Pulmonary artery hypertension in heart transplant recipients: how much is too much?* 

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Abstract

OBJECTIVES: Unresponsive pulmonary hypertension (PH) may contraindicate heart transplant since it implies poor early outcomes. The present study reports the effectiveness of oral perioperative sildenafil in allowing heart transplant candidacy and surgery in a selected group of patients initially deemed ineligible because of PH.

METHODS: Between May 2005 and December 2009, 31 consecutive patients (5 females, 9 with a history of idiopathic cardiomyopathy and 16 with a history of coronary artery disease, 10 with previous sternotomies) were selected for oral sildenafil because of unresponsive PH at baseline right heart catheterization (RHC). After a 12-week trial, RHC disclosed PH reversibility (mean pulmonary vascular resistance index: 9.57 ± 4.07 WU, mean transpulmonary gradient: 14.47 ± 5.66 mmHg and mean systolic pulmonary artery pressure: 68.96 ± 15.15 mmHg), allowing listing despite a higher risk for early post-transplant RV failure. Transplant protocol included donor/recipient size matching ≥0.8 and inhaled nitric oxide in the early postoperative period followed by reinstitution of oral sildenafil.

RESULTS: All patients underwent heart transplantation. Mean overall graft ischaemic time was 179 ± 47 min; mean donor recipient weight ratio was 1.04 ± 0.17. Right ventricular failure developed in three patients (9.6%) and hospital mortality was 3.2%. Protocol RHC disclosed pulmonary haemodynamic profile normalization within the third postoperative month allowing weaning from sildenafil in the 30 hospital survivors. One-year RHC confirmed PH reversal (n = 29 patients, all who survived up to 1 year).

CONCLUSIONS: This pilot prospective uncontrolled trial suggests that oral sildenafil is effective in allowing candidacy, safe transplantation and postoperative pulmonary profile normalization in potential recipients initially disqualified because of PH.

Keywords: Pulmonary hypertension • Heart transplantation • Risk factors

INTRODUCTION

Pulmonary hypertension (PH) due to heart failure (HF), or type 2 PH according to the Dana Point classification, is a complex pathophysiological and haemodynamic condition due to dysregulation of vascular smooth muscle tone and structural remodeling [1]. The former is reversible over a period of minutes to days by pharmacological vasodilators, whereas the latter is relatively fixed and may resolve only slowly, over months to years. These abnormalities are related to pulmonary vascular endothelial dysfunction with lack of sensitivity to endogenous and exogenous vasodilators, either nitric oxide (NO) released from pulmonary vascular endothelium or exogenous agents acting through NO, endothelin or prostaglandin (PG) signalling pathways [2].

Despite a growing body of knowledge, currently there is no specific and definitive therapy for type 2 PH; however, it prompts reduced exercise capacity, increased short- and long-term morbidity and mortality along with a potential for disqualification from heart transplant candidacy [1, 3–5]. Indeed cardiac transplantation (HTX), in the setting of PH, significantly increases the risk of acute right ventricular (RV) failure which, in turn, still accounts for nearly 50% of all cardiac complications and up to 19% of all early postoperative deaths [6]. These observations are reflected in the listing criteria for HTX published by the International Society for Heart and Lung Transplantation (ISHLT) [3].

Sildenafil is a specific phosphodiesterase type 5 (PDE5) inhibitor that prevents the catabolism of cyclic guanulate monophosphate, the second messenger of NO in vascular smooth muscle cells. PDE5 activity is increased in the systemic and pulmonary vasculature as well as in the kidney in HF. Evidence from basic research studies suggests that PDE inhibition has favourable
direct myocardial effects through the blockade of adrenergic, hypertrophic and proapoptotic signalling. Besides, clinical studies show that sildenafil increases myocardial contractility and reduces LV afterload, blunts adrenergic stimulation, and improves lung diffusion capacity as well as pulmonary haemodynamics at rest and during exertion with an increase in peak VO₂ [1]. Sildenafil has a favourable safety profile without oxygen desaturation or significant changes in heart rate or blood pressure. The only commonly reported side effect is flushing. Several case series reported that oral sildenafil decreased pulmonary vascular resistance (PVR) in selected patients with severe PH to a transplantable level [7–10].

