Research Article

Comparison of drugs for pulmonary hypertension reversibility testing: A meta-analysis

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ABSTRACT

Multiple drugs are used for reversibility testing of pulmonary hypertension (PH) in advanced heart failure (HF), especially in the process of heart transplant evaluation. Effects of these drugs were never systematically compared. The aim of this meta-analysis was to compare hemodynamic effects of different drugs. We identified 20 prospective studies reporting hemodynamic variables before and after acute pharmacologic testing for PH reversibility in patients with advanced HF. The data from individual studies were grouped by an outcome measure and analyzed. A mixed model meta-analysis was performed using SAS to give weighted mean effect of pre- and post-test change and inverse variance. The mean effects were weighted by the published sample size. Prostacyclin, inhaled or intravenous, and prostaglandin E1 (PGE1) had the most potent effect on pulmonary vascular resistance (PVR). Sodium nitroprusside and nitroglycerin decreased pulmonary capillary wedge pressure (PCWP), and mean pulmonary arterial pressure (MPAP) better than other drugs. Sildenafil provided overall good hemodynamic outcomes but was not the strongest drug with regard to any particular outcome. PCWP, MPAP, and systolic pulmonary arterial pressure respond better to nitroglycerin and sodium nitroprusside than to other drugs in the setting of reversibility testing. Prostacyclin and PGE1 are superior to other drugs in their acute effects on PVR.

Key Words: heart failure, heart transplantation, pulmonary hypertension

Pulmonary hypertension (PH) complicates the course of heart failure (HF) and worsens the prognosis in heart transplant recipients. It is well-established that pulmonary vascular resistance (PVR) >2.5 Wood units (WU), which is present in about 30% of heart transplant candidates, is an important risk factor for early death after the transplant.[1,2] According to the criteria of the International Society for Heart and Lung Transplantation, PVR >5 WU or transpulmonary gradient (TPG) >15 mmHg is a relative contraindication to cardiac transplantation.[3] However, if PVR can be reduced to ≤ 2.5 WU without compromising systemic blood pressure, patients can be accepted as candidates for cardiac transplantation.

Multiple drugs, including vasodilators, inotropes, inhaled nitric oxide (NO), prostaglandin E1 (PGE1), intravenous or inhaled prostacyclin, and sildenafil have been utilized for evaluation of reversibility of PH. The choice of an agent primarily depends on the experience of a particular center. Published reports consist of only single center studies, usually with a small number of patients, describing either their results from reversibility testing with a single agent or comparing several agents. The objective of this meta-analysis is to compare the effects of currently used drugs for PH reversibility testing on different outcomes important for clinical decision making.

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MATERIALS AND METHODS

We searched PubMed from 1960 through 2010, Embase, Scopus, and Google Scholar for the articles reporting pharmacologic testing for PH, and then manually examined references in the found articles. Specific terms used for the searches included “reversibility testing,” “pulmonary

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hypertension," "inhaled nitric oxide," "prostaglandins," "prostacyclin," "sildenafil," "pulmonary vascular resistance," "transpulmonary gradient," and combinations of the above.

We selected papers in which the same group of patients was studied before and after the intervention, without dropouts. The papers where original hemodynamic information for the group of patients could not be extracted from the text were excluded. The papers we selected for the meta-analysis had to meet the following inclusion criteria:

1. Prospective studies
2. Patients population: Advanced HF with PH
3. Hemodynamic parameters recorded before and after pharmacologic test
4. Hemodynamic data reported as mean ± standard deviation (SD) or mean ± standard error (SE)
5. At least one of the following hemodynamic outcomes was reported: PVR, systolic pulmonary arterial pressure (SPAP), or mean pulmonary arterial pressure (MPAP)
6. The tested drug was given at a predetermined dose over a predetermined time interval, after which hemodynamic parameters were measured.

