

In 6 patients, the number of arrhythmia episodes declined during the first 24 hours after the initiation of sympathetic blockade (Figure). In all 6 patients, LSGB significantly reduced the total number of episodes and the number of episodes in the first 24 hours after the intervention ($P < .05$). Electrical storm recurred in 3 patients (37%) during the first 24 hours after the cessation of sympathetic blockade. Of these patients, 2 responded to repeat LSGB. The third patient responded to conventional therapy and thus there was no further requirement for sympathetic blockade.

Mortality was 50% (patients 2, 3, 6, and 8), but only 1 death (patient 6) was due to arrhythmia. Catheter ablation of ventricular tachycardia was performed in patient 4, and patient 5 underwent heart transplantation. The follow-up of each patient is presented in the Table. In all patients, sympathetic blockade was transitory and its use did not interfere with conventional treatments, including definitive treatments such as catheter ablation and heart transplantation. There were no complications related to the procedure.

The results of our study suggest that TSB is a useful technique for the control of refractory ES. In our study, we used standard techniques for transient sympathetic blockade without having to resort to definitive methods. This contrasts with other studies reporting the use of interventions such as surgical sympathectomy⁵ or videothoracoscopy ablation of the sympathetic chain ganglia in the pleural cavity.

The main limitations of our study are the small sample size and its observational and retrospective nature. In addition, due to patient care and organizational issues, it was not possible to retrospectively determine the exact number of patients presenting

with refractory ES during the study period (March 2012 to December 2014).

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Available online 11 December 2015

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<http://dx.doi.org/10.1016/j.rec.2015.08.024>

Use of Atrial Septostomy to Treat Severe Pulmonary Arterial Hypertension in Adults



Septostomía auricular en el tratamiento de la hipertensión arterial pulmonar grave del adulto

To the Editor,

Elective atrial septostomy (AS) can provide additional clinical benefits to adults receiving targeted triple therapy (endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostanoids) for severe pulmonary arterial hypertension (PAH). Elective AS can be used as a bridge to lung transplantation when medical treatment is ineffective or as a definitive treatment when transplantation is contraindicated. Clinical guidelines recommend AS for PAH patients in functional class III or IV with refractory right heart failure or severe exercise-induced syncopal symptoms, either as a pretransplant treatment or as a palliative measure when no other treatment options are available.¹ However, this intervention has been little used in our setting.

We present experience with elective AS in PAH patients under targeted triple therapy at a referral center. To our knowledge, this is the largest series in Spain describing results obtained with this technique in the context of current PAH treatment.

Since 2005 we have performed 11 balloon AS procedures and 1 stent fenestration of the atrial septum in a total of 10 patients (8 women, mean age 43.5 years). Patient data and procedures are summarized in the Table. All patients were in PAH functional class III or IV and all were taking epoprostenol, either in targeted triple

therapy with endothelin receptor antagonists and phosphodiesterase-5 inhibitors (7 patients), or in double therapy with phosphodiesterase-5 inhibitors (3 patients). Patients were prepared for AS by blood transfusion and treatment with inotropes and intravenous diuretics. Elective AS was not used as a rescue procedure in end-stage disease. A transeptal puncture was made with a Brockenbrough needle followed by gradual balloon dilatation, according to the protocol described by Sandoval et al.² The procedure was carried out without sedation in order to properly monitor changes in peripheral artery oxygen saturation. As stipulated in the protocol,² the transeptal opening was expanded gradually, initially with a balloon diameter of 4 mm and then sequentially with balloons dilated to 8, 12, and 16 mm. Each dilatation was followed by a 3 minute pause, at the end of which readings were taken of left ventricular end-diastolic pressure and arterial oxygen saturation. Final aperture size was determined individually for each patient, with dilatation stopped when any of the following conditions were met: elevation of left ventricular end-diastolic pressure > 18 mmHg, reduction in peripheral artery oxygen saturation to < 80% or by > 10% relative to the basal level, or dilatation of the interatrial septum to the maximum aperture (16 mm). The procedure was guided by intracardiac echocardiography in 2 patients and by fluoroscopy alone in the others. For the patient who underwent stent fenestration of the interatrial septum, we used the diabolo-shaped stent configuration described by Stümper et al,³ without sedation and with monitoring by fluoroscopy and intracardiac echocardiography. After making the transeptal puncture with a Brockenbrough needle, an Inoue guide wire was advanced into the left atrium and the interatrial opening

