Early right ventriculo-arterial uncoupling in borderline pulmonary hypertension on experimental heart failure

Alberto Pagnamenta,1 Céline Dewachter,1 Kathleen McEntee,1 Pierre Fesler,1 Serge Brimioulle,2 and Robert Naeije1

1Department of Physiology, Faculty of Medicine, and 2Department of Intensive Care, Erasme Academic Hospital, Free University of Brussels, Brussels, Belgium

Submitted 3 May 2010; accepted in final form 26 July 2010

Pulmonary hypertension on experimental heart failure. J Appl Physiol 109: 1080–1085, 2010.—Pulmonary hypertension on heart failure (HF) limits exercise capacity and survival probably because of associated right ventricular (RV) failure. This study investigated the mechanisms of RV function adaptation to early pulmonary hypertension in experimental HF. Seven weeks of rapid ventricular pacing in six dogs induced a HF characterized by cardiomegaly and decreased left ventricular ejection fraction. Compared with eight control dogs, pulmonary hypertension was borderline, with a mean pulmonary artery pressure increased to only 23 ± 2 (means ± SE) mmHg. However, the pulmonary vascular impedance spectrum was globally shifted to higher pressures, with an increase in 0 Hz stiffness (SE) mmHg. There was no change in RV end-systolic elastance (Ees), but arterial elastance (Ea) was increased to 1.8 ± 0.3 vs. 0.9 ± 0.1 mmHg/ml in controls so that RV-arterial coupling defined by the Ees-to-Ea ratio (Ees/Ea) decreased to 0.8 ± 0.1 vs. 1.5 ± 0.1 in controls (P < 0.01). Inhaled nitric oxide, 40 ppm or 5 μg·kg−1·min−1 nitroprusside iv, did not affect Ees/Ea. Fifty milligrams (iv) of milrinone increased Ees/Ea to 1.6 ± 0.2 by an isolated increase in Ees. We conclude that overpacing-induced HF is accompanied by a borderline pulmonary hypertension but profound RV-arterial uncoupling explained by the failure of RV systolic function to adapt combined effects of increased pulmonary arterial resistance and elastance.

overpacing; pulmonary vascular resistance; pulmonary vascular impedance; right ventricular function

PULMONARY HYPERTENSION IS A COMMON COMPLICATION of heart failure (HF) (15). In these patients, pulmonary arterial pressure (Ppa) is increased as a passive consequence of upstream transmission of left atrial pressure (Pla), but there may be an increased gradient between Ppa and Pla because of additional effects of pulmonary vascular tone and remodeling (15, 21). Pulmonary hypertension in HF has been identified as an independent predictor of decreased exercise capacity and survival, and this is likely explained by an associated afterload-induced alteration in right ventricular (RV) function (13, 15, 23). Uncoupling of RV function from the pulmonary circulation could contribute to exercise ventilation inefficiency, which has been shown in recent years to be of great clinical and prognostic relevance in HF (33).

The gold standard for the evaluation of patients with pulmonary hypertension is right heart catheterization with measurements of right atrial and pulmonary vascular pressures and cardiac output (22). However, these measurements neglect the natural pulsatility of the pulmonary circulation and cannot, therefore, provide a complete description of all the forces opposing pulmonary arterial flow (5). The correct evaluation of RV hydraulic load, or afterload, can be provided pulmonary vascular impedance (PVZ), calculated from a spectral analysis of pulmonary arterial pressure and flow waves and actually determined by a dynamic interaction between resistance, compliance, and wave reflection (5). As for RV function, this is best globally defined by a pressure-volume relationship and adaptation to afterload estimated from the ratio of end-systolic elastance (Ees) and arterial elastance (Ea) (31). It has indeed been demonstrated that RV function adaptation to afterload is initially systolic, with maintenance of an optimal Ees-to-Ea ratio (Ees/Ea) ≈ 1.5, allowing for flow output at a minimal amount of energy cost (31).