The data were extracted from the selected studies and incorporated into the database, and the pre- and post-test hemodynamic data were entered for each drug. The data were then grouped by outcome measure and the pre-post change was also calculated for each drug. For each outcome variable to estimate the pre-post change effect of the drug, a meta-analysis was performed using Mixed Models in SAS. The mixed model approach used random effect models to estimate the overall effect size, taking into consideration the between-study variance, and also used the fixed effects model to study the inter-study variances. Maximum log likelihood estimator was used to test the heterogeneity. To control for different study sizes, the effect was weighted by study sample size.

The methodology incorporated standard mean difference and allowed us to test for heterogeneity using a random effect mixed model. Because, in many papers, oxygen was given before other agents, and hemodynamic variables were recorded before and after oxygen, we included oxygen and used it as a reference point for comparison of effects of other drugs on the outcomes.

To compare different drugs against one another, we assessed the inter-drug effects using pairwise comparison with least square means. All statistics were done with SAS 9.2 (Cary, N.C., USA).

We analyzed the data for the following pharmacologic agents: Sodium nitroprusside, milrinone, nitroglycerin, dobutamine, inhaled nitric oxide (NO), PGE1, inhaled prostacyclin, intravenous prostacyclin, and sildenafil. The outcomes we studied included PVR, MPAP, TPG, cardiac index (CI), and pulmonary capillary wedge pressure (PCWP).

RESULTS

We initially identified 24 studies addressing the study question. Four of them were excluded from the final cohort for the analysis. Our rationale for the exclusion of these studies is provided, as follows. The study by O'Dell et al.[4] reported the experience with nesiritide which was not tested in any other study. It was also retrospective and did not include standard dosing or time interval; the infusion lasted as long as the patients' clinical condition required. The study of inhaled milrinone by Sablotzki et al.[5] was not included because of uncertainty about the dose calculation and comparison with intravenous milrinone. Similarly, the work of Braun et al.[6] was excluded because of unique design when they administered both oxygen and sublingual nitroglycerin before the study drug. Finally, the study of Wasler et al.[7] was excluded because they were administering PGE1 for several days and not as an acute test. The remaining 20 studies were included in the final analysis (Table 1).

In some studies, oxygen was used before the tested drugs. According to some reports it can decrease PVR and TPG by itself,[19] while in other reports it did not cause any significant changes in hemodynamic parameters.[14] Oxygen was used as a reference point for our calculations. Some authors tested several drugs on the same group of patients. In these instances, patients' data were entered separately into the analysis for each of the corresponding drugs. Enoximone and dipyridamole, tested only in one study each, were not included into the analysis.

Comparative effects of different drugs on the outcomes are presented in Tables 2-6 and Figures 1-5. In terms of reduction in PVR, the statistical comparison of drugs showed that prostacyclin, both inhaled and intravenous, were not significantly different from either PGE1 or inhaled NO ($P > 0.05$). Each of the drugs decreased PVR by more than 2 WU. All other drugs, including sildenafil, dobutamine, milrinone, and nitroglycerin, showed more modest effect on PVR, nitroglycerin the weakest in the group. Still, the PVR reduction was significant for all drugs.

With regard to the effect on MPAP, nitroprusside was clearly the best, followed by sildenafil, nitroglycerin, prostacyclin, and PGE1. Neither NO nor dobutamine were very effective in comparison with them. The absolute decrease reached almost 15 mmHg for sodium nitroprusside, and ranged between 8 and 10 mmHg for either form of prostacyclin, sildenafil, and nitroglycerin.

