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RESEARCH ARTICLE

Percutaneous Transluminal Caval-Flow Regulation PTCR®: A New Alternative Therapy to Reshape the Future Treatment of Heart Failure

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ABSTRACT

Percutaneous Transluminal Caval-flow Regulation (PTCR) is an emerging alternative therapy to treat patients with acute heart failure (AHF). AHF represents the first cause of hospitalization in elderly persons and is the main determinant of the huge healthcare expenditure related to heart failure (HF). Despite therapeutic advances, the prognosis of AHF is poor, with in-hospital mortality ranging from 4% to 7%, 60 to 90-day mortality. To reverse this situation, a balloon catheter medical device has been designed to produce cyclic occlusions of the Inferior Vena Cava (IVC) supported by the phases of respiration, thus having subtotal occlusion during expiration and total occlusion during inspiration, producing an intermittent regulation of venous return or preload from the IVC to the right atrium. This PTCR procedure is minimally invasive. It is performed through the insertion of the balloon catheter via the femoral vein. This catheter is advanced to the IVC guided by echocardiogram or fluoroscopy to be placed prior to drainage of the hepatic vein. At this point, the balloon is inflated up to 70% to 80% of the diameter of the IVC in expiration, which has to be previously evaluated by echocardiography. Then inspiratory collapse (20 to 30% average) of the IVC diameter produces total occlusion during inspiration and a partial or subtotal occlusion during expiration, thereby regulating caval flow in an intermittent manner.

This innovative procedure is aimed at regulating the hypervolemia present in the IVC, normalizing venous return, preload, intracardiac pressures, biventricular diastolic and systolic diameters, diastolic and systolic volume, thus, obtaining reduction of total cardiac burden (TCB) and producing a reversal of ventricular remodeling. In this manner the heart returns close to its original design, with improvement in ejection fraction (EF) and cardiac output.

Keywords: Percutaneous Transluminal Caval-flow Regulation, Inferior Vena Cava Heart Failure, Catheter Balloon, Medical Devices, Cardiac Output. Ejection Fraction

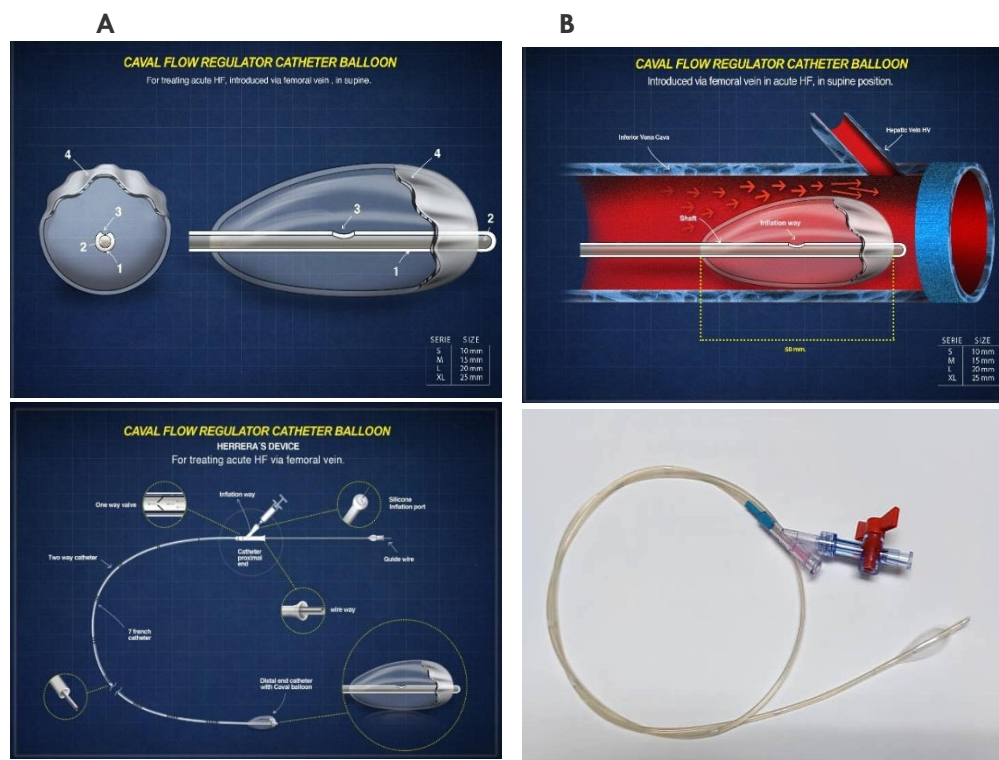
Abbreviations: HFrEF: Heart failure with Reduced Ejection Fraction, PTCR: Percutaneous Transluminal Caval Flow Regulation, HV: Hypervolemia, TCB: Total Cardiac Burden, ED: Expiration Diameter, ID: Inspiration diameter, IVC: inferior vena cava, CO: Cardiac Output, AHF: acute heart failure, HF: heart failure, EF: ejection fraction