Table
Patient Data and Atrial Septostomy Procedures

Patient	PAH etiology	Sex	Age, y	Indication for AS	Targeted PAH therapy	Preparatory treatment for AS	Basal right atrial pressure, mmHg	Basal pulmonary artery pressure, mmHg	Pre-AS aortic O ₂ saturation, %	Pre-AS CO, L/min	Pre-AS LVEDP, mmHg	Maximum balloon diameter, mmHg	Post-AS aortic O ₂ saturation, %	Post-AS CO, L/min	Post-AS LVEDP, mmHg	Clinical progress
1	Idiopathic	Male	39	Refractory right heart failure	Epoprostenol + sildenafil	Furosemide infusion + IV levosimendan + transfusion, 2 units	8	55/26.36	96	2.56	9	14	88	3.07	9	LT 7 months post-AS
2	Toxic oil syndrome	Male	30	Refractory right heart failure	Epoprostenol + sildenafil	Furosemide infusion + IV dobutamine + transfusion, 2 units	12	102/36.64	92	2.54	8	10	84	2.8	14	Death due to disease progression 10 months post-AS
3	Toxic oil syndrome	Female	54	Refractory right heart failure	Triple therapy	Furosemide infusion + transfusion, 3 units	17	100/34.60	89	1.8	6	8	81	2.12	8	Death due to disease progression 19 months post-AS
4	Toxic oil syndrome	Female	52	Refractory right heart failure	Triple therapy	Furosemide infusion + IV dobutamine	4	80/36.54	90	3.2	5	14	91	3.2	5	Death due to disease progression 6 months post-AS
5	Idiopathic	Female	20	Exercise-induced syncope	Triple therapy	1st: None required 2nd: None required	1st: 7 2nd: 9	1st: 74/30.55 2nd: 84/32.52	1st: 96 2nd: 88	1st: 3.9 2nd: 3	1st: 7 2nd: 10	1st: 16 2nd: 8	1st: 90 2nd: 82	1st: 4.9 2nd: 3.5	1st: 8 2nd: 13	Alive 55 months post-AS; on HLT waiting list
6	Idiopathic	Female	64	Exercise-induced syncope	Triple therapy	1st: Transfusion, 3 units 2nd: None required	8	70/29.46	95	4.99	13	1st: 16 2nd: IAS stent	92.5	5.7	17	Alive 44 months post-AS; in functional class II
7	Systemic lupus erythematosus	Female	40	Refractory right heart failure	Triple therapy	IV dopamine + ultrafiltration + transfusion, 2 units	13	57/16.36	90	2.40	10	12	77	3.96	10	Death 7 days post-AS
8	Familial idiopathic	Female	40	Exercise-induced syncope	Triple therapy	IV dobutamine + furosemide infusion + transfusion, 1 unit	17	115/49.75	94	2.66	8	12	86	3.21	13	LT 8 months post-AS
9	Idiopathic	Female	58	Exercise-induced syncope	Triple therapy	None required	5	80/36.49	90	2.48	6	16	88	2.63	7	LT 2 months post-AS
10	Idiopathic	Female	38	Exercise-induced syncope	Epoprostenol + sildenafil	None required	9	80/38.58	98	7	1	16	91	8.5	1	Alive 1 month post-AS; on LT waiting list

AS, atrial septostomy; CO, cardiac output; HLT, heart and lung transplant; IAS, interatrial septum; IV, intravenous; LT, lung transplant; LVEDP, left ventricular end-diastolic pressure; PAH, pulmonary arterial hypertension.

