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Letter to the Editor

Benefit of prostaglandin infusion in severe heart failure Preliminary clinical experience of repetitive administration

Walter Serra [a,*], Luisa Musiari [b], Diego Ardissino [a], Tiziano Gherli [a], Alberto Montanari [b]

[a] Division of Cardiology, Heart–Lung Department, Parma Hospital, Italy
[b] Institute of Semeiotica Medica, University of Parma, Italy

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Abstract

Background: Prostaglandin E1 (PGE1) is a potent vasodilating drug, which has been used in treatment of primary pulmonary hypertension. However intravenous PGE1 infusion may be of benefit and also has been proposed as a therapeutic tool in patients with end-stage heart failure.

The aim of this prospective not randomized study was to assess the clinical and instrumental effects of this agent in patients with severe heart failure and pulmonary hypertension.

Methods: To investigate the effects of PGE1 in congestive heart failure we selected 22 consecutive patients (16 males, 6 females, mean age 63±2 years) in the mean NYHA class III, because they had pulmonary hypertension (PAPs>3 m/s and left ventricular ejection fraction (LVEF) ≤35% by echocardiography. A control group of 23 patients (19M, 4F mean age 62±5 years; 9 patients were in the NYHA class IV and 14 in the NYHA class III), with the same instrumental and clinical data, received an optimized oral treatment with beta-blockers, ACE-inhibitors, furosemide and digitalis. Right heart catheterization was performed to confirm and determine the type of pulmonary hypertension, before starting the PGE1 infusion. Clinical and echocardiography evaluation was performed during follow-up. PGE1 was infused at a mean dose of 10 ng/kg/min for a total of 24 h over three consecutive days every three months.

Results: Right heart catheterization confirmed a high systolic pulmonary pressure in all patients; pre-capillary pulmonary hypertension (mean PAP>25 mm/Hg) was 25%.

During a mean follow-up of 36±6 months, 16 patients died (10 in the control group and 6 in the PGE1 group). The Kaplan-Meier 3-years survival analysis was not statistically significant (Log-rank test), but at 2 months survival rates began to diverge; 36 months survival: 72.7% in the PGE1 group and 56% in the control group. The mean LVEF increased from 25.78% to 32.1% in the PGE1 group and from 23.38% to 26.15 in the control group ($p<0.001$); the NYHA mean class improved from 3.18 to 2.24 in the PGE1 group and from 3.46 to 3.38 in the control group ($p<0.05$). The PAP decreased from 57.65 to 40.82 mm/Hg ($p<0.001$). An AICD was implanted in 3 patients in the first group and in 5 patients in the control group. Two patients were added to the heart transplantation list.

Conclusion: These preliminary data suggest that intermittent PGE1 infusion in patients with advanced congestive heart failure and high pulmonary pressure is able to improve NYHA mean class ($p<0.05$), ventricular contractility (LVEF $p<0.001$), pulmonary pressure and clinical data.

It hasn't been associated to morbid events or increased risk of death.

Keywords: End-stage heart failure; Prostaglandins, Pulmonary hypertension

1. Introduction

Prostaglandins are potent pharmacological agents with vasodilatory effects, formed of 20 carbon atom fatty acids. They have previously been used in the treatment of pulmonary hypertension, secondary to simple congenital

* Corresponding author. Divisione di Cardiologia, Azienda Ospedaliera-Universitaria di Parma, Via A. Gramsci, 14, 43100 Parma, Italy. Tel.: +39 0521/991070.

E-mail address: wserra@libero.it (W. Serra).

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heart disease like interatrial and interventricular defects, duct-dependent atresia of the tricuspid Fallot's tetralogy, etc [1]. Intravenous PGE1 infusion may be of benefit and also has been proposed as a therapeutic tool in patients with end-stage heart failure [9,12,14].

Already at the end of the 1970s Olsson and Carlson [2], noted an improvement in cardiac performance after intra-arterial administration of PGE1 for peripheral vascular disease.

The physiopathological rationale underlying their use in heart failure is based on results published in literature showing that they have haemodynamic effects: reduction of mean pulmonary pressure and pulmonary resistance, via an endothelium-dependent mechanism and increased cardiac index with no change in heart rate [3,4]. An effect on systemic resistance and arterial blood pressure is manifested only at doses over 20 g/kg/min [5].