Introduction

According to the American Heart Association there are approximately 6.2 million heart failure (HF) patients in the US alone¹, 64.3 worldwide in 2018, HF was mentioned in 379,800 death certificates (13.4%)¹. HF costs the nation an estimated \$30.7 billion in 2012². This total includes the cost of health care services, medications to treat HF, and lost work days. Nearly 1 in 4 HF patients are

readmitted within 30 days of discharge and approximately half are readmitted within 67. These patients have to go to the hospital every 90 days for 4–5 day decongestant treatment with the use of potent diuretics. 25% of the 6.2 million HF patients in the US represent 1.7 million patients who are our target patients for use of our procedure Transluminal Caval flow Regulation PTCR and Catheter Medical Device (figure 1).

Figure 1 Caval Flow Regulating Catheter Balloon



A Caval balloon en short and longitudinal axis view. **B** Caval balloon in side IVC before hepatic vein drainage. **C** Catheter Balloon schematic view for femoral vein insertion. **D** catheter balloon prototype for using in acute Heart Failure.

This great reality shown with its statistics, creates a rather bleak picture because until now current therapies have not been able to, significantly, reduce hospital readmissions of patients with acute or chronic decompensated HF nor treat pulmonary congestion, which endangers patient’s life.

With this review of our article where we show our experience in humans using our procedure, we want to make it well established that, with the results obtained, our procedure and device represent a

new alternative to treat HF patients with great advantages over current therapies. This is due to the fact that it is a safe temporary therapy, without collateral effects, and very effective in achieving hemodynamic and echocardiographic benefits. Thus, meaning a true innovation, capable of changing the paradigm of HF treatment with great benefits for patients and great savings for the state health service.

Table 1: Epidemiology and natural history of HF in Europe

INCIDENCE OF HF	THE PREVALENCE OF HF
Currently, the incidence of HF in Europe is about 3/1000 person-years (all age-groups) or about 5/1000 person-years in adults	True prevalence is likely to be higher. The prevalence increases with age: from around 1% for those aged <55 years to >10% in those aged 70 years or over.

Table 2: Facts about heart failure in the United States.

Prevalence	Annual Mortality	Costs
About 2% total population, 6.2 million adults in the United States have heart failure [3].	In 2018, heart failure was mentioned on 379,800 death certificates (13.4%) [3].	Heart failure costs the nation an estimated \$30.7 billion in 2012 [4]. This total includes the cost of health care services, medicines to treat heart failure, and missed days of work

Heart failure projected to increase dramatically, according to new statistics

HEART FAILURE PROJECTION IN FUTURE

The number of people diagnosed with heart failure is increasing and projected to rise by 46 percent by 2030, resulting in more than 8 million people with heart failure, according to the American Heart Association's 2017 Heart Disease and Stroke Statistics Update (link opens in new window) published Wednesday 2.

Source: American Heart association.

Early feasibility study protocol to be conducted in United State to evaluate safety of our procedure PTCR and Caval Flow Regulating Catheter Balloon in 30 acute heart failure patient to comply with FDA regulatory pathway.