Table 1: Studies included in the meta-analysis

Author, year	*N*	Pharmacologic agents	Outcomes	Timing of hemodynamic measurements	Acceptable for heart transplant
Alaeddini et al., 2004[8]	14	Sildenafil 25-50 mg PO	PVR, CO, MPAP, SPAP, PCWP	Within 2 h	
Angel Gómez-Sánchez et al., 2004[9]	7	Sildenafil 100 mg PO	PVR, TPG, MPAP		
Lepore et al., 2005[10]	11	Nitric oxide 80 ppm, inhaled Sildenafil 50 mg PO	PVR, CI, MPAP, PCWP	5-15 min 1 h	
Haraldsson et al., 1998[11]	10	Nitric oxide 40 ppm, inhaled; prostacyclin 10 mcg/mL, inhaled	PVR, TPG, CO, MPAP, PCWP	10 min	
Lepore et al., 2005[12]	9	Nitric oxide 80 ppm, inhaled; dipyridamole 0.2 mg/kg, then 0.0375 mg/kg, IV	PVR, CI, MPAP, PCWP	5-15 min	3 of 7 patients (42.8%) reduced PVR to <200 dynes
Loh et al., 1994[13]	19	Nitric oxide 80 ppm, inhaled	PVR, TPG, CI, MPAP, PCWP	10 min	
Mahajan et al., 2007[14]	21	Nitric oxide 20 ppm, inhaled; nitric oxide 40 ppm, inhaled	TPG, CI, MPAP, PCWP	15-20 min	13 responders but only 9 (42.8%) reduced PVR to <4 WU; TPG decreased to <15 mmHg; 7 patients transplanted
Pagano et al., 1996[15]	10	Nitric oxide 10 ppm, inhaled; sodium nitroprusside 10 mcg/kg/min, IV; sodium nitroprusside maximal dose, IV; prostacyclin 5 ng/kg/min, IV; prostacyclin maximal dose, IV	PVR, TPG, CO, MPAP, PCWP	10 min	
Pamboukian et al., 1999[16]	19	Milrinone 50 mcg/kg, IV	PVR, TPG, CO, MPAP, PCWP	5-15 min	
Sablotzki et al., 2002[17]	14	Nitric oxide 30 ppm, inhaled; prostacyclin 50 mg, inhaled	PVR, TPG, CI, MPAP, PCWP	5 min	
Radovancevic et al., 2005[18]	19	Nitric oxide 40-80 ppm, inhaled; PGE1 0.05-0.5 µg/kg/min, IV	PVR, TPG	10 min	TPG was lowered to <12 mmHg in 14 patients (73.7%). Of these, 6 (46%) responded to both PGE1 and NO, 4 (27%) responded only to PGE1, and 4 (27%) responded only to NO
Semigran et al., 1994[19]	16	Nitric oxide 80 ppm, inhaled; sodium nitroprusside maximally tolerated dose, IV	PVR, TPG, CI, MPAP, PCWP	5 min	13 accepted (81.2%), 7 transplanted; <200 dynes
von Scheidt et al., 2006[20]	92	PGE1 173 ng/kg/min, IV	PVR, TPG, CO, MPAP, PCWP	10 min	A final PVR<2.5 WU was reached in 70 patients (76%), and a final TPG <12 mmHg in 74 patients (80%)
Freitas et al., 2009[21]	14	Sildenafil 100 mg, SL	PVR, CO, MPAP, SPAP	1 h	
Kieler-Jensen et al., 1994[22]	12	Nitric oxide 20 ppm, inhaled; nitric oxide 40 ppm, inhaled; nitric oxide 80 ppm, inhaled; sodium nitroprusside 2 mcg/kg/min, IV; prostacyclin 11 ng/kg/min, IV	PVR, TPG, CO, MPAP, SPAP, PCWP	10 min	
Fojón et al., 2005[23]	19	Nitric oxide 5-20 ppm, inhaled	PVR, TPG, SPAP	Not reported	14 listed (74%), 11 transplanted, no RV failure; criteria not specified
Murali et al., 1992[24]	39 9 12	PGE1 0.02-0.3 mcg/kg/min, IV Nitroglycerin 150 mcg/min, IV Sodium nitroprusside 0.5-1.5 mcg/kg/min, IV	PVR, TPG, CO, MPAP, SPAP, PCWP	10 min	TPG <15 mmHg in 31 patients (79%) 3 (33%) 4 (33%)
Murali et al., 1991[25]	8 7 29 11 11	Nitroglycerin 15-25 µg/kg/min, IV Sodium nitroprusside 1-1.5 µg/kg/min, IV PGE1 2-10 ng/kg/min, IV Dobutamine 7.5-15 µg/kg/min Enoximone	PVR, TPG, CO, MPAP, SPAP, PCWP	10 min	
Givertz et al., 1996[26]	27	Milrinone 50 µg/kg, IV	PVR, TPG, CI, CO, MPAP, SPAP, PCWP	5-20 min	
Weston et al., 2001[27]	6	Prostacyclin, inhaled, 0.25-1 mg; sodium nitroprusside 0.25 µg/kg/min titrated for hemodynamic effect	PVR, TPG, CO, MPAP, PCWP	10 min	4 of 6 transplanted