The aim of this study was to assess the effect of long-term oral therapy with sildenafil in patients with end-stage HF who were deemed ineligible for heart transplant because of severe PH.

METHODS

Study design and aims

The present study, conducted in accordance with the ethical guidelines of the Declaration of Helsinki II, was approved by the Institutional Review Board. Written informed consent was obtained from all patients. This prospective, non-randomized, open label uncontrolled pilot trial, evaluated the effects of treatment with oral sildenafil in patients with end-stage HF who were initially disqualified from HTX candidacy because of severe PH. The trial basically tested two hypotheses: (i) a 12-week PDE5 inhibition trial may render PH reversible to transplantable level; (ii) chronic oral sildenafil may prevent major complications during the early post-transplant course and ameliorate postoperative pulmonary profile. The primary outcome measures were: changes in pulmonary haemodynamics, transplant eligibility and post-transplant outcomes (incidence of RV dysfunction, early and 1-year survival along with pulmonary haemodynamic profile after the procedure). Patients ≤65 and ≥18 years old, able to understand and willing to sign the informed consent form, with left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) <0.35] and stable New York Heart Association class III HF for at least 3 months despite maximal medical therapy were enrolled if free from: unstable angina, uncontrolled serious ventricular arrhythmias, haemodynamic instability.

Right heart catheterization protocol and schedule

Right heart catheterization was performed using a standard clinical protocol. Baseline right atrial, pulmonary arterial (PA) and pulmonary capillary wedge (PCWP) pressures were obtained. Cardiac output (CO) was assessed by thermodilution as the mean of three to five separate measurements, and cardiac index (CI) was calculated as CO/body surface area (litres/min/m²). Transpulmonary gradient (TPG) and PVR were calculated using the following formulas: TPG (mmHg) = mean PA–PCWP, and PVR (WU) = TPG/CO. PVR index (PVRi) was calculated as PVR/body surface area. Haemodynamic assessment was performed at rest in all patients. Whenever on baseline haemodynamic assessment PVR was >3 WU and TPG was >15 mmHg at rest, a vaso-dilator and/or inotropic infusion was used according to published guidelines. Patients with irreversible PH (PVR >6 WU, unresponsive to vasodilators) were disqualified from orthotopic heart transplantation and entered the sildenafil trial; then right heart catheterization was repeated at the end of the 12th week of oral PDE5 inhibition, to reevaluate candidacy. After heart transplantation, routine right heart catheterization data were obtained while performing postoperative endomyocardial biopsies according to a standard schedule [11].

Haemodynamic parameters at 3 month and 1 year after heart transplantation were included in the analysis.

Sildenafil treatment

Patients meeting the above inclusion criteria were administered sildenafil at a dose of 25 mg by mouth three times per day, until treated every 2 weeks to 75 mg three times daily if no severe side-effect had occurred (symptomatic hypotension, gastric reflux, headache and facial flushing). Study medication was added to the patient’s conventional HF therapy. Treatments with intravenous epoprostenol, oral bosentan, intravenous or inhaled iloprost or subcutaneous treprostinil, nitrate therapy and supplementation with L-arginine were prohibited. Notably, all patients received sildenafil during the first post-transplant day through a nasogastric tube while on tailored inodilator therapy. Down-titration of sildenafil was achieved over the first two postoperative months using invasive haemodynamic monitoring; complete withdrawal was allowed only after the third postoperative months if satisfactory compensation was achieved [11].

