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Acute effect of sildenafil on central hemodynamics in mechanically ventilated patients with WHO group III pulmonary hypertension and right ventricular failure necessitating administration of dobutamine☆,☆☆

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ABSTRACT

Background/Objectives: Sildenafil decreases pulmonary vascular resistance index (PVRI), in patients with pulmonary hypertension (PH). We investigated sildenafils' effects on central hemodynamics of mechanically ventilated patients with WHO group-III PH and RV failure necessitating dobutamine administration.
Methods: Prospective non-controlled study involving 12 (9 males, 59 ± 4 years old), patients with the above characteristics. All patients in phase-1 (days 1–2) received dobutamine (5 μg/kg/min IV). During phase-2 (days 3–6), sildenafil was started via nasogastric tube (80 mg/day) and dobutamine discontinuation was attempted. Patients were designated responders or non-responders based on whether dobutamine could be stopped or not. Phase-3 lasted from day 7 to day of weaning from mechanical ventilation; or if weaning failed, until day 20 following admission (end-of-study). Invasive and echocardiographic parameters were repeatedly recorded throughout the study.
Results: Significantly changed parameters ($P<0.025$) from baseline to phase-1, -2 and -3 (%change of mean ratios), in responders ($n=7$) included among others PVRI (−40%, −51%, −42%), RV stroke work index (RVSWI: 43%, 79%, 41%) and cardiac index (49%, 54%, 48%), which also differed significantly from non-responders ($N=5$). In phases-1 and -3 non-responders had not significant changes, in phase-2 PVRI (27%) and RVSWI (−22%) changed significantly. In contrast to non-responders, all responders were weaned from mechanical ventilation until the end-of-study ($P<0.025$).
Conclusions: Sildenafil may improve central hemodynamics and RV function indices in ventilated patients with WHO group-III PH and RV failure requiring dobutamine infusion, when they respond favorably to the latter. Accordingly, an adequate RV systolic reserve may be mandatory for sildenafil to exert its actions.

1. Introduction

Several respiratory disorders may affect pulmonary vasculature and result in a form of secondary pulmonary hypertension (PH), classified as group-III in the World Health Organization (WHO) classification [1]. The latter, overloads the right ventricle (RV), leading in hypertrophy and dysfunction [2]. Patients with secondary PH due to lung pathology often develop acute respiratory failure requiring mechanical ventilation. This may have a further negative impact on RV systolic function by augmenting RV afterload due to increased transpulmonary and pleural pressures, furthermore it decreases systemic venous return (RV preload) and RV diastolic filling, resulting in a reduced cardiac output [3]. In such cases, various inotropes such as dobutamine, milrinone and lately calcium sensitizers are commonly administered in an attempt to improve hemodynamics by enhancing biventricular function [4–7]. Most frequently dobutamine is administered, however this may be associated with side-effects, such as systemic hypotension, myocardial ischemia and proarrhytmia [5].

The ideal treatment for such patients should reduce pulmonary resistance, and increase RV inotropy [8]. Agents that decrease RV afterload by reducing pulmonary vascular resistance can result in an upward and leftward shift of the Frank–Starling curve, thus augmenting RV output while reducing the RV end diastolic pressure [5]. Sildenafil (Viagra, Pfizer, New York), an inhibitor of phosphodiesterase type 5 (PDE5), causes major vasodilatation in the pulmonary arterial network, decreasing significantly RV afterload [9] and is effective and

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well tolerated in patients with idiopathic PH [10,11]. Interestingly, experimental data suggested that sildenafil may also increase the contractility of the hypertrophic pressure overloaded RV, in which PDE5 is markedly upregulated [8,12]. Therefore PDE5 inhibitors might represent an ideal treatment for the failing RV, which has consistently been shown to be a crucial determinant of prognosis in many cardiovascular diseases [4].

We conducted this prospective non-randomized, non-controlled, single arm interventional trial, to examine the acute effects of sildenafil administration on central hemodynamics, in mechanically ventilated patients with WHO group-III PH and RV failure necessitating the administration of dobutamine.

2. Materials and methods

2.1. Patients

Twelve patients with secondary PH (WHO group-III) due to chronic obstructive pulmonary disease (COPD) were enrolled prospectively in two centers (Athens, Larissa), and the same equipment was used for treatments and measurements. All patients were intubated and mechanically ventilated because of acute respiratory insufficiency; thus they were admitted to the intensive care unit. Family members provided written, informed consent for all patients and the study was approved by the Institutional Review Board. Inclusion criteria were:

1) Secondary PH associated with disorders of the respiratory system or hypoxemia (WHO Group-III PH). PH (Pre-capillary) was documented invasively by right heart catheterization according to the latest ESC guidelines [13].
2) RV systolic dysfunction documented by 2-D echocardiography.
3) Decreased cardiac output necessitating the administration of inotropes (dobutamine). Cardiac output was estimated invasively by the thermodilution technique.

