treatment [13].

Additionally, the creation of ASDs is a well reported occurrence of transseptal treatments (e.g., electrophysiology ablation procedures, atrial appendage closure, percutaneous mitral valvuloplasty, MitraClip, etc). These residual iatrogenic ASDs are not associated with clinical sequel of embolism/stroke, cyanosis, right HF or complications due to hemodynamic relevant interatrial shunting [22–24]. Therefore, defects of less than 5 mm are left untreated except if right ventricular volume overload is evident. Indeed, these patients are generally asymptomatic whereas defect sizes ≥10 mm often cause right volume overload and pulmonary over circulation [13].

After some studies suggesting that atrial septal balloon septostomy may be useful in the setting of LV dysfunction with acute HF to permit left heart decompression and recovery of LV function, different techniques to create interatrial communications that had been previously tried for the treatment of pulmonary hypertension, were adopted [25–30]. This includes balloon dilatation, fenestrated ASD occluders (Figure 1A) or even stent implantation (Figure 1B) [15]. All these techniques suffer from disadvantages. Nevertheless, these approaches demonstrate the clinical need and most importantly preliminary demonstration of the safe use of interatrial shunting.

Therefore, the creation of a left-to-right shunt for the treatment of left-sided HF is not a new hypothesis but, as a matter of fact, only recent development of specific devices has permitted to consider this approach as a mechanism to permanently relief elevated LAP in patients with chronic HF.

Left-to-right interatrial shunts: initial preclinical evidences

Published data and feasibility studies in an HF animal model demonstrate that shunting of 1000–1500 cc/min for 6 mmHg pressure gradient (between LAP and right arterial presure [RAP]) and 1500–1900 cc/min for 10 mmHg pressure gradient is expected to result in a reduction in LAP of 20 and 30%, respectively, without significantly increasing right atrial pressure [31].

A left-to-right atrial shunt is considered clinically significant when the pulmonary-to-systemic flow ratio (Qp:Qs) ratio is >1.5 or if it causes dilation of the right heart chambers. Therefore, the shunt diameter of the new specific systems is designed to be within a Qp:Qs ≤ 1.5. However, Qp:Qs does not only rely on the size of the created ASD; ventricular compliance and interatrial pressure gradient also play an important role. Although in congenital ASDs the orifice must be at least 10 mm in diameter to carry a significant left-to-right shunt, in HF patients the elevated LAP leads to a left-to-right pressure gradient most likely higher than in congenital ASDs. As a result, the created ASD should be smaller in size. On the other hand, to achieve shunting flow of ~1500 cc/min in the majority of pressure ranges for the indicated population, the shunt must have a diameter of at least 5mm.

To the date, only one animal study with the creation of a percutaneously implanted left-to-right shunt has been reported (Table 1) [8]. Models of HFREF were created by means of serial/selective coronary embolizations resulting in chronic left HF. The animals were assigned either to serve as controls (n = 5) or had the V-Wave device deployed into the fossa ovalis (n = 8). After recovery, they were evaluated weekly for up to 12 weeks. The deployed shunts acutely lowered LAPs without increasing right-atrial/pulmonary–artery pressures. Shunt-treated sheep had improved LV function when compared with controls and lower LA filling pressures. To remark, the 12-week survival in treated animals was 80%, while none of the untreated controls survived the monitoring period.

Also a computed simulation study has been performed to predict response to left-to-right shunt creation in cases of HFPEF [31]. This is particularly useful as there is no accepted large animal model due to the heterogeneity of the disease. The model simulated rest and exercise hemodynamics in HFPEF based on

Table 1. Main data of all (preclinical and clinical) published series concerning percutaneously implanted shunting device in the interatrial septum as treatment for systolic and diastolic heart failure.