Principles of surgical, critical peritransplant and long-term care

Principles of surgical, intraoperative and postoperative care along with details on immunosuppressive regimen were reported extensively elsewhere [11–13]. Donor and recipients were matched for ABO blood type compatibility and size (generally a maximum 20% body weight mismatch was allowed). Prospective human leukocyte antigen (HLA) matching was not used with the exception of recipients with high levels of panel reactive anti-HLA antibodies (>20%) who underwent a prospective cross-match. Male donors <40 years of age and female donors <45 years of age met criteria as suitable donors provided there was no evidence of pre-existing heart disease or impaired myocardial dysfunction by echocardiography. High inotropic support of donor heart, defined as dopamine or dobutamine at a dose of 10 µg/kg/min or as the need for norepinephrine, with echocardiographic evidence of LVEF >40% after haemodynamic optimization did not prevent graft usage. Need for excessive inotropic support (dopamine or dobutamine at a dose of 20 µg/kg/min or similar doses of other adrenergic agents despite optimization of preload and after load) was instead considered a contraindication to organ harvesting as per current guidelines. Older individuals also were considered suitable as donors provided that coronary atherosclerotic lesions could be excluded, ideally by cardiac catheterization. Individuals with serologies positive for hepatitis B and hepatitis C were matched with very high-risk recipients in the emergency setting or standard recipients with specific immune-competence and underwent a close infectivology follow-up according to the rules of the national quality control centre (Centro Nazionale Trapianti). Donors with serologies positive for human immunodeficiency virus or non-
primary brain cancer were excluded. Donor heart procurement was performed with standard technique and the grafts were protected with 2 l of cold (4–8°C) Celsior solution and topical saline slush. Excised grafts were then immersed in 1 l of cold Celsior solution and stored under ice in closed cardiac storage container for transportation. All recipients underwent standard orthotopic transplantation using the biatrial technique described by Lower and Shumway. Definition and flowcharts for the diagnosis of RV failure along with treatment strategies followed current recommendations and the institutional management protocol has been fully elucidated elsewhere [14–15]. Briefly RV failure was defined as central venous pressure >20 mmHg, an RV end-diastolic pressure >15 mmHg, a PCW pressure <15 mmHg, a mean pulmonary artery pressure >20 mmHg and a CI <1.5 l/min/m². Treatment goals were: (i) preserved coronary perfusion through maintenance of systemic blood pressure; (ii) optimized RV preload; (iii) reduced RV afterload by decreasing PVR and (iv) limiting pulmonary vasoconstriction through ventilation with high inspired oxygen concentrations (100% FiO₂), increased tidal volume and optimal positive-end expiratory pressure ventilation. In particular, tailored fluid administration, dobutamine, isoproterenol and PGE₁ were mainstays of the initial therapy. Inhaled NO was instituted before leaving the operating room in cases where the initial therapy showed little impact. Since vasoconstriction of pulmonary blood vessels may just follow awakening from anaesthesia, the patients were left intubated, sedated and even paralyzed until achievement of an effective control of PVR. Intra-aortic balloon counterpulsation was employed in patients with impaired left ventricular function to reduce RV afterload and PVR by optimizing left ventricular performance. Early postoperative reinstatement of full dose oral sildenaﬁl through nasogastric tube was adopted in all cases to allow faster extubation and prevent rebound pulmonary vasoconstriction following NO weaning. Definitions of multiple organ failure, acute kidney injury and graft rejection strictly adhere to current guidelines and were reported elsewhere [12–13]. Hospital mortality was defined as all deaths occurring during the same hospital stay period of the operation plus those deaths occurring after hospital discharge but within 30 days of the procedure.

Statistical analysis

Data are expressed as mean ± SD for continuous variables and as percentages for categorical variables. Paired Student t or the Wilcoxon signed-rank test was used to assess the effect of treatment on differences in the change in continuous variables measured at the various time points of the study protocol. Choice of statistical tool was based on the distribution. All statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Study sample features

Between May 2005 and December 2009, 216 patients were evaluated for heart transplant candidacy: 38 displayed type 2 irreversible PH; four were haemodynamically unstable and required both tailored inotropic and vasoactive support and mechanical circulatory support (three intraaortic balloon pumping, one extracorporeal membrane oxygenation); while two received bosentan therapy according to their referring physician’s preference. Thirty-two consecutive patients, complying with inclusion criteria, consented to Sildenaﬁl pilot trial.