PO: orally; **IV:** intravenously; **PVR:** pulmonary vascular resistance; **MPAP:** mean pulmonary arterial pressure; **SPAP:** systolic pulmonary arterial pressure; **CO:** cardiac output; **CI:** cardiac index; **PCWP:** pulmonary capillary wedge pressure; **TPG:** transpulmonary gradient; **ppm:** parts per million; **SL:** sublingually; **PGE1:** Prostaglandin E1

Table 2: Effect of different drugs on PVR

Drug	Change in PVR	Lower confidence interval	Upper confidence interval	*P* value
Prostacyclin inhaled	−2.60	−4.152	−1.048	0.004
Prostacyclin IV	−2.48	−3.442	−1.518	<0.0001
Prostaglandin E1	−2.35	−2.712	−1.981	<0.0001
Sildenafil	−1.67	−2.122	−1.208	<0.0001
Milrinone	−1.52	−2.560	−0.481	0.010
Nitroglycerin	−0.60	−0.941	−0.259	0.003
Nitric oxide	−2.03	−2.404	−1.648	<0.0001
Nitroprusside	−1.74	−1.965	−1.515	<0.0001
Dobutamine	−1.40	−1.698	−1.102	<0.0001
Oxygen	−0.91	−1.047	−0.782	<0.0001

PVR: pulmonary vascular resistance

Table 3: Effect of different drugs on MPAP

	Change in MPAP	Lower confidence interval	Upper confidence interval	*P* value
Prostacyclin inhaled	−8.79	−15.40	−2.18	0.02
Prostacyclin IV	−8.84	−14.56	−3.12	0.01
Prostaglandin E1	−7.62	−10.38	−4.86	<0.0001
Sildenafil	−9.63	−15.04	−4.22	0.01
Milrinone	−6.43	−10.66	−2.20	0.01
Nitroglycerin	−9.00	−18.33	0.33	0.07
Nitric oxide	−1.80	−4.45	0.85	0.20
Nitroprusside	−14.94	−18.70	−11.18	<0.0001
Dobutamine	−1.00	−9.09	7.09	0.81
Oxygen	0.11	−3.54	3.76	0.95

MPAP: mean pulmonary arterial pressure

Table 4: Effect of different drugs on TPG

Drug	Change in TPG (mmHg)	Lower confidence interval	Upper confidence interval	*P* value
Prostacyclin inhaled	−5.81	−9.53	−2.086	0.001
Prostacyclin IV	−4.48	−7.64	−1.324	0.005
Prostaglandin E1	−4.62	−5.89	−3.346	<0.0001
Milrinone	−1.46	−3.99	1.068	0.237
Nitroglycerin	−1.00	−5.61	3.606	0.603
Nitric oxide	−6.37	−7.78	−4.959	<0.0001
Nitroprusside	−0.79	−2.63	1.052	0.131
Dobutamine	1.00	−2.94	4.940	0.570
Oxygen	−1.36	−4.20	1.482	0.285

TPG: transpulmonary gradient

Table 5: Effect of different drugs on CI

Drug	Change in CI	Lower confidence interval	Upper confidence interval	*P* value
Prostaglandin E1	0.22	−0.11	0.55	0.23
Sildenafil	0.45	0.21	0.69	0.01
Milrinone	0.6	0.27	0.93	0.01
Nitric oxide	0.07	−0.07	0.21	0.34
Sodium nitroprusside	0.7	0.37	1.03	<0.01
Oxygen	0.125	−0.04	0.29	0.18

CI: cardiac index

TPG was reduced to the greatest extent by NO, and then by inhaled or intravenous prostacyclin and PGE1, and to a lesser degree by sodium nitroprusside. Inhaled NO was statistically a better drug than dobutamine and nitroprusside for TPG reduction.