Materials And Method

Patients with heart failure, 18 years of age or older, who met the inclusion criteria and signed an informed consent were evaluated. In a period of time between the months of February and July 2014, inclusive, a Doppler echocardiogram was performed prior to the coronary angiography and the diameters of the right and left cavities were evaluated, as well as the LV filling pattern. Subsequently, right catheterization was performed and right atrial, right ventricular, pulmonary arterial pressure, and capillary pulmonary wedge pressures were measured, then Percutaneous Transluminal Caval flow Regulation was performed for 30 minutes and the aforementioned pressures were reassessed again with the caval catheter balloon and a new Echocardiogram to measure left and right chamber diameter, LV filling pattern, E/E' ratio after caval flow regulation with IVC balloon. Doppler echocardiogram. A E33 Phillips Echocardiography system equipment was used, and standard echocardiographic images were obtained, M mode, BD, Doppler, in the lateral decubitus position in views for the sternal, apical of 4 and 2 cavities, the measurements were made following the standards of the American Association of Echocardiography (ASE), and the LV volumes and the ejection fraction were calculated using the biplane method by Simpson, the M mode were done according to the ASE standards, the filling of the LV was evaluated by placing the sample volume of the Doppler cursor, at the tips of the mitral valve, 3 measurements were made and averaged to have a reliable value. Tricuspid regurgitation were expressed in degrees I-IV,

according to the maximum regurgitation velocities, obtained by continuous Doppler.

IVC Echo: images of the IVC were acquired, in the supine position, in a subcostal view, in the long axis, with knee flexion and IVC diameter were performed 2 cm from the entrance to the right atrium, and the IVC flow velocity were evaluated with pulsed Doppler, at the entrance of the IVC to the right atrium.

Right Catheterization: It was performed following the Seldinger technique, approaching the right femoral vein, advancing to the right atrium, right ventricle, and right pulmonary artery. The catheter used was a conventional catheter for this type of technique, - prior to IVC flow regulation with caval balloon, and after IVC flow regulation, the right side pressures were made prior to IVC flow regulation with caval balloon.

Percutaneous Transluminal Caval flow Regulation (PTCR): It was performed after the right catheterization and the approach was through the right femoral vein following the Seldinger technique, advancing in to the IVC and then positioning itself in the proximal portion of the IVC, before the drainage of the suprahepatic vein. At this site, the balloon was inflated with 0.9% saline solution until it reaches 90% of the IVC diameter during inspiration and will remain there for 30 minutes to perform new pressure measurements in the RA, right ventricle, pulmonary vascular resistance, and pulmonary capillary wedge pressure (by right catheterization).

Subsequently, the echocardiogram was performed to reassessed left ventricle diameters, E/A ratio and E/E' left atrial diameter and aortic volume time

integral. After the measurements, the balloon was deflated and removed.

Risks and complications: the risks and complications of these procedures are mild bruising at the puncture site, in 1% of cases but this disappears spontaneously in about 10 or 15 days, slight bleeding may also occur that subsides with a compressive bandage, in some patients cases of cellulite may occur, which generally resolves with the use of antibiotics, it is possible that symptoms of hypotension may occur as a consequence of the IVC flow Regulation with a balloon such as: dizziness, which resolves with administration of solutions or suspending the percutaneous transluminal caval flow regulation procedure.

Coronary Angiography Risks inherent to the procedure are widely known in a hemodynamics unit and consist of: ventricular and supraventricular cardiac arrhythmias, severe hypotension, syncope, coronary artery dissection, myocardial infarction, cerebrovascular accident.

Study Design

Research Protocol Flow Chart

Step 1 Coronary Angiography with patient on stable condition.

Step 2 Right side pressure assessment, RAP, RVP, PAP, PCWP

Step 3 IVC Balloon restrictor insertion via right femoral vein.

Step 4 IVC Echo Evaluation to check intermittent restriction

Step 5 IVC Balloon keeps inflated during 30 minutes.