Because of the prognostic impact of both pulmonary hypertension and altered RV function in HF, we thought it of interest to investigate the mechanisms of abnormal coupling of the RV to the pulmonary circulation in an experimental model of the disease. We reported previously on a few weeks of overpacing in dogs to induce severe dilated cardiomyopathy, characterized by marked cardiomegaly and decreased ejection fraction, but only mild increase in pulmonary vascular pressures and resistance (23, 28). We specifically sought to determine whether mild pulmonary hypertension in HF would nevertheless be a cause of RV- arterial uncoupling by either an underestimation of afterload or inherent limitation systolic function.

METHODS

A total of 14 beagle dogs (11–15 kg) were included in the study. HF was induced by 7 wk of overpacing in six of them. The other eight dogs served as controls. The investigation was approved by the Institutional Animal Care and Use Committee of the Free University of Brussels and was conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, revised 1996).

The overpacing model of HF. The overpacing was instituted as follows. After premedication with midazolam (0.1 mg·kg iv) and methadone (0.3 mg/kg iv), anesthesia was induced and maintained with propofol (5 mg·kg followed by 5 mg·kg−1·h−1). The animals were ventilated with an inspired O2 fraction (FIO2) of 0.4, a respiratory rate of 12 breaths/min, and a tidal volume adjusted to maintain CO2 expiratory pressure between 30 and 35 mmHg. Under sterile operating conditions, a transvenous bipolar pacemaker lead (Fineline II, model 4471; Guidant, Brussels, Belgium) was surgically implanted in the RV apex under fluoroscopic control, and a multiprogrammable
pulse generator (Insignia; Guidant) was inserted in the cervical region in a subcutaneous pocket and connected to the pacemaker lead. After a 2-wk recovery period, the dogs were subjected to 7 wk of rapid RV pacing with weekly increments: 180, 200, 220, and 240 beats/min for the 4 last wk, as described previously (23, 28). Progression of HF was monitored on a weekly basis, with dogs in sinus rhythm (30 min after transient inactivation of the pacemaker) by clinical examination and transthoracic echocardiography (Pandion; Pie Medical Benelux, Zaventem, Belgium).

Invasive hemodynamic measurements. Just before the invasive experiments, the ventricular pacemaker was deactivated in the dogs with tachycardiomypathy. The dogs were anesthetized with morphine (0.1 mg/kg) and α-chloralose (80 mg/kg), followed by a continuous infusion of α-chloralose at the rate of 20 mg/h supplemented with morphine (0.5 mg·kg⁻¹·h⁻¹). Paralysis was obtained with pancuronium bromide (0.2 mg·kg⁻¹·h⁻¹). The dogs were ventilated (Eletma 900 B servo-ventilator; Siemens Elena, Solna, Sweden) via a cuffed endotracheal tube with a FIO₂ of 0.4, a respiratory rate of 10 breaths/min, a tidal volume of 15–25 ml/kg adjusted to maintain arterial PCO₂ between 35 and 45 mmHg, and a positive end-expiratory pressure of 5 cm H₂O. End-expiratory pressures remained at 5 cm H₂O and peak inspiratory pressures between 30 and 35 cm H₂O. Periodic deep inspirations were administered to prevent atelectasis formation. Body temperature was maintained at 36–38°C using an electric heating pad. When metabolic acidosis occurred, it was corrected with a slow infusion of sodium bicarbonate. Throughout the experiments, NaCl 0.9% was infused at ~10 ml·kg⁻¹·h⁻¹ to maintain a Pla between 5 and 10 mmHg.

A balloon-tipped, flow-directed pulmonary catheter (Model 131HI-7F; Baxter Edwards, Irvine, CA) was inserted through the left external jugular vein and positioned using the pressure wave form into a branch of the pulmonary artery for measurements of Ppa, right atrial pressure (Pra), cardiac output (Q), and central temperature and for mixed venous blood sampling. A polyethylene catheter was inserted in the abdominal aorta via the right femoral artery for measurements of systemic arterial pressure (Psa) and for arterial blood sampling.