Author	Population	Device	Age	FU (weeks)	BL LAP	LAP FU	BL PAP	PAP FU	BL LVEF	LVEF FU	Qp:Qs	BL 6MWT	6MWT FU	Survival at FU (%)	Ref.
Keren G *et al.*†	13 sheep (5 controls, 8 cases)	V-Wave	–	20	23±2	11±2	45±3	45±3	27±3	47±5	1.2 [1.2–1.4]	–	–	80	[8]
Amat-Santos *et al.*^	6 patients	V-Wave	66±7	12	20 [18–22]	14 [11–14]	25 [20–30]	25 [17–26]	32 [20–35]	33 [20–35]	1.1 [1.1–1.2]	274 [186–358]	314 [205–480]	100	[5]
SØndergaard *et al.*‡	11 patients	IASD	70±12	4	19 [6–25]	13 [9–18]	31 [19–39]	26 [19–39]	57±9	57±9	–	338 [52–540]	387 [104–522]	100	[7]

†Systolic HF studies.
‡Diastolic HF study.
BL: Baseline; FU: Follow-up; HF: Heart failure; IASD: Interatrial septal device system; LAP: Left atrial pressure; LVEF: Left ventricular ejection fraction; 6MWT: 6-minutes walking test.
Qp:Qs: Pulmonary to systemic flow ratio.

two previous studies [32–38]. The results show potential benefits both at rest and exercise as depicted in Table 1, with a mean decrease of LAP of 3 mmHg at rest and 11 mmHg at peak exercise. Although left cardiac output decreased 0.5 l/min at rest and 1.3 l/min at peak exercise with parallel increase in right cardiac output, no increase in pulmonary artery and right atrial pressure occurred thank to the decrease in wedge pressure. A majority of these effects were achieved with a shunt diameter of less than 9 mm.

These positive initial experiences encouraged to performing initial shunt implantations in humans under compassionate clinical use protocols.

Initial experience with intera-atrial shunts in humans: proof of concept

The population for which these new shunting devices are indicated includes patients suffering from clinical sequel due to high LAP, which represents ~90% of the patients hospitalized for pulmonary congestion [39–41]. The reduction of this pressure below 18 mmHg could potentially improve the patient's lung congestive state with direct and positive effect on ventilation, dyspnea and hospitalization rates [42–44].

Two short series have reported the use in humans of these left-to-right shunting specific devices to the date (Table 1). The first one represents the initial experience with the V-Wave device (V-Wave Ltd, Or Akiva, Israel) (Figure 2). Five patients with HFREF were included [5]. The other study included 11 patients with HFPEF treated with the implantation of the Interatrial Septal Device System (IASD; DC Devices Inc., Tewksbury, MA, USA) (Figure 3) [7].

The V-Wave device is a dedicated device, designed to be implanted percutaneously in the fossa ovalis. It intends to address some of the limitations characterizing atrial septostomies. Is is composed by a self-expandable hour-glass shaped nitinol shunt, with an ePTFE encapsulation and three porcine pericardial leaflets sutured together. The V-Wave delivery catheter is a 14Fr catheter intended to deliver the crimped shunt. On the distal end of the delivery catheter some hooks engage the right end of the device. The shunt can be release once in the target position with the opening of these hooks and after pulling back the delivery catheter. Once implanted, the pressure gradient existing between the left and right atria enable flow from the left to the right atrium through a diameter of ~5 mm. Oral anticoagulation was recommended for 3 months.

The IASD is also a dedicated device comprised of nitinol with an outer and inner diameters of 19 and 8 mm, respectively. Therefore, a permanent 8 mm ASD is created. The legs of the device are flat on the LA side to minimize the risk of thrombus formation. A 16 Fr sheath is placed in the femoral vein and a proprietary delivery catheter is used to deliver the implant to the desired location at the fossa ovalis. After the procedure, patients were treated with aspirin (lifelong) and clopidogrel per institutional standards. No anticoagulation is recommended as there is not a valve sutured inside the nitinol structure.

Potential risks & limitations of this new approach

Despite initial encouraging results, as the myocardial underlying disease is not the target, a limited prognostic impact in terms of survival could be expected. However, at this stage of the disease even if improvement is restricted to symptoms and rehospitalizations rate, this therapy may represent a paradigm shift in therapeutics of HF.

There are some risks during the procedure and in the follow-up that should be also addressed. This includes biological reactions such as thrombogenicity,