CI and cardiac output (CO) were less consistently reported and meaningful calculations were available only for few medications (sildenafil, milrinone, and sodium nitroprusside increased CI by 0.45, 0.6, and 0.7 mL/kg/min, respectively).

Table 6: Effect of different drugs on PCWP

Drug	Change in PCWP (mmHg)	Lower confidence interval	Upper confidence interval	*P* value
Prostacyclin inhaled	−2.65	−9.27	3.97	0.44
Prostacyclin IV	−1.73	−7.37	3.91	0.56
Prostaglandin E1	−4.4	−6.71	−2.09	0.01
Sildenafil	−3.02	−7.25	1.21	0.18
Milrinone	−5.59	−9.49	−1.69	0.01
Nitroglycerin	−8	−17.37	1.37	0.11
Nitric oxide	3.8	1.25	6.35	0.01
Sodium nitroprusside	−13.92	−17.62	−10.22	<0.0001
Dobutamine	−1	−8.98	6.98	0.81
Oxygen	0.8	−2.73	4.33	0.66

PCWP: pulmonary capillary wedge pressure

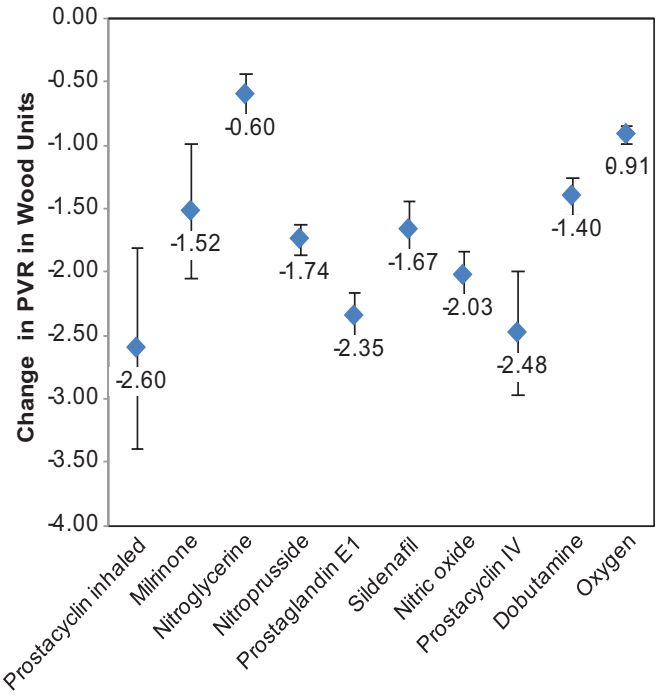

Figure 1: Effect of different drugs on pulmonary vascular resistance.

The PCWP, as expected, was most dramatically decreased with sodium nitroprusside, and then by nitroglycerin and milrinone, and it slightly increased with inhaled NO. Sodium nitroprusside was statistically a better drug than all the analyzed drugs for PCWP, decreasing it by 14 mmHg, followed by nitroglycerin with an 8 mmHg decrease.

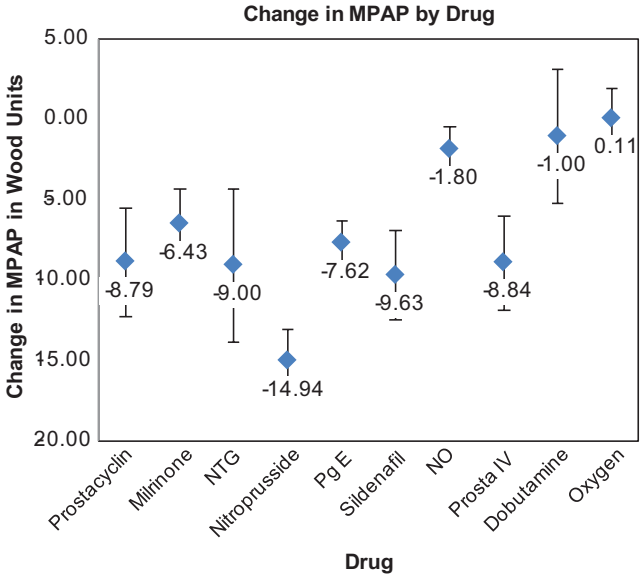

Figure 2: Effect of different drugs on mean pulmonary arterial pressure.