Step 6 After 30 minutes with the balloon inflated (right side pressures must be checked again).

Step 7 Doppler echocardiogram to assess echo variables.

Step 8 IVC balloon and Cournand catheter were deflated and removed.

Step 9 End of Case Study

Sample Size

9 patients were enrolled, and 6 were evaluated, aged 18 or more years of both sexes, heart failure was defined as (EF <40% and high Pro_BNP > 400 Picogr / ml), who underwent to selective coronary

angiography, and who met the inclusion and exclusion criteria of our approved protocol by the Ethics Committee of the ASCARDIO Institution, and signed informed consent.

Inclusion criteria:

1. Patient age 18 or older both sexes.
2. Chagasic patients should have serology (+) for Chagas disease.
3. They had to have a signed an informed consent.
4. Exhibit signs and symptoms of heart failure. (EF <40% and Pro_BNP high > 400 Picogr / ml).
5. They may be taking treatment for heart failure.

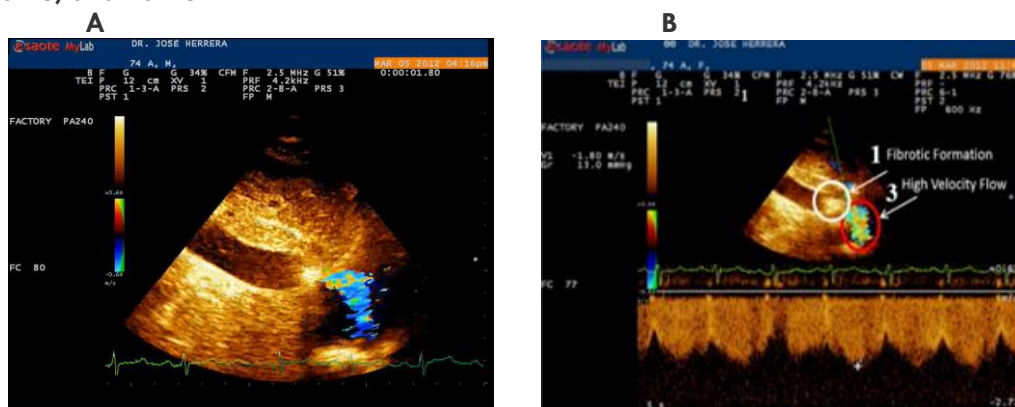
Exclusion criteria:

1. Dialysis patients.
2. Ultra filtration patients.
3. Patient in hypovolemic shock.
4. Artificial stimulation biventricular patients.
5. Patients with pleural effusion and / or pericardial.
6. Patients with Valvulopathies.

PTCR is mimicking a spontaneous natural phenomenon capable of regulating hypervolemia and cardiac venous return called Dynamic Inferior Vena Caval Stenosis^{6,7} (figure 2). This spontaneous natural phenomenon is produced by the development of a fibrocalcic formation in the right Cavo-diaphragmatic junction, producing intermittent occlusions of the IVC flow supported by the respiratory phases; thus, we have total occlusion of the IVC during inspiration and subtotal during expiration. Inspiratory vena cava collapse plays an important role in producing intermittent inferior vena cava occlusions, resulting in intermittent venous blood flow from the IVC to the right atrium. This spontaneous natural phenomenon produces an effect similar to that of a valve, capable of reducing venous return, therefore preload, total cardiac load resulting in a marked decrease in biventricular diameters and volumes.