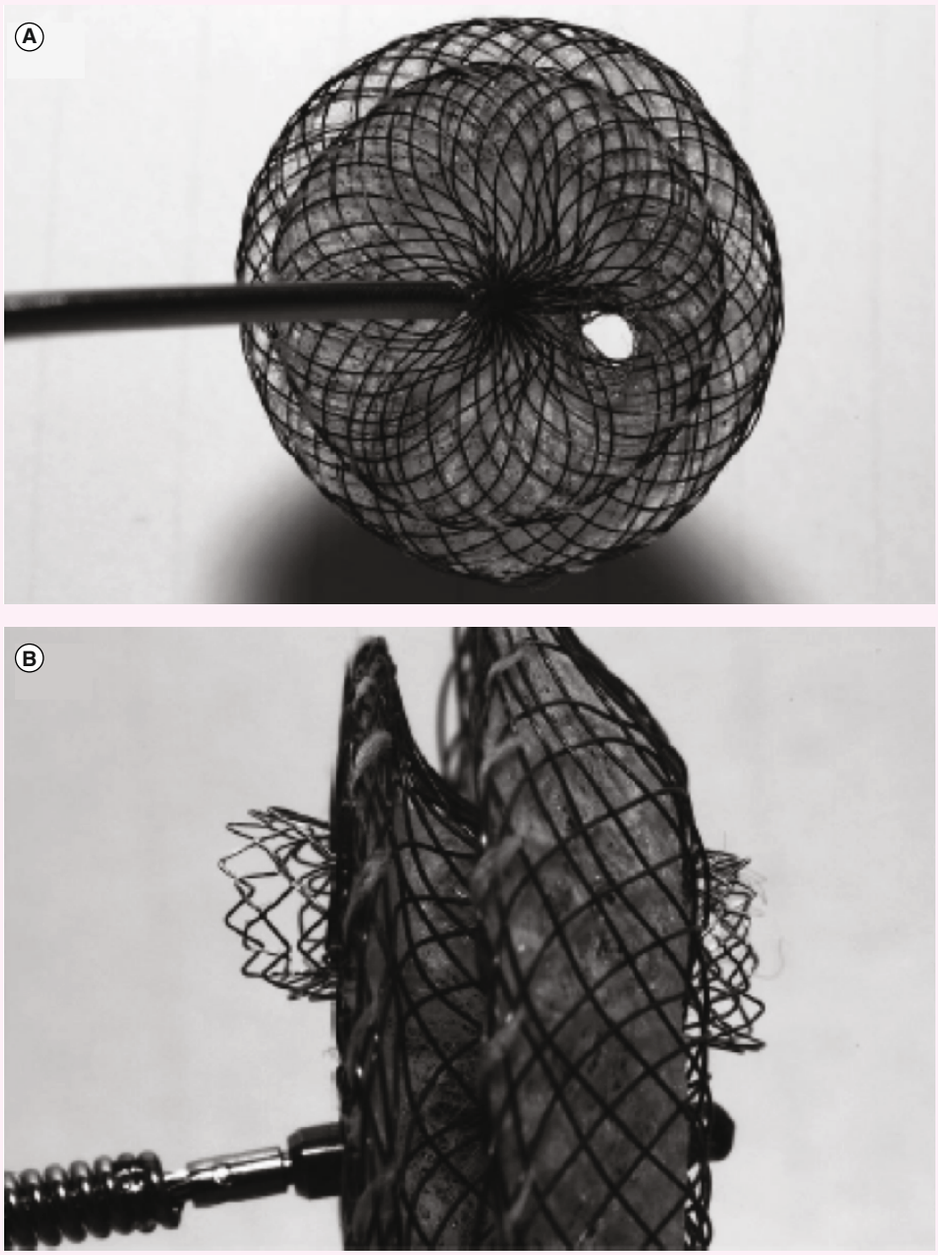

Figure 1. Homemade device designed to treat and allow the closure of a large interatrial septal defect in a patient with pulmonary hypertention. (A) The hole created in the closure device aims to allow right-to-left shunt during rising moments of pulmonary pressure. **(B)** In this case, a stent has been implanted within the hole created in the closure device to diminish the risk of closure.
Images reproduced with permission of [15].

inflammatory response, allergic reactions, damage to adjacent structures (cardiac tamponade due to perforation) or device embolization that are comparable to that of other similar procedures as ASD closure.