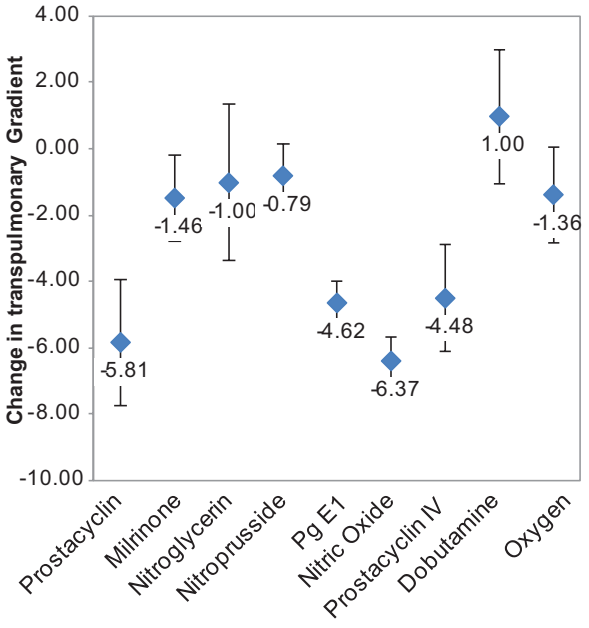

Figure 3: Effect of different drugs on transpulmonary gradient.

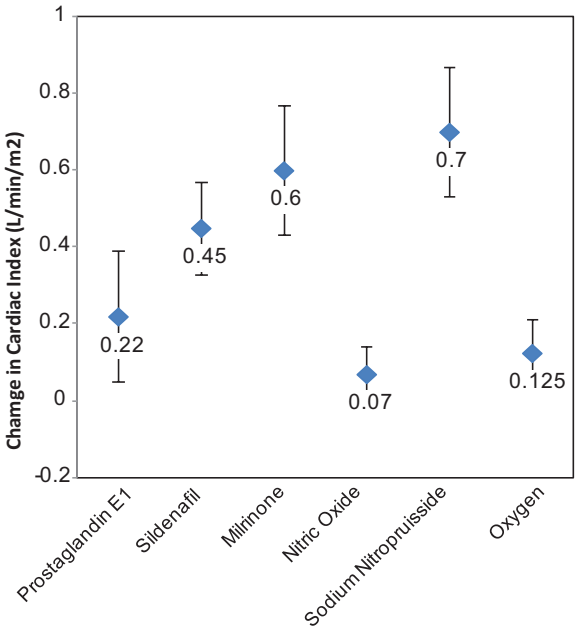

Figure 4: Effect of different drugs on cardiac index.