See video of spontaneous natural phenomenon caval flow regulator (dynamic IVC stenosis or IVC flow regulating valve)

Figure 2. Caval Flow Regulation By Spontaneous Natural Phenomenon (Dynamic IVC Stenosis Or IVC Valve) and Its Flow



A) Caval Flow Regulation By Spontaneous Natural Phenomenon, B) IVC flow regulation and its flow
See video CaseHP

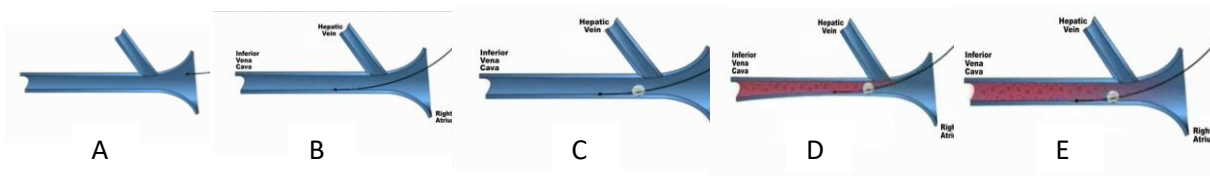
How The PTCR Procedure Is Performed

The methodology to implement the PTCR procedure consists of a series of rules that guarantee the function of regulating venous return, preload and therefore the total cardiac burden (Figure 3).

The diameter of the caval balloon is related to the anteroposterior diameter of the IVC at the time of

inspiratory collapse. For example, if the expiratory diameter is 18 mm and the collapse is 30% (5,4 mm), it would suffice to subtract 18mm (diameter in expiration) – 5,4mm (diameter in inspiration) = Balloon size must be inflated until reaching 12,6 mm, the balloon is designed to remain free floating in the IVC lumen and so on for any other case.