On the contrary some other risks are exclusive from these devices, including excessive flow with right chambers deterioration or pulmonary hypertension and paradoxical emboli. Initial results do not report this kind of secondary effects; nevertheless, long-term follow-up will have to confirm this point. In congestive HF patients, except for rare cases such as severe Valsalva maneuvers, the LAP will exceed the right atrial pressure. However, during Valsalva or if pulmonary pressure rises in the follow-up, this flow could reverse and lead to paradoxycal emboli. A similar mechanism may lead to secondary hypoxemia. Accurate invasive right heart pressure evalu-

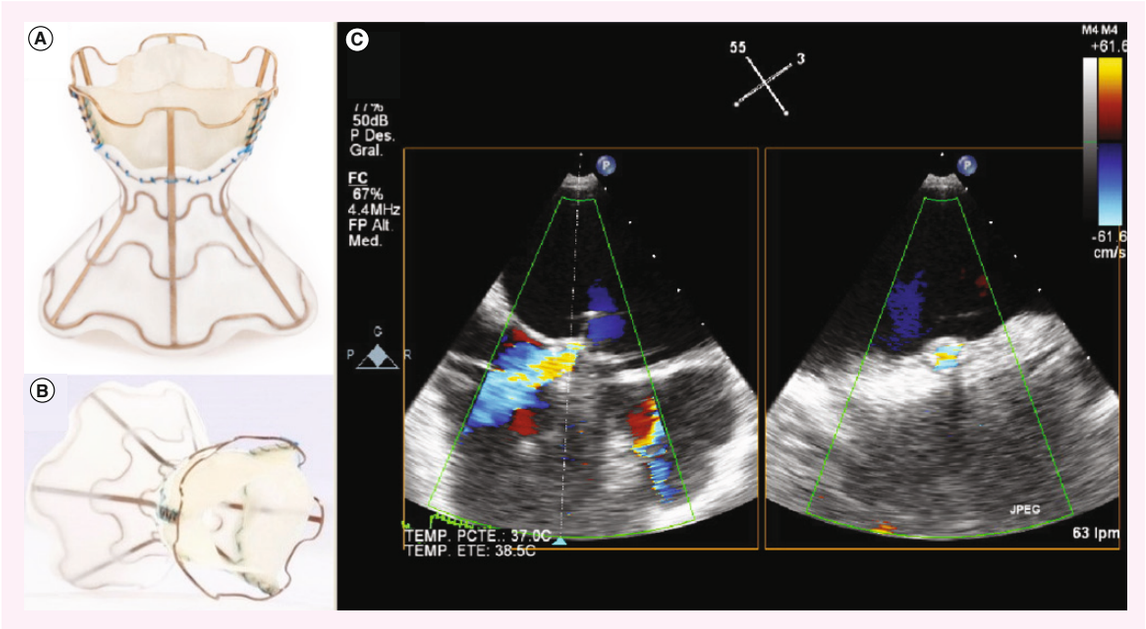

Figure 2. The V-Wave system. (A and B) Bench images of the V-Wave device. **(C)** Implanted V-Wave device (color-doppler images with transesophageal echocardiography).

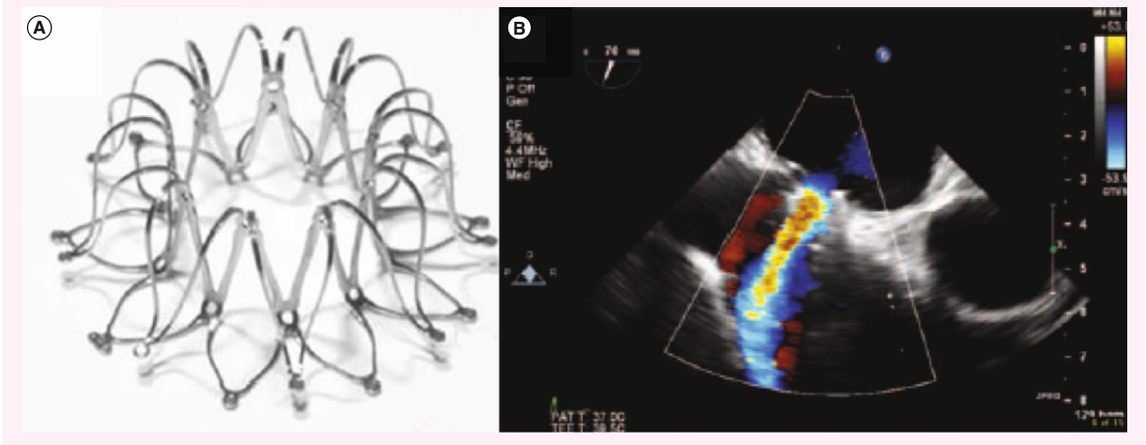

Figure 3. Interatrial septal device (IASD) system. (A) Bench images of IASD. **(B)** Implanted IASD system once implanted (color-doppler images with transesophageal echocardiography).
Images reproduced with permission of [7].