Clinical features, pulmonary profile and transplant candidacy after 12 weeks of PDE5 inhibition

No deaths occurred during this phase but one patient was withdrawn from the trial due to worsening of cardiac compensation following an appropriate implantable cardioverter-defibrillator discharge. Up-titration of loop diuretics was required in 16 patients, down-titration in two. Right heart catheterization disclosed reversibility of PH in actively treated patients with significant reduction of both TPG and PVR. Patients were then listed, even though the newly acquired haemodynamic profile could be classified as high risk for early post-transplant RV failure according to current ISHLT guidelines (mean PVRI: 9.57 ± 4.07 WU, mean TPG 14.47 ± 5.66 mmHg and mean systolic pulmonary artery pressure: 68.96 ± 15.15 mmHg). Table 1 summarizes main candidate characteristics. Table 2 reports baseline and 12-week haemodynamic parameters.

Heart transplant features and outcomes

The 31 patients who completed the sildenaﬁl trial were all subsequently transplanted. Mean waiting time on the list was 182.7 ± 309.7 days. 41.9% of the patients were hospitalized at the time of transplant but none required intubation, renal replacement therapy (RRT) or mechanical circulatory support. Preoperative right heart catheterization parameters are reported in Table 1. Mean donor age was 31.7 ± 11, leading causes of death were trauma (41.9%) and stroke (32.3%); high inotropic support at harvesting was needed in 41.9%. Mean donor/recipient weight ratio was 1.04 ± 0.17, overall graft ischaemic time was 179 ± 47 min

<table>
<thead>
<tr>
<th>Table 1: Recipients characteristics</th>
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<tr>
<td><strong>Characteristic</strong></td>
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<tr>
<td>Age, year (mean ± SD)</td>
</tr>
<tr>
<td>Female sex (n)</td>
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<tr>
<td>Primary cause of HF</td>
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<tr>
<td>Coronary artery disease</td>
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<tr>
<td>Myopathy</td>
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<tr>
<td>Valvular</td>
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<tr>
<td>Miscellaneous</td>
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<tr>
<td>Previous cardiac surgery (n)</td>
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<tr>
<td>Preoperative eGFR (mean ± SD; ml/min)</td>
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<tr>
<td>Heart failure pharmacotherapy</td>
</tr>
<tr>
<td>Diuretic</td>
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<tr>
<td>ACE inhibitor or angiotensin receptor blocker</td>
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<tr>
<td>β-Adrenergic receptor antagonist</td>
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<tr>
<td>Spironolactone</td>
</tr>
<tr>
<td>Digoxin</td>
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<tr>
<td>Cardiac resynchronization therapy</td>
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<tr>
<td>Implantable cardiac defibrillator</td>
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<td>Peak VO₂, ml × kg⁻¹ × min⁻¹</td>
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eGFR: estimated glomerular filtration rate.
Pulmonary haemodynamic profile

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Baseline before sildenafil (n = 31)</th>
<th>After 12-week sildenafil (n = 31)</th>
<th>P-value (baseline vs 12-week sildenafil)</th>
<th>HTX (anaesthesia induction) (n = 31)</th>
<th>3 months (n = 30)</th>
<th>1 year (n = 29)</th>
<th>P-value (immediate pre HTX vs 3-month and 3-month vs 1 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PAP, (mmHg)</td>
<td>46.5 ± 6</td>
<td>37.1 ± 7</td>
<td>&lt;0.001</td>
<td>36.5 ± 8</td>
<td>22.3 ± 4</td>
<td>23.4 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>27.3 ± 3</td>
<td>22.4 ± 6</td>
<td>0.048</td>
<td>23.1 ± 5</td>
<td>12.8 ± 1.8</td>
<td>13.5 ± 1.3</td>
<td>**NS</td>
</tr>
<tr>
<td>TPG (mmHg)</td>
<td>19.2 ± 5*</td>
<td>14.5 ± 6</td>
<td>&lt;0.001</td>
<td>14.3 ± 7</td>
<td>9.7 ± 3</td>
<td>10.8 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>3.43 ± 0.5</td>
<td>3.51 ± 0.4</td>
<td>NS</td>
<td>3.6 ± 0.8</td>
<td>5.2 ± 0.4</td>
<td>5.3 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR (WU)</td>
<td>6.6 ± 4*</td>
<td>5.41 ± 3</td>
<td>&lt;0.001</td>
<td>4.2 ± 4</td>
<td>2.3 ± 2</td>
<td>2.1 ± 2</td>
<td>&lt;0.001</td>
</tr>
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*aUnresponsive to vasodilator challenge
*Immediate pre HTX vs third postoperative month.
**NS
**Third postoperative month vs first postoperative year.