A left lateral thoracotomy was performed. A balloon-tipped, flow-directed pulmonary catheter (model 131HI-7F) was inserted in the left atrium via the atrial appendage to measure Pla. A 16- to 24-mm nonconstricting ultrasound flow probe (T101; Transonic Systems, Ithaca, NY) was positioned around the main pulmonary artery for the measurement of instantaneous pulmonary Q. The Transonic flowmeter system is linear to 60 Hz, with a flat amplitude response to 35 Hz. A 5F high-fidelity manometer-tipped catheter (model SPC 350; Millar Instruments, Houston, TX) was introduced through the RV into the main pulmonary artery, and its tip was positioned just distal to the flow probe for the measurement of instantaneous Ppa. Another 5F high-fidelity manometer-tipped catheter (model SPC 350) was introduced into the RV for the measurement of instantaneous RV pressure (Prv). The frequency response of the micromanometer system is flat beyond 200 Hz. The chest was tightly closed, pleural air was evacuated, and the lungs were reexpanded with several large volume inspirations.

Measurements. Heart rate (HR) was determined from a continuous electrocardiogram. Vascular pressures were measured using Gould Statham P50 transducers (Gould, Oxnard, CA). The pressure and flow signals were displayed on a monitor (Sirecust 404; Siemens, Erlangen, Germany) and recorded on a six-channel Gould recorder (model 2605S; Gould, Instruments Division, Cleveland, OH). The pressure transducers of the fluid-filled catheters were zero-referenced at mid-chest, and vascular pressures were recorded at end expiration. Q was measured by thermodilution as a mean of at least three successive measurements (CO-set; Baxter Edwards, Santa Ana, CA). The zero Q from the ultrasonic flow probe was adjusted to the end-diastolic value, assumed to be zero. The instantaneous RV and pulmonary pressures and flow signals were sampled at 200 Hz using an analog/digital converter (DAS 8-PGA; Keithley-Metabyte, Taunton, MA), stored, and analyzed on a personal computer.

Pulmonary vascular resistance (PVR) was calculated as (Ppa – Pla)/Q and corrected for body surface area. PVZ was calculated from the Fourier series expressions for pressure and flow signals, as reported previously (10). Five end-expiratory heartbeats were analyzed for each data collection interval. Pressure and flow harmonics with amplitude of <1% of pressure and of flow pulse amplitude were considered as noise and excluded from PVZ calculations. The PVZ modulus was computed as the ratio between pressure and flow moduli and its phase computed as the difference between flow and pressure phases. The impedance at 0 Hz (Zo) was taken as the total resistance (Ppa/Q), and the characteristic impedance (Zc) was calculated as the average of impedance moduli between 2 and 15 Hz.

A single-beat method was used to calculate Ees, pulmonary artery effective elastance (Ea) from instantaneous RV pressure curves, and synchronized pulmonary blood flows, as reported previously (4). The method relies on the measurement of a relative change in RV volume and flow, the integration of pulmonary flow and on the calculation of maximal RV pressure (Pmax) from the early and late systolic portions of the RV pressure curve (4). Practically, four to nine good quality beats were sampled at the end of expiration and integrated into a single one during the Fourier transform and subsequent automatic analysis by the software. We previously showed a good agreement between calculated Pmax and the Pmax of a nonejecting beat (4). Ventricular-arterial coupling efficiency was assessed by Ees/Ea.

Arterial and mixed venous blood gases were measured immediately after the samples were drawn by an automated analyzer (ABL 2; Radiometer, Copenhagen, Denmark) and corrected for temperature.

Experimental protocol. As soon as the animals were in steady-state conditions (stable HR, Psa, Ppa, and Q) for 20 min, a first baseline set of all hemodynamic and blood gas measurements was obtained, and instantaneous Ppa, Prv, and flow signals were sampled for PVZ, Ees, and Ea calculations.

In the animals with HF, the same measurements were repeated in the following sequence: 10 min after the institution of 40 ppm inhaled nitric oxide (iNO), control after return of HR, Psa, and Ppa values to baseline levels; 10 min after the institution of continuous intravenous nitrosopride progressively increased to 5 µg·kg⁻¹·min⁻¹, control after return of HR, Psa, and Ppa values to baseline levels; and 10 min after administration of a single intravenous bolus of 50 µg/kg milrinone given over 1 min.