ation before the intervention is key to diminish these risks. Also, this issue has been addressed by the V-Wave system with the use of an internal valve to ensure left-to-right unidirectional flow. It is noteworthy that no cases of paradoxical emboli of hypoxemia have been reported to the date with none of these devices or after iatrogenic creation of ASD. Finally, the need for antithrombotic treatment after the implant may increase the rate of bleeding events. The completion of the 'Reduce LAP-HF Trial' and 'The V-Wave shunt: FIM Safety and Feasibility Study' (ClinicalTrial.gov) will help to better understand these potential risks and the efficacy of this new approach.

Conclusion

LA decompression through unidirectional left-to-right interatrial shunt represents a new concept for the treatment of patients with HF. Initial limited series with two different specific devices have demonstrated the feasibility and safety of applying this new therapy with an improvement in functional, quality of life and hemodynamic parameters at short- and mid-term. Further studies are warranted in order to determine the long-term prognostic implications of this intriguing hypothesis and to confirm the hemodynamic and functional positive impact.

Future perspective

HF is a new epidemy due to a rising prevalence as a result of improved therapies that increase life expectancy. However, this growing population tends to progressively deteriorate leading to a decrease in quality of life and high healthcare related costs due to frequent readmissions, among others. Moreover, in the subset of patients with HF and preserved ejection fraction, very little is known concerning therapeutic strategies with prognostic impact. Therefore, new alternatives are claimed by experts in the field of HF.

Interatrial shunting has been previously used as a palliative therapy in several scenarios; however, recently new devices have been developed to modulate the amount of shunting blood and flow direction, in order to allow long-term tolerance of this strategy and minimize deletereous effects. This new strategy seems to minimize symptoms, reduce rehospitalizations and costs and could potentially improve outcomes. If long-term and randomized studies confirm this point, a wide range of patients could be candidates for this therapy. Moreover, patients with lower deterioration (i.e., NYHA class II) and the growing group of patients with diastolic dysfunction may represent a huge target population for these new percutaneous devices.

Financial & competing interests disclosure

Rodés-Cabau is consultant for V-Wave Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Executive summary

Background

- Heart failure (HF) is a highly prevalent health problem in our society with major impact on quality of life, survival and, still, important therapeutic limitations.
- Elevated left atrial filling pressure has been associated to poor prognosis leading to development of new percutaneous therapies designed to decrease this pressure.

Therapeutic blood shunting: origin of the hypothesis

- Initial experiences in the 60s for congenital heart diseases creating left-to-right or right-to-left shunts explored this field.
- Limited duration of the shunt created by simple balloon-dilation at the interatrial septum discouraged to continue with this approach.
- Also, some cases of acute HF after atrial septal defects closure suggested the potential value of this shunts as a mechanism to palliate HF symptoms.
- Recently, the use of this strategy in patients under left ventricular assist devices with left overload has been demonstrated helpful.

Left-to-right interatrial shunts: preclinical evidences

- Animal tests agree to suggest that subacute HF models presented improved outcomes after percutaneously implanted interatrial blood-shunting devices.
- However, limited information is available concerning chronic HF.
- Some computer simulation models seem to support the good behavior of these new devices in HF.

Initial experience with left-to-right interatrial shunts in humans

- Preliminary experiences with homemade devices and two specific new systems (the interatrial septal device system and the V-Wave) have been reported as 'first-in-human' pilot studies.
- In all cases, symptomatic improvement was found at mid-term (>3 month follow-up) and no major complications were reported.

Potential risks & limitations of this new approach

- This concept is not aimed to treat the myocardial disease, therefore only symptomatic release but moderate impact on major outcomes could be found.
- There are some nonspecific risks including thrombus formation or device embolization that do not differ from similar procedures.
- Some specific potential risks should be prevented and monitored, including paradoxical emboli or right heart deterioration.

Conclusion

- Left atrial decompression through unidirectional left-to-right interatrial shunt represents a new concept for the treatment of patients with HF.
- This approach has been proven safe and feasible by short series.
- Moreover, symptomatic improvement occurred in all cases.
- Further studies are needed to determine the long-term prognostic implications of this intriguing hypothesis and to confirm the hemodynamic and functional positive impact.

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