and first postoperative Troponin I release averaged 10.1 ± 6.6. RV failure developed in three patients (9.6%) [95% confidence interval (CI: 1.4%) 0–20.7%]. Seven patients needed prolonged intubation (>72 h), acute kidney injury >50% developed in 12.8% with RRT needed in 6.5%. Hospital mortality was 3.2% [95% (CI: -3.4%) 0–9.8%] (due to multi organ failure in a patient with sepsis after prolonged RRT). Three patients developed acute rejection and needed re-hospitalization and steroid pulse therapy. Overall 1-year mortality was 6.5% (one death occurred nearly 6 months after the surgical procedure due to accelerated cardiac allograft vasculopathy in a patient with low compliance to the immunosuppressive therapy) and follow-up was 100% complete.

Pulmonary profile after heart transplant and weaning from PDE5 inhibition

Table 2 reports haemodynamic parameters obtained in all the surviving patients at the following timepoints: anaesthesia induction (n = 31 pts), 3 months (n = 30 pts, due to one hospital death) and 1 year postoperatively (n = 29 pts, due to the 6th month death reported above). Sildenafil discontinuation was allowed in all patients after the third postoperative month given the favourable pulmonary profile. This profile remained unchanged up to 1 year. Outpatient clinic long-term follow-up is underway.

Safety of PDE5 inhibition

Mean adverse events of sildenafil therapy were: ventricular arrhythmias in two patients, symptomatic hypotension in nine, headache on more than one occasion in six, flushing in two and myalgia in four.

DISCUSSION

The outcomes of this prospective, non-randomized, open label uncontrolled pilot trial suggest that a 12-week treatment with oral sildenafil is able to allow transplant candidacy in selected patients initially disqualified because of severe type 2 PH. Long-term oral perioperative PDE5 inhibition in such candidates' subset allows a smooth perioperative course with satisfactorily low incidence of RV graft dysfunction and complete normalization of pulmonary haemodynamic profile within 3 months and stability through the first postoperative year.

Available data disclose that at least one-third of HF patients referred for heart transplant have refractory PH, probably due to the fact that modern medical treatment long delays listing. As authoritative reported by Beyersdorf et al. [5], heterotopic HTX, combined heart-lung transplantation and right ventricle-sparing transplantation, that have been proposed as alternative surgical options, proved clearly inferior to orthotopic HTX.

More recent publications have shown that ‘fixed’ PH can be reversed by temporary left ventricular assist device (LVAD) support even in the presence of markedly elevated PVR (>7 WU). Reported long-term post-HTX outcome after LVAD support approaches that of HTX in patients without fixed PVR. However, LVAD complications (morbidity and mortality) remain a concern if this kind of treatment is chosen [5].