Exclusion criteria were: hospitalization during the last 6 months for unstable angina or myocardial infarction, administration of nitrates, secondary PH due to left ventricular (LV) systolic or diastolic failure, and/or other causes of secondary PH (e.g., pulmonary embolism). Also, patients were excluded if they exhibited, upon admission, acute respiratory distress syndrome (ARDS) and/or septic shock. Finally, patients necessitating administration of any additional vasoactive medication due to hemodynamic instability were excluded.

2.2. Study protocol

The study protocol, which is outlined in Fig. 1, was conducted in three phases and lasted 20 days. During all phases synchronous echocardiographic and hemodynamic

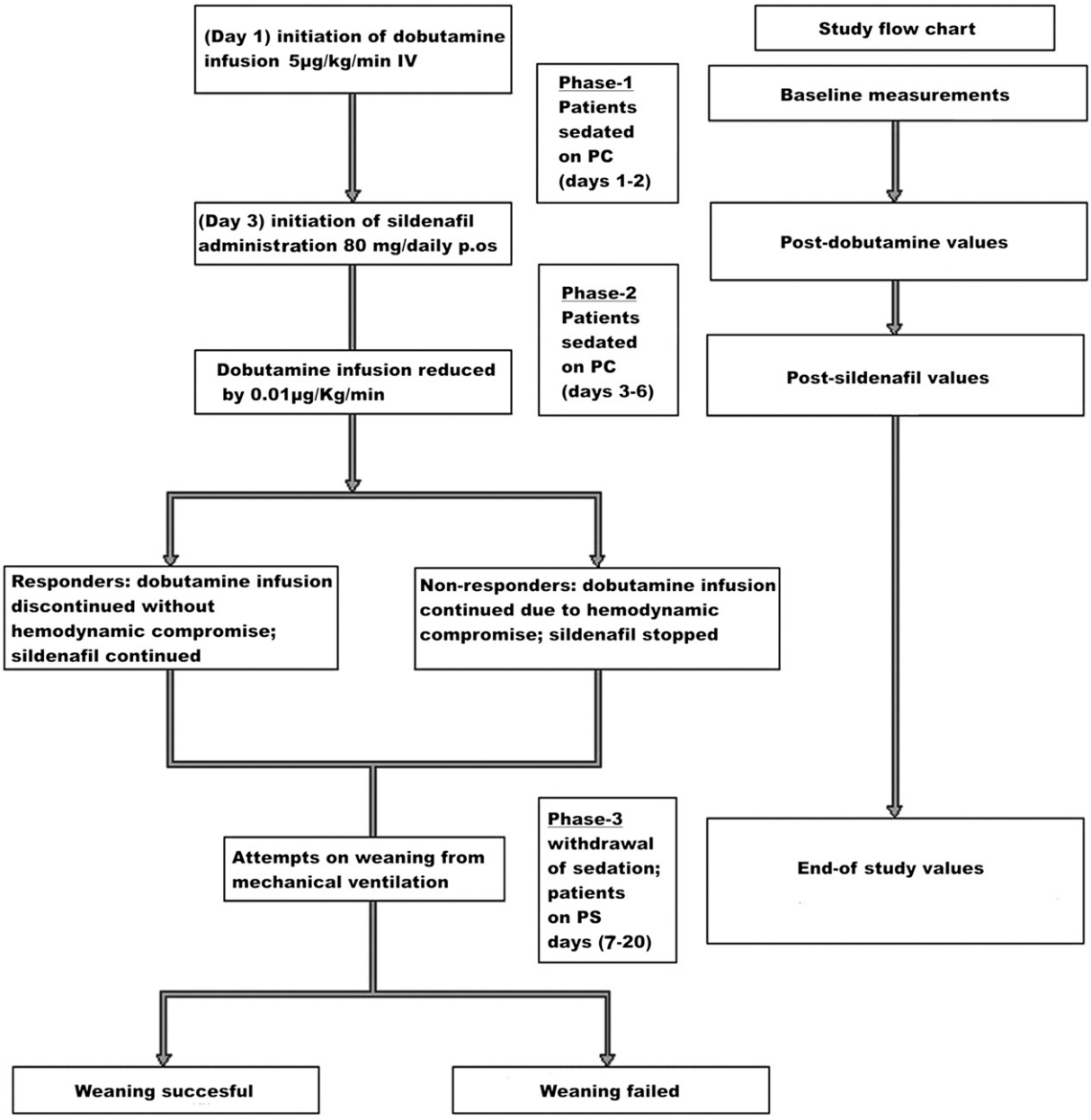

Fig. 1. Study flow chart (PC: synchronous intermittent mandatory ventilation-pressure control, PS: pressure support).