The documented, neurohormonal effects of the drugs result in a reduction of atrial natriuretic peptide and norepinephrine, as reported by Hulsmann and colleagues [6] while those on the kidney result in an increased renal perfusion, increased diuresis and increased elimination of sodium and potassium [7–10].

These occur through the antagonistic effects of PGE1 on angiotensin II in the systemic vascular resistance and on excretion of sodium and water on one hand, and through mechanisms which lead to apoptosis in the diseased heart on the other.

A modulating effect on cytokines production during reperfusion after coronary angioplasty or cardiac surgery is described [11], moreover, a synergistic action on the inhibition of platelets is referred using PGE1 and acetylsalicylic, by antagonism of cyclo-oxygenases and thromboxane A2 [12–14].

Clinical experience of the use of prostaglandins in treatment of heart failure is limited to patients on the heart transplantation waiting list [16,17] or to the use of prostacyclin in the FIRST [15,19] study which was prematurely interrupted because of an increase in mortality in the group treated with the drug. There are, however, substantial differences between the PGI2 and PGE; the former is a potent systemic vasodilator with consequent deleterious effects on ischaemic myocardium, while the latter is degraded in the pulmonary vessels and has systemic effect only at doses greater than 20 ng/g/min [18,19].

Table 1
Clinical data

Tab I : Clinical data of subjets submitted to study

	Controls	PGE1 Infusion
Number	23	22
Sex (m/f)	19/4	16/6
Age (years)	62.0±5.0	63.0±2.0
Ethiology	Ischaemic 12 Dilated c. 11	Ischaemic 11 Dilated c. 11
NYHA	3.46±0.52	3.18±0.64

Table 2
Basal echocardiographics data

Tab II : Basal echocardiographics data

	Controls	PGE1 Infusion
LVTD (ml)	212.0±3.75	224.6±4.7
FEVS (%)	23.38±5.25	25.78±7.59
Dt-E (msec)	193±2.1	170±1.7
PaPs (mmHg)	47.38±3.42	57.65±3.42

2. Method

The aim of our study was to evaluate the efficacy and safety of intravenously infused prostaglandins in a selected group of 22 patients (16 males, 6 females, mean age 63± 2 years), with a severe heart failure. Inclusion criteria were: NYHA class III–IV, left ventricular ejection fraction <35%, pulmonary hypertension by echo (PAPs>3 m/s) confirmed by right heart catheterization. 23 patients, NYHA class IIII–IV with left ejection fraction <35% and pulmonary hypertension, were a control group.

Patients with acute coronary artery disease were excluded. 7 of these pts had tolerated a trial with beta-blockers; 10 pts had undergone treatment with inotropes or vasodilators (dobutamine, nitroprusside) with scarce results. 11 pts had ischaemic heart disease, 11 pts had idiopathic dilated cardiomyopathy: all patients had significant mitral regurgitation. In the control group 9 pts had ischaemic heart disease, 14 pts had dilated cardiomyopathy; NYHA class was III–IV. They were treated with optimize oral drugs;

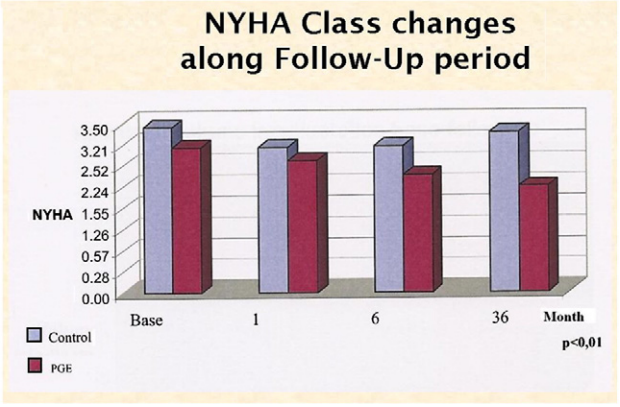

Fig. 1. Baseline NYHA class vs follow-up data.