Less invasive approaches have been proposed to attempt PH reversal, including cardiac resynchronization therapy, long-term prostacyclin administration, long-term inotropic therapy, the so-called ‘vasodilator conditioning’ with milrinone or dobutamine and nesiritide. Varying rates of success has been reported with such approaches [1, 4, 16]. In an attempt to augment this process, the oral PDE5 inhibitor, sildenafil, appears to be a good candidate. Our cohort mirrors the findings by Lewis et al. who simultaneously measured exercise capacity and haemodynamics before and after treatment with sildenafil or placebo for 12 weeks to evaluate the chronic effects of PDE5 inhibition on cardiopulmonary exercise capacity, RV and LV performance and pulmonary and systemic vascular tone in 34 patients with symptomatic HF and PH. This drug improved exercise capacity and reduced resting and exercise PA pressure, systemic and PVR while increasing the resting and exercise CI without altering mean arterial pressure, heart rate or PCW pressure [17]. Several mechanisms were postulated for such results. Primary improvement of RV systolic function by afterload reduction, but also...
optimization of left ventricular performance by either reduction of systemic vascular resistance and/or increased contractility had been hypothesized [1, 17]. With regard to sildenafil potential to allow for transplantation candidacy, present data support and extend the pioneering case series by Gómez-Moreno et al. [7], Jabbour et al. [8], Zakliczynski et al. [9] and the more recent research correspondence by Perez-Villa et al. [10]. In this respect, the present study reports on a larger study population with all patients actually undergoing transplantation, whose outcomes, both clinical and haemodynamic, have been fully elucidated up to 1 year postoperatively. Intriguingly our results are also closely consistent with those recently forwarded by Tedford et al. who reviewed the effects of sildenafil administered to patients with persistent PH after LVAD implantation. As reported by this latter study, in patients with severe persistent PH (TPG of 25, after reduction of the PCWP to 12 mmHg by the LVAD), after 2–4 weeks of oral PDE5 inhibitor therapy, mean pulmonary artery pressure decreased by ~one-third, with an increase in CO contributing to a decrease of PVR by ~50%. The majority of the patients treated with sildenafil by Tedford et al. had a sufficient reduction in pulmonary resistance to make them eligible for transplantation, and 10 out of 26 patients studied have been transplanted. Significantly only 1 of 10 had RV dysfunction and the remainder had an uncomplicated post-transplant course [18, 19], outlining the potential of sildenafil to allow for a smooth early postoperative course. To date, there is no reliable haemodynamic threshold beyond which post-transplant RV failure is certain to occur, nor are there values below which RV failure is always avoidable. The differing levels of validity of these threshold values may be due to three basic causes: (i) different methodologies used to study, categorize and manage PH in HTX candidate; (ii) multiplex aetiology of graft failure (donor baseline characteristics and management, routes of graft preservation, donor/receptor matching criteria, surgical procedure, reperfusion damage, perioperative critical care management); (ii) modes of outcome reporting (death from graft failure vs 30-day mortality). Such discrepancies may account for the different prognostic value attributed to pre-existing severe PH on early and late transplant outcomes. Nevertheless, there is a general consensus, as reported in ISHLT guidelines, that severe PH should be considered at least a relative contraindication when PVR is >5 WU or the PVRi >6 or the TPG exceeds 16–20 mmHg. The same document states that if pulmonary artery systolic pressure exceeds 60 mmHg in conjunction with any of the preceding three variables, the risk of RV failure and early death is increased [3]. Actually such a haemodynamic profile was present in all patients in our series who experienced a 9.6% incidence of non-fatal acute RV failure, which is homogeneous with that (graft failure: 7.3% and hospital mortality: 8.9%) of a contemporary series of heart transplant recipients, with 1×PVR <3 performed in this centre. In this respect, it is important to remember that, as for institutional protocol, chronic oral pre-transplant PDE5 inhibition was followed by early post-transplant sildenafil therapy reinstitution [11]. Present results indeed add to those previously reported by our institution and to those by Klodell et al. [20], who recently reported using sildenafil to successfully wean from inotropic support and inhaled NO 10 newly implanted LVAD patients in whom previous therapy down-titration had failed because of rebound PH or increased right heart dysfunction. Finally, reversal of PH was definitively achieved by the third postoperative month. Such results are again in accordance with those previously published by these authors and others and should be read in the light of the negative prognostic value that persistent PH exerts on long term survival after transplantation, as well as the suggestion that persistence of the sildenafil effect on the pulmonary circulation beyond an acute vasomotor effect might be due to pulmonary vascular remodelling [21]; an hypothesis never tested in humans.