The dose of 40 ppm iNO was based on previous studies that showed it most effective to decrease pulmonary vascular tone without systemic hemodynamic effects in experimental animals (10). NO was supplied from a pure NO source tank (Oxhydrique, Machelen, Belgium) and delivered through the endotracheal tube. The inspired fraction of NO was monitored by chemiluminescence after calibration against standard NO concentration (model 42 chemiluminescence NO-NO₂-Nox analyzer; Thermo Environmental Instruments, Franklin, MA). Inspired or expired NO₂ remained <1 ppm.

The dose of 5 µg·kg⁻¹·min⁻¹ nitrosopride was chosen because of its maximal effects on pulmonary vascular tone without excessive decrease in Psa (10).

The dose of 50 µg/kg milrinone as a bolus has previously been reported in studies on the reversibility of PVR in patients with HF evaluated for cardiac transplantation (12, 27).

Statistical analysis. Results are expressed as means ± SE. The statistical analysis consisted in a repeated-measures analysis of variance. When the F ratio of the analysis of variance reached a P < 0.05 critical level, modified t-tests were used to compare two different situations (34).

RESULTS

There were no significant differences in arterial blood gases between HF dogs and controls (Table 1). The different phar-
maculopapular interventional had no effect on arterial blood gases, except for a decrease in arterial PO2 (PaO2) following the administration of milrinone (Table 1). There were no differences in any measurements between the baseline and control without pharmacological interventions, and therefore, only one of these series of measurements is reported in the tables.

Effects of overpacing-induced cardiomyopathy. Compared with the controls, overpacing-induced HF was associated with increased HR and decreased Q (Table 1). Pulmonary vascular pressures, Ppa, and PVR were increased, and Psa was decreased. The increase in Ppa in dogs with HF was marginal, corresponding to “borderline” pulmonary hypertension, as recently defined by a Ppa between 20 and 25 mmHg (15).

Overpacing-induced HF was associated with increases in Zo, first harmonic impedance (Z1), Zc, and Ea, with no change in Ees and a decrease in Ees/Ea (Table 1). Typical changes in PVZ spectrum and RV-arterial coupling are illustrated in Fig. 1.

Effects of pharmacological interventions. iNO had no hemodynamic effect except for a decrease in Ppa and Zo (Tables 1 and 2). Nitroprusside increased HR and decreased Zo, Ps, Psa, Ppa, Pfa, PVR, and Zc but had no effect on Zc, Ees, Ea, and Ees/Ea. Milrinone increased HR and Q, decreased Ppa, Pfa, Psa, PVR, Zo, Zc, and Zc, had no effects on Ea, and increased Ees/Ea by a marked increase in Ees (Fig. 1).

DISCUSSION

The present results show that 1) overpacing-induced HF in dogs is associated with a deterioration in RV-arterial coupling because of the absence of adapted increase in RV contractility in the presence of borderline pulmonary hypertension and 2) increased afterload in pulmonary hypertension on HF may be markedly underestimated by the exclusive use of steady-flow pressure and resistance measurements.

Pulmonary hypertension secondary to HF is explained by upstream transmission of pulmonary venous pressure, with variable participation of increased resistance on both increased tone and vascular remodeling (15, 23). Accordingly, mean Ppa is correlated to Pfa, either directly measured or indirectly estimated by an occluded or wedged Ppa (11, 26), and decreases proportionally to decreased Pfa after cardiac transplantation (26). Increased PVR in HF is related to disturbed endothelial NO and endothelin-1 signaling (23), which is already significant in early-stage HF, with only mild increases in Pfa, Ppa, and PVR (9, 29) like in the present study.

Both increased Ppa and decreased RV ejection fraction have been shown to be potent predictors of survival in HF (11). Irreversible increases and Ppa and PVR are predictors of increased mortality after cardiac transplantation (7, 17). These observations support the notion that the prognosis in HF patients is largely dependent on the adaptation of RV function to increased afterload (13, 23). However, RV afterload cannot be determined accurately from steady-flow hemodynamic measurements (5). A quantification of RV afterload requires instantaneous pressure, flow, and volume measurements for the determination of a PVZ spectrum or calculation of a pulmonary arterial elastance (5, 31). In the present study, the shift of the whole PVZ spectrum to higher ratios of pressure and flow moduli was indicative of an increased afterload caused by increases in both resistance and elastance. This was confirmed by an out-of-proportion increase in Ea. Previous studies in patients with chronically increased pulmonary venous pressure on either