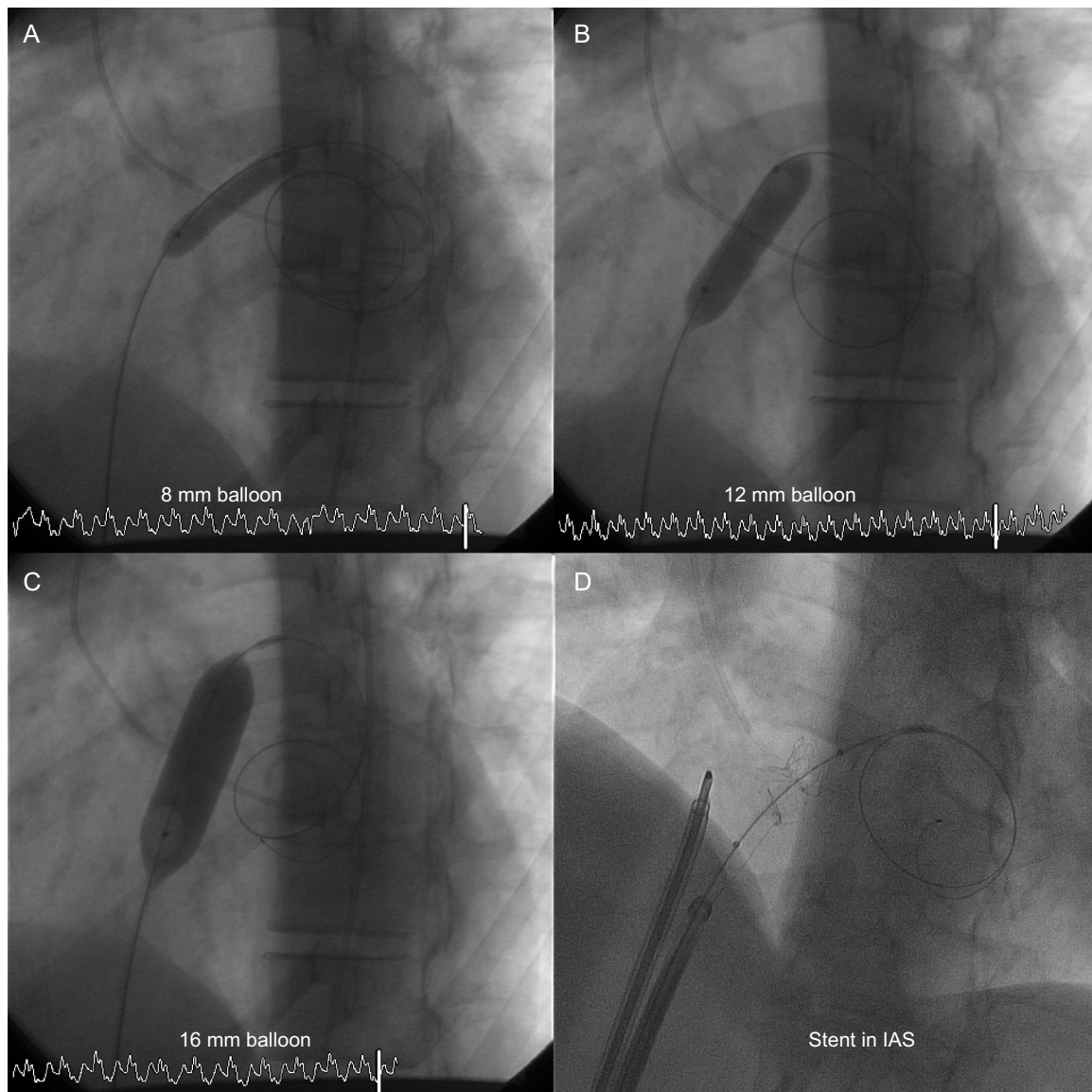


Figure. A-C: Atrial septostomy with progressive balloon dilatation. D: Stent fenestration of the atrial septum. IAS, interatrial septum.

was dilated with a dilator and a Mullins sheath. This was then replaced with a 12 French sheath, while maintaining the Inoue guide wire in the left atrium. A 19 mm Palmaz® Genesis™ stent (Johnson & Johnson) was mounted on a 16 mm × 40 mm valvoplasty balloon, around which a central 5 mm diameter bow was tied with an epicardial pacing wire. The mounted stent was delivered through the sheath along the Inoue guide wire. Fluoroscopy and intracardiac echocardiography guidance was used to center the pacing wire loop at the opening of the interatrial septum, and the balloon was inflated. The pacing wire loop restricts expansion of the center of the stent and thus results in a diabolo-shaped configuration centered across the atrial septum; the fenestration diameter is predetermined by the diameter of the pacing wire loop around the balloon. In all patients, balloon AS resolved refractory right heart failure and eliminated exercise-induced syncope. The first patient developed complete atrioventricular blockade. No other complications were encountered with the technique. The mean follow-up period was 24 months (range, 1-67 months). During follow-up, the transseptal fenestration closed spontaneously in

3 patients (33%): in 1 patient the peripheral artery oxygen saturation contraindicated repeat AS, in another we performed stent fenestration of the atrial septum (Figure), and in the third we performed a repeat AS at 18 months. Overall survival was 90% at 30 days, 75% at 6 months, and 57% at 1 year. One patient died 1 week after AS during anesthesia for implantation of a Hickman catheter; 3 others died due to disease progression. Of the surviving patients, 3 underwent successful transplantation, 2 were on the transplant waiting list, and the patient with the stent fenestration of the interatrial septum showed no reclosure or device migration after 44 months.