Study overview

Several study limitations should be considered for a thorough data interpretation. The small sample size of this pilot uncontrolled trial on highly selected patients prevents extrapolation to the large HF population with severe type 2 PH. Study outcomes rely on clinical parameters and haemodynamic evaluation. Target event definition followed current guidelines but comparisons with available data from the literature remains difficult, in a field where institutional protocols, frequently based on long-term/large series experiences predominate. The thermolodization technique has its limitations especially when measuring CO and derervatives in patients with either very low output conditions or significant tricuspid regurgitation. Despite patients being stable by inclusion criteria stable and pure pressure measurements being taken into consideration some of these limitations still persist. Although sildenafil was well tolerated in this trial, long-term studies with a greater number of patients are necessary to confirm the safety profile of this agent and its chronic effects on cardiovascular performance since some experimental and clinical data postulated relevant side effects (i.e. excessive preload reduction with associated reduction in CO; reduced heart rate augmentation with exercise; and increased intrapulmonary right-to-left shunt flow) [17].

CONCLUSIONS

In the setting of a limited sample of highly selected patients, this pilot prospective uncontrolled trial suggests that sildenafil is effective in allowing transplant candidacy in patients initially disqualified because of non-reversible PH. Early post-transplant course in such a sample, with preoperative chronic PDE5 inhibition and rapid reinstitution of oral sildenafil after HTX, is not aggravated by excess acute graft dysfunction rates. Post-transplant pulmonary haemodynamic profile normalizes within 3 months allowing sildenafil discontinuation. Persistence of these haemodynamic outcomes is confirmed up to 1-year follow-up. This study added a step in the understanding of the appropriate use of PDE5 inhibitors in HF patients with persistent PH, while several pivotal issues remain unexplored, including target treatment population, timing of PDE5 therapy and possible adjunct of upcoming alternative strategies.

Conflict of interest: none declared.

REFERENCES

APPENDIX. CONFERENCE DISCUSSION

Dr D. Loisance (Paris, France): Your study has a few limitations, the first being an issue with the definitions. You consider as hypertension, pulmonary hypertension, a patient who is not responsive to short-term vasodilator or inotropic support during the catheterization.

Dr De Santo: It is up to three days of inotropic support in the latest modification of the protocol.

Dr Loisance: So you did the right heart catheterization after a period of three days?

Dr De Santo: We assess the patients at baseline. We do the first right heart cath. If it does not work, namely if you have pulmonary hypertension, we keep the patients hospitalized, bring them to the ICU under inotropic support and then reevaluate them after two to three days. But if they ultimately do not respond, we qualify them as nonresponders.

Dr Loisance: Yes. But your answer now is very different from your manuscript. You should clarify that in the manuscript because it differentiates a weak point of your study. You have to define very clearly which kind of patients will be going to be included in this sildenafil study.

Dr De Santo: I just mentioned the protocol, but I can clarify.

Dr Loisance: You mentioned in the manuscript according to ISHLT guidelines.

Dr De Santo: That is the way it is described in the guidelines.

Dr Loisance: Thank you for the clarification.

Dr M. Maruszewski (Zabrze, Poland): In patients with preoperative pulmonary hypertension, the most common complication we see after heart transplantation is early right ventricular failure or biventricular failure. Could you comment on that in terms of your results? Did you observe that in your cohort?

Dr De Santo: We had a 9.6% rate which means 3 patients out of 31. We have been looking at the levels of pulmonary pressure profiles that we measured at the latest cath and also at the right catheterization during the induction of anaesthesia for transplantation to look for features, special features, in these patients. But we were not able to clarify that there was a different pulmonary profile in this specific subset. Also, from the donor point of view, we had no great difference in these three patients. What we found instead was that two of them were redo procedures, and we had massive blood usage during the intraoperative phase and the early postoperative phase, and this is a known drawback of transfusion. For another patient, as much as we tried, we had no other explanation for the occurrence of graft failure.