### Table 1. Steady-flow hemodynamic data and arterial blood gases in control dogs (n = 8) and in dogs with overpacing-induced congestive HF (n = 6) before and after administration of NO, sodium nitroprusside, and milrinone

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls</th>
<th>HF</th>
<th>NO</th>
<th>Nitroprusside</th>
<th>Milrinone</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2, mmHg</td>
<td>194 ± 7</td>
<td>192 ± 19</td>
<td>180 ± 12</td>
<td>164 ± 24</td>
<td>152 ± 26†</td>
</tr>
<tr>
<td>PaCO2, mmHg</td>
<td>38 ± 2</td>
<td>42 ± 2</td>
<td>43 ± 2</td>
<td>43 ± 2</td>
<td>40 ± 2</td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.01</td>
<td>7.37 ± 0.02</td>
<td>7.36 ± 0.01</td>
<td>7.38 ± 0.02</td>
<td>7.38 ± 0.02</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>103 ± 5</td>
<td>146 ± 13*</td>
<td>148 ± 11</td>
<td>166 ± 12†</td>
<td>183 ± 17†</td>
</tr>
<tr>
<td>CI, l/min/m²</td>
<td>3.9 ± 0.2</td>
<td>2.8 ± 0.2*</td>
<td>2.9 ± 0.2</td>
<td>20.7 ± 0.2</td>
<td>3.2 ± 0.3†</td>
</tr>
<tr>
<td>Psa, mmHg</td>
<td>103 ± 5</td>
<td>78 ± 3*</td>
<td>82 ± 5</td>
<td>68 ± 4†</td>
<td>68 ± 4†</td>
</tr>
<tr>
<td>Ppa, mmHg</td>
<td>17 ± 1</td>
<td>23 ± 2*</td>
<td>19 ± 1†</td>
<td>18 ± 1†</td>
<td>19 ± 1†</td>
</tr>
<tr>
<td>Pfa, mmHg</td>
<td>8 ± 1</td>
<td>11 ± 1*</td>
<td>10 ± 1</td>
<td>9 ± 1†</td>
<td>9 ± 1†</td>
</tr>
<tr>
<td>Psa, mmHg</td>
<td>5 ± 1</td>
<td>11 ± 1*</td>
<td>10 ± 1</td>
<td>9 ± 1†</td>
<td>8 ± 1†</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. Z0, impedance at 0 Hz (total resistance); Z1, 1st harmonic impedance; Zc, characteristic impedance; Ees, end-systolic elastance; Ea, arterial elastance; Ees/Ea, Ees-to-Ea ratio. *P < 0.05 compared with controls; †P < 0.05, NO, nitroprusside, or milrinone compared with HF without drugs.

### Table 2. Pulsatile-flow hemodynamic data in control dogs (n = 8) and in dogs with overpacing-induced congestive HF (n = 6) before and after administration of NO, sodium nitroprusside, and milrinone