Figure 3. How The Balloon Works

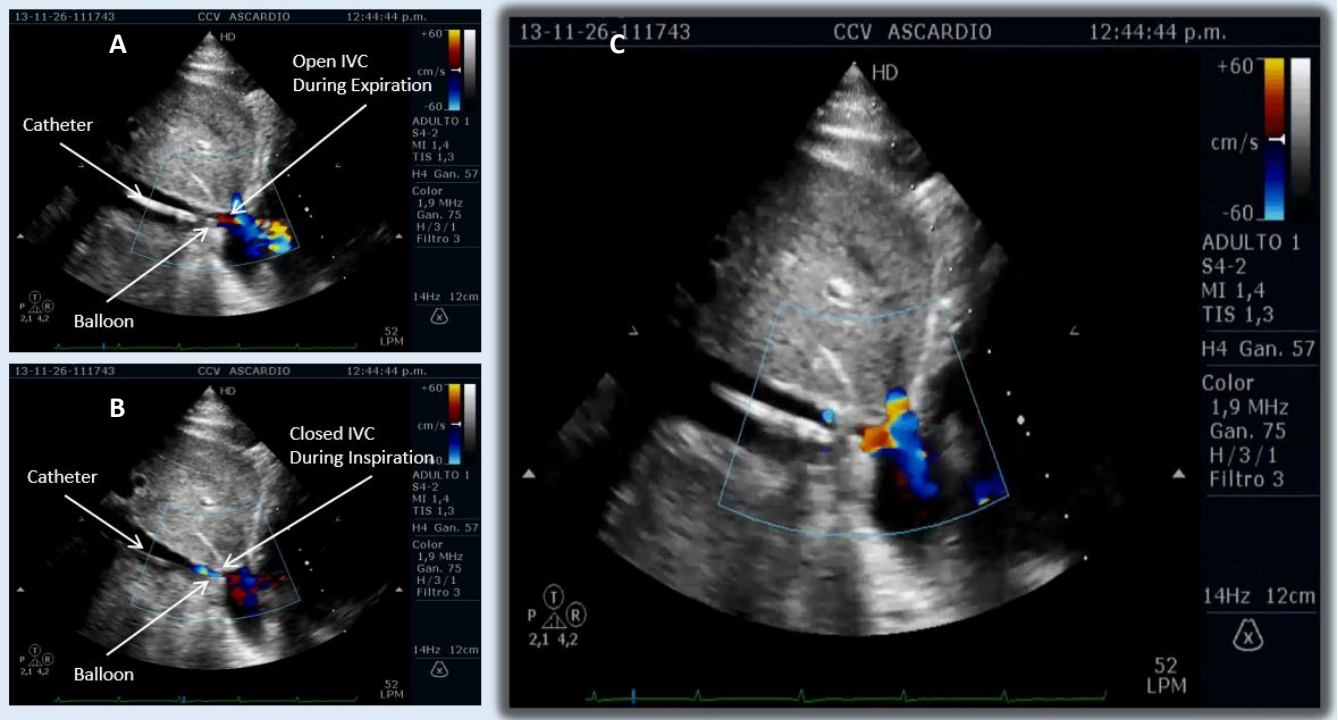


- A) Insertion of the balloon catheter in the IVC via the subclavian vein.
- B) Location of the catheter in the IVC.
- C) Inferior vena cava IVC balloon inflation.
- D) Inspiratory collapse of the IVC producing total occlusion and preload regulation.
- E) IVC in expiration producing sub-total occlusion

For a better understanding, please see videos:

- **How the Caval Flow Regulator Balloon works**
- **Percutaneous Transluminal Caval Flow Regulation**

Figure 4 PTCR in the First Patient

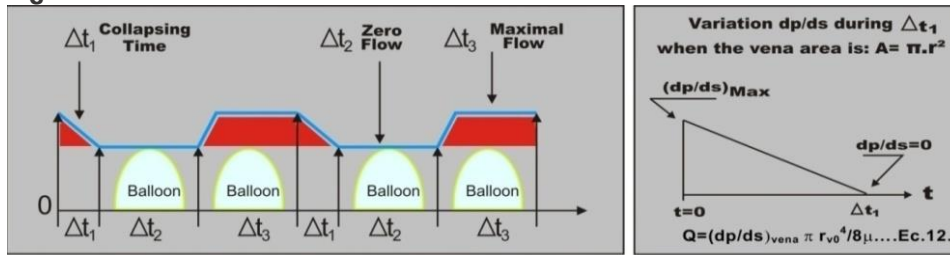


A. Balloon in IVC during expiration (high velocity flow is shown). B Balloon in IVC during inspiration a not flow is shown. IVC catheter balloon video showing how the balloon works (see video PTCR First In Human)

Mathematical Model To Explain The Operation Of The PTCR

Cyclic variation of the radius r of a section of the vena cava near the balloon. The maximum radius is r_0 vena cava. At time of collapse Δt_1 , the radius decreases from r_0 to the balloon radius r_b . During the time Δt_2 , the vein remains radius $r=r_b$ no flow. During the time Δt_3 , the vein returns to its normal radius and blood flows into the atrium. The balloon acts as a regulator of preload (flow to the heart). (Figures 3, 5)

Figure 5. Preload Reduction Model



It is important to know that the final equation shown in Figure 5 is preceded by multiple mathematical equations that support the feasibility of this intermittent caval flow regulating procedure using a balloon capable of producing total or subtotal occlusions supported by the patient's respiratory phases (see supplementary material considerations about design of balloon.pdf).

PTCR is a minimally invasive percutaneous therapy, supported by the patient's physiology, designed to fulfill two important functions. The first is to reduce hypervolemia present in 90% of cases with HF³; thereby reducing total cardiac burden. The second function is to prevent the increased blood pressure

in the atrium in patients with HF from being transmitted to the IVC during inspiration, thereby reducing the pressure in the IVC and favoring renal venous return. The higher the breathing frequency, the greater the preload regulation⁸.

Acute hemodynamic and echocardiographic effects experience in 6 patients with HF treated using PTCR⁹, showed a cyclic occlusion of the IVC and an intermittent reduction in caval flow (cardiac preload) as reported by the authors. PTCR resulted in a significant reduction in mean right atrium pressure, systolic right ventricular pressure, mean pulmonary artery pressure, and mean pulmonary

capillary wedge pressure with no significant increase in cardiac output.

It is worth saying that this reduction of the average intracardiac pressures, approximately 30% ⁶, with respect to their initial measurements during the use of the PTCR, means a pseudo normalization of the intracardiac pressures and a very close return to the original cardiac design, significantly reducing pulmonary congestion.