Dr Maruszewski: Did you use inhaled nitric oxide with these patients postoperatively?

Dr De Santo: We use nitric oxide within the OR, and we restart oral sildenafil through the nasogastric tube so you can prevent rebound when you go down-to-titrate the nitric oxide.

Dr Maruszewski: What was the duration of the postoperative sildenafil treatment in these patients?

Dr De Santo: Three months. We have been looking at right heart catheterization measurements by the time of planned endomyocardial biopsies. All the patients were left on therapy until the second month. Then if they were treatable, we down-titrated within the next month, and, if positive, by the end of the third month, we allowed them to be weaned off.

Dr M. Morphuis (Bad Oeynhausen, Germany): I have one short question. Only two patients were treated with a combined therapy, sildenafil and bosentan. All the other patients were treated by bosentan only, so they were kept hospitalized, brought them to the ICU under inotropic support. If it does not work, namely if you have pulmonary hypertension, we keep them hospitalized, bringing them to the ICU under inotropic support and then reevaluate them after two to three days. But if they ultimately do not respond, we qualify them as nonresponders.

Dr De Santo: Okay. And what is your opinion on Iloprost inhalation?

Dr Loisance: Okay. And do you perform NO testing before you operate on these patients or before you transplant them to look at how they react on NO?

Dr De Santo: No. That does not mean that we had combined therapy. We had a 9.6% rate which means 3 patients out of 31. We have been looking at the levels of pulmonary pressure profiles that we measured at the latest cath and also at the right catheterization during the induction of anaesthesia for transplantation to look for features, special features, in these patients. But we were not able to clarify that there was a different pulmonary profile in this specific subset. Also, from the donor point of view, we had no great difference in these three patients. What we found instead was that two of them were redo procedures, and we had massive blood usage during the intraoperative phase and the early postoperative phase, and this is a known drawback of transfusion. For another patient, as much as we tried, we had no other explanation for the occurrence of graft failure.

Dr Maruszewski: What was the duration of the postoperative sildenafil treatment in these patients?

Dr De Santo: Three months. We have been looking at right heart catheterization measurements by the time of planned endomyocardial biopsies. All the patients were left on therapy until the second month. Then if they were treatable, we down-titrated within the next month, and, if positive, by the end of the third month, we allowed them to be weaned off.

Dr M. Morphuis (Bad Oeynhausen, Germany): I have one short question. Only two patients were treated with a combined therapy, sildenafil and bosentan. All the other patients were treated by bosentan only, so they were kept hospitalized, brought them to the ICU under inotropic support. If it does not work, namely if you have pulmonary hypertension, we keep them hospitalized, bringing them to the ICU under inotropic support and then reevaluate them after two to three days. But if they ultimately do not respond, we qualify them as nonresponders.

Dr De Santo: Okay. And I think in your patients, because to transplant the patient with a mean pulmonary pressure of about 37 as I saw in your paper...
Dr Morshuis: It is quite high, I think. Did you select a certain kind of donor, so, in fact, young healthy men?

Dr De Santo: We use oversize. We use donors with inotropic support or even donors that are older. But we always try to have a donor/recipient ratio over 0.8, but actually if you look at the paper, in our more recent practice the donor/recipient weight ratio has been greater than 1.

Dr Morshuis: And my last question. I think your pulmonary pressure was high, but also the wedge pressure was very high, so the transpulmonary gradient of your patients was not that high. And I think that will be the reason that the transplants went very well. Do you agree or do you have another opinion?

Dr De Santo: Some of them did not have a high transpulmonary gradient, but have high systolic pulmonary pressure. I think that this is a bias of all the subsets that have been studied up to now both with drugs or with left ventricular assist devices. Because for certain, pulmonary hypertension is something that is related to the history of the patients, the way you manage them over the years, and the loading condition of the patients. So if the pulmonary hypertension is really fixed, you cannot manage it. But if you do not spend the time to look for reversibility, you discard these patients and this is not a good thing.