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls</th>
<th>HF</th>
<th>NO</th>
<th>Nitroprusside</th>
<th>Milrinone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zo, dynes-cm⁻³-m⁻²</td>
<td>455 ± 41</td>
<td>669 ± 69*</td>
<td>540 ± 41†</td>
<td>561 ± 32†</td>
<td>519 ± 87†</td>
</tr>
<tr>
<td>Zc, dynes-cm⁻³-m⁻²</td>
<td>97 ± 15</td>
<td>159 ± 27*</td>
<td>147 ± 23</td>
<td>167 ± 36</td>
<td>129 ± 29†</td>
</tr>
<tr>
<td>Zc, dynes-cm⁻³-m⁻²</td>
<td>104 ± 7</td>
<td>183 ± 20*</td>
<td>174 ± 14</td>
<td>177 ± 26</td>
<td>143 ± 24†</td>
</tr>
<tr>
<td>Ees, mmHg/ml</td>
<td>1.2 ± 0.1</td>
<td>1.4 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td>1.6 ± 0.2</td>
<td>2.1 ± 0.2†</td>
</tr>
<tr>
<td>Ea, mmHg/ml</td>
<td>0.9 ± 0.1</td>
<td>1.8 ± 0.3*</td>
<td>1.6 ± 0.2</td>
<td>1.8 ± 0.3</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>Ees/Ea</td>
<td>1.4 ± 0.1</td>
<td>0.8 ± 0.1*</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>1.6 ± 0.2†</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. Z0, impedance at 0 Hz (total resistance); Z1, 1st harmonic impedance; Zc, characteristic impedance; Ees, end-systolic elastance; Ea, arterial elastance; Ees/Ea, Ees-to-Ea ratio. *P < 0.05 compared with controls; †P < 0.05, NO, nitroprusside, or milrinone compared with HF without drugs.
mitral stenosis (19) or advanced HF (20) had reported an increase in both low- and high-frequency PVZ suggestive in increases in both pulmonary vascular resistance and elastance. The present results show that the increases in both resistance and elastance occur early in the course of the disease to increase RV afterload that is out of proportion with that estimated by single PVR or Ppa determinations.

The essence of the normal ventricular response to increased afterload is homeometric by an increase in contractility matching Ees to increased Ea (31). This has been confirmed for the RV in conditions of acute increase in afterload, after induction of hypoxic vasoconstriction (4), or chronic increase in afterload, for example, after a few months of aorta-pulmonary shunting (30). Patients with severe pulmonary arterial hypertension present with an increased RV contractility, yet not sufficient to cope with increased afterload, so that the Ees/Ea decreases, indicating pending RV failure (18). This is obviously likely to occur in earlier stages of the disease in the presence of disease processes, limiting the capability of RV systolic function to adapt (6). In the present experiments, RV function was already depressed by the overpacing, and accordingly uncoupled from the pulmonary circulation, whereas pulmonary hypertension was only borderline. Left atrial pressure was increased, but marginally, contrasting with the severity of left ventricular dysfunction typical of the overpacing-induced HF model (24). However, Pla was measured at rest and in conditions of general anesthesia. It is thus likely that the pulmonary circulation is exposed to higher and variable Pla in conscious and active animals with overpacing-induced HF, contributing to remodeling and increased PVZ.

iNO, nitroprusside, and milrinone are among vasodilators used to test for reversibility of increased PVR in patients with HF evaluated for cardiac transplantation (1, 7, 12, 25, 27). It is assumed that the lowest PVR obtained through pharmacological manipulation is a reasonable estimate of the afterload that the transplanted RV will have to face postoperatively (7, 17). This may not always be the case, since preoperative administration of vasodilators may fail to decrease Pla, which is the major determinant of pulmonary hypertension in HF (26). However, many vasodilators have been shown to decrease PVR in advanced HF, with variable efficacies related to a combination of effects on tone, cardiac output, and Pla.

iNO in HF decreases PVR and does not usually affect cardiac output but may increase Pla (1, 3, 14, 21). The latter has been explained by a decreased pulmonary venous resistance, allowing for an increased venous return to the failing left ventricle, rather than by identifiable negative inotropic effects (2, 14). The only effect of iNO in the present study consisted of a decrease in Ppa, PVR, and Zo, compatible with previously reported potent pulmonary vasodilating effects. However, like that reported previously in normoxic or hypoxic dogs (10), iNO had no effect on PVZ spectrum, Ea, Ees, or Ees/Ea, compatible with a site of action limited to pulmonary-resistive vessels. Nitroprusside in HF decreases systemic and pulmonary resistances and filling pressures of both ventricles, with no change or an increase in cardiac output depending on the balance between preload and afterload reductions (7, 25). There has been a suggestion that nitroprusside might have positive inotropic effects (28), but this may be related to reflex sympathetically activated. In the present study, nitroprusside
Dose-response curves for PVR have been reported previously to obtain the largest possible decrease in RV hydraulic load. Hemodynamic effects, as reported previously (10), to given at the maximum tolerated doses without excessive systemic activation, as indicated by increased Ees and Ees/Ea. Milrinone decreases PVR in HF by a combination of positive inotropic effects to increase cardiac output and a decreased pulmonary vascular tone (12, 27). In the present study, milrinone increased Ees/Ea essentially by a positive inotropic effect. There were decreases in PVR and in low- as well as high-frequency PVZ, but these effects were insufficient to affect afterload as measured by Ea. Milrinone decreased PaO2 in relation probably to a decrease in hypoxic pulmonary vascular tone and resultant increased perfusion of less well- or nonventilated lung areas. A trend toward decreased PaO2 was also apparent with nitroprusside, but this did not achieve significance. Both drugs have been shown to be potent pulmonary vasodilators (9, 10). It is interesting that iNO did not decrease in PaO2, in contrast with previously demonstrated more effective inhibition of hypoxic pulmonary vasocostriction in normal dogs (10). Absence of associated changes in cardiac output might explain this apparent discrepancy.