The utility of AS in patients receiving targeted triple therapy for PAH has not been evaluated. In most published series, only a very low percentage of patients received targeted triple therapy.^{4,5} In our series, all patients received epoprostenol, 7 of them in targeted triple therapy and 3 in double therapy with phosphodiesterase-5 inhibitors. Even in the context of this optimal treatment, AS provided additional clinical benefit in all patients, improving functional class and resolving refractory right heart failure and syncope. These benefits were achieved both when AS was used as

a preparation for lung transplantation and in patients in whom medical treatment had failed and there were no therapeutic alternatives. The failure of AS to become established as a general treatment is likely due to the relatively high associated procedural and periprocedural mortality (5% and 16%, respectively),⁵ and also to uncertainty about the optimal timing of the intervention for maximum benefit. Some studies suggest that AS would be beneficial at early stages of disease development; nonetheless, in most countries with access to high-cost medical treatments and lung transplantation, AS is conducted at late disease stages, when medical treatment has failed or as a last resort before transplantation. However, AS in terminal disease stages is associated with high mortality, and the procedure is therefore not recommended in end-stage patients.^{4,5} In our series, AS was indicated in advanced disease stages when medical treatment had failed, but not as a rescue treatment in end-stage patients. The patient who died 1 week after AS had needed ultrafiltration and inotrope therapy as preparation for the procedure, and it is possible that the indication for AS was borderline in this case. No patient died as a result of the procedure. Survival in our series at 30 days was 90%, and at medium term was in line with published data related to disease progression: 75% at 6 months and 57% at 1 year.^{1,4,5}

In our experience, elective AS is a therapeutic option for PAH patients in whom optimal medical treatment has failed. The procedure is associated with low periprocedural morbimortality, and delivers functional improvement in most severe PAH patients with refractory right heart failure or low cardiac output. Moreover, elective AS is effective both as a bridge to lung transplantation and as an adjunct to medical treatment.

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Available online 28 November 2015

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<http://dx.doi.org/10.1016/j.rec.2015.09.006>

Growth Differentiation Factor 15, a New Prognostic Marker in Diabetic Cardiomyopathy



El factor de diferenciación de crecimiento 15, un nuevo marcador pronóstico en la miocardiopatía diabética

To the Editor,

The various clinical guidelines and consensus statements recommend a multifactorial approach to diabetes mellitus, acting on glycemia and the other associated risk factors to obtain the greatest possible reduction in macrovascular and microvascular morbidity and mortality.¹ Diabetic cardiomyopathy (DCM) is usually asymptomatic in the initial stages.² Growth differentiation factor 15 (GDF-15) is a cytokine secreted by macrophages and cardiac myocytes in response to oxidative stress and inflammation.³

Our group recently described the usefulness of GDF-15 as a screening tool in the diagnosis of DCM in asymptomatic patients with type 2 diabetes mellitus.⁴ The study aimed to describe the prognostic value of GDF-15 at 1 year in a cohort of patients with DCM, evaluating the relationship between the levels of this biomarker and the combined primary endpoint of heart failure with hospital admission and/or angina with hospital admission.

The details of the study have previously been described.⁴ Briefly, the study prospectively included 213 asymptomatic patients with type 2 diabetes mellitus. Diabetic cardiomyopathy was defined, according to the criteria of the European Society of

Cardiology and the European Association of Diabetes, as left ventricular diastolic dysfunction (tissue Doppler with an E/É ratio ≥ 15) in the absence of hypertension, ischemic heart disease, or other structural heart disease.⁵ For the analysis, the outcomes at 365 days of the 45 patients who had DCM were studied, as was the relationship between DCM and GDF-15 concentration.

Continuous variables are expressed as mean \pm standard deviation for those with a normal distribution or median [interquartile range] for those with an abnormal distribution. Categorical variables are expressed as number (percentage). Quantitative variables were compared using the Student *t* test or Mann-Whitney *U* test. The association between qualitative variables was determined using the Pearson chi-square test or Fisher exact test. Survival analysis was performed using Cox regression, with variables with a *P*-value $< .2$ on univariate analysis being included in the model. Risk proportionality assumption was evaluated by Schoenfeld residual analysis. The statistical analysis was performed with the SPSS program, version 20 (SPSS Inc., Chicago, Illinois, United States).

The study population characteristics are shown in the Table. The primary endpoint of the study occurred in 12 patients (26.7%). There were no statistically significant differences between the 2 groups in baseline characteristics (age, sex, left ventricular ejection fraction, hypercholesterolemia, and smoking), treatment, or laboratory data. Concentrations of GDF-15 were higher in patients with DCM who experienced a combined event than in those with no events (6458.9 pg/mL [5359.7–8681.9 pg/mL] vs 4706 pg/mL [3719–6463 pg/mL], *P* = .007) (Figure). Combined events occurred at a mean time of 162 ± 89 days. In the Cox survival