The size of the balloon was calculated with the help of a mathematical equation using an example and the diameter of the ideal balloon to produce preload regulation is related to the diameter of the

IVC, during the inspiratory collapse produced by the inspiratory phase of respiration.

This study was designed to evaluate 10 patients, but only 6 met the inclusion criteria in the study, so this number of patients is our greatest limitation. It is recommended to carry out a further study involving a greater number of patients.

No procedure-related complications were observed in this study and there was no liver or kidney function impairment in the short or long 2-year follow-up.

Results of the first human experience using PTCR

Table 3 Hemodynamic Data Results

Hemodynamic Variable	Before Balloon	During Balloon	% Change	P Value ≤
1. mRAP (mmHg)	9.00	5.17	-42.59%	0.005
2.- sRVP (mmHg)	44.17	30.83	-30.19%	0.003
3.- mPAP (mmHg)	37.50	28.00	-25.33%	0.043
4.- mPCWP (mmHg)	25.50	17.50	-31.37%	0.016
5.- C.O. (l/min)	4.09	4.50	9.92%	0.175

Table 4 Echo Data Results

Echo Variable	Before Balloon	During Balloon	% Change	P Value ≤
1.- LVEDD cm	6.43	5.76	-11.0%	0.009
2.- LVESD cm	5.19	4.78	-7.9%	0.010
3.- LVDV ml	187.67	160.82	-14.4%	0.036
4.- LVSD ml	123.23	101.62	-17.0%	0.041
5.- EF% Simpson	33.49	40.85	21.9%	0.115
6.- E/A ratio	1.72	1.37	-20.5%	0.051

Discussion

After observing these results, we are convinced that the PTCR (figure 4)(see video PTCR First In Human) procedure leads to great hemodynamic, echocardiographic, and clinical benefits for the patient by achieving a reduction in total cardiac burden, producing a significant reduction in biventricular volumes and diameters (Table 3 and Table 4) when used alone: 30 minutes in each evaluated patient. It is becoming an emerging therapy to treat patients with both acute and chronic HF, evolving the chronic heart failure treatment paradigm in cardiology, given the versatility of the catheter that allows the IVC to be accessed either through the subclavian vein or the femoral vein. This emerging therapeutic strategy

could be very useful as well, to effectively and safely treat pregnant patients where traditional treatment cannot be used due to side effects and stillbirth, and also this therapy can be used in patients with HF postpartum, in this way avoid the passage of drugs through breastfeeding.

Future Directions

The PTCR is a procedure to reduce the total cardiac burden without side effects and very low complications. In an effective way, constitutes an innovation in the management of HF, demonstrated in recently published results⁶. This procedure can be used to treat patients with acute and chronic HF and given the versatility of the balloon catheter medical device, it can be inserted via the femoral

vein to treat cases of patients with acute HF or via the subclavian vein to treat patients with chronic HF so that they can go home with their total cardiac load-regulating balloon for more than 3 months. Thus markedly decrease readmissions at 90 days, 160 days and annual mortality due to HF. In this way quality of life is given to the patient, prompt incorporation into family and working activities and a large reduction in health spending for the state. Based on these statements, the PTCR will have the potential to reduce the total cardiac burden of cardiovascular disease.

The offer of a Grant made by the National Institute of Health NIH/NHLBI, has allowed us to work on the realization of a protocol for an early feasibility study, which will be conducted in an academic partner hospital in the USA, and will allow us to evaluate the safety of our procedure in 30 Acute Heart Failure Patients to comply with the FDA regulatory pathway and thus obtain a Pre-Market Approval

Conclusion

PTCR is a new alternative therapy to reduce total cardiac burden and treat patients with heart failure, reducing intracardiac pressures, biventricular volumes, ventricular diameters, ventricular filling pressure and ventricular wall stress, resulting in clinical benefits such as reduced congestion, lung and improving cardiac output, without side effects. It has demonstrated to date to be a safe and effective procedure.

More studies are needed with a larger number of patients to confirm our initial observation in our study.

Acknowledgement

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