In patients with severe HF, a low dose of intravenous nitroprusside (32 g/min ± 20 SD) has been reported to decrease low-frequency PVZ, represented by Zc, indicating an improvement in pulse wave velocity. A higher dose of nitroprusside (66 g/min ± 41 SD) decreased PVR, Zc, and wave reflections, increasing the forward flow and decreasing RV power requirement per unit forward flow (20). The absence of a significant effect of nitroprusside on the spectrum of PVZ in the present study is probably related to less severe HF and limited increase in pulmonary vascular tone. In patients with HF on severe aortic stenosis, nitroprusside increased Q, decreased Psa, and decreased occluded Ppa (16). The hemodynamic data from these studies were modeled using theoretical pressure-volume relationships, and the results suggested a participation of positive inotropic effects (28). Nitroprusside had no effect on Ees in the present study, confirming previous observations in normoxic or hypoxic dogs (10). There might have been a trend toward increased Ees, but, as already mentioned, this would be most likely related to reflex sympathetic activation, as indicated by concomitantly increased HR and decreased Psa.

Tachycardia-induced cardiomyopathy simulates idiopathic dilated cardiomyopathy rather than ischemic or hypertensive cardiomyopathy (32). Overpacing induces a global biventricular failure and may, therefore, be associated with earlier and more severe RV-arterial uncoupling. In addition, overpacing induces a severe HF in only a few weeks, which does not allow for chronic pulmonary vascular and myocardial remodeling to fully develop. All of these are important limitations to the extrapolation of the present findings to patients with HF.

Another limitation of the present study is that no dose-response curves were considered for the pharmacological interventions. Both iNO and intravenous nitroprusside were given at the maximum tolerated doses without excessive systemic hemodynamic effects, as reported previously (10), to obtain the largest possible decrease in RV hydraulic load. Dose-response curves for PVR have been reported previously over a wide range of doses of intravenous milrinone, ≤300 mg/kg, in rabbits with experimental pulmonary hypertension (8). However, in the present study, borderline blood pressure and tachycardia prevented the increase of milrinone to doses >50 μg/kg, which were used previously to test for the reversibility of PVR in HF patients evaluated for cardiac transplantation (12, 27).

In conclusion, early HF on tachycardiomyopathy is associated with a profound RV uncoupling despite only a mild increase in pulmonary vascular pressures. This is explained by altered systolic function of the RV in the context of the induced cardiac disease and by the underestimation of afterload by steady-flow hemodynamic evaluations.

ACKNOWLEDGMENTS

Present address of P. Fesler: Dept. of Internal Medicine, Centre Hospitalier Universitaire, 191 Avenue du Doyen Gaston Giraud, 34295 Montpellier, France.

Present address of A. Pagnamenta: Dept. of Intensive Care Medicine, Regional Hospital Mendrisio, Via Turconi 23, 6850 Mendrisio, Switzerland.

GRANTS

A. Pagnamenta was supported by the Lega Polmonare Ticinese (Lugano, Switzerland), the Fondazione Dr. P. L. Crivelli (Lugano, Switzerland), and the Fondazione Dr. E. Balli (Bellinzona, Switzerland).

This study was supported by the Funds for Medical Scientific Research Belgium (Grants 3.4551.05 and 3.4637.09).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