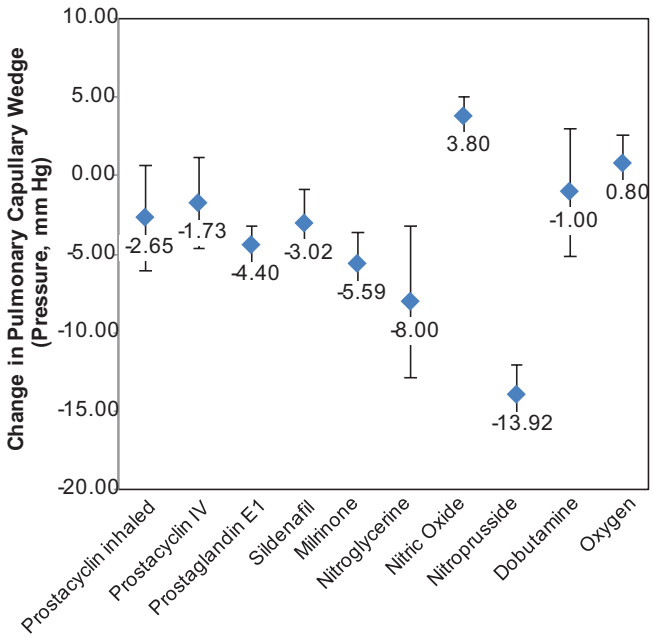

Figure 5: Effect of different drugs on pulmonary capillary wedge pressure.

The data are very inconsistent in terms of the clinical outcomes (i.e., how many patients became eligible for heart transplant as a result of the testing). Different authors used different criteria which made the comparison almost impossible. Only a few papers report the number of patients whose PVR decreased to less than 2.5 WU, or TPG to less than 15 mmHg. Based on these data, outcomes were usually suboptimal with nitroglycerin and sodium nitroprusside (Table 1). The responders constituted only 33% for each of them.[24] Much better results were achieved with PGE1 (76-80%).[20,24] Radovancevic et al.,[18] who tested both PGE1 and inhaled NO, reported that TPG was lowered to < 12 mmHg in 14 patients (73.7%). Of these, six (46%) responded to both drugs, four (27%) responded only to PGE1, and four (27%) responded only to NO. Lepore et al.[12] and Mahajan et al.[14] provided an identical number of responders to inhaled NO (42.8%), but the latter authors used liberal criteria of PVR less than 4 WU. Semigran et al.[19] reported a very high percentage of responders to inhaled NO and sodium nitroprusside (81.2%). In none of the studies were there deaths in the early post-transplant period due to right ventricular failure.

DISCUSSION

In this meta-analysis, we summarized and analyzed the data published in small single center series on hemodynamic effects of various drugs used for reversibility testing of PH in advanced HF. We found that prostacyclin, in either inhaled or intravenous form, is better than the majority of published drugs for reduction of both PVR and TPG.

There were several challenges in conducting this study because the data were coming from multiple sources and there was no unified protocol. As shown in Table 1, drugs were used in various ways and doses. For instance, inhaled NO was given at a rate ranging from 5 to 80 parts per million (ppm). Fortunately, some investigators compared the effects of multiple doses and found no difference.

In the study by Fojón et al.,[23] NO concentration ranged from 5 to 20 ppm, and concentrations of 10 ppm and higher did not produce any further hemodynamic changes. No difference was found in hemodynamic effects of NO in the dose of 20 versus 40 ppm,[14] 10 to 30 ppm,[17] 10 and 20 ppm,[15] or 20, 40, and 80 ppm.[22] Based on these findings, we pooled all the data on NO regardless of used concentration.

The situation was even more difficult with prostacyclin, given by some in the inhaled form and by others intravenously. Because we were not sure how to bring the doses to some common denominator, we analyzed them as two different entities. Sildenafil in the dose of 50 mg decreased MPAP better than a dose of 25 mg, but hemodynamic data were presented by authors for the whole group,[8] which forced us to pool all doses of this drug together and analyze them as a whole.

The comparison of two or more agents in the same group of patients was reported by several authors, but small sample sizes made these comparisons inconsistent. According to some data, inhaled prostacyclin and NO, as well as NO and PGE1, effected PVR and TPG similarly.[17,18] On the other hand, inhaled prostacyclin or PGE1 caused greater decrease in pulmonary artery systolic pressure (PASP), MPAP, and TPG than nitroprusside.[24,27]

Interestingly, many authors reported that prostacyclin and sildenafil increased CI more than other agents.[12,17,28-30] With regard to mean or SPAP, the data vary the most. Inhaled prostacyclin decreased MPAP to a greater degree than NO in one study,[17] while in another study the changes in the MPAP between the two drugs were similar.[29]

It has been described that NO causes some elevation in PCWP.[10] Increase in left ventricular filling due to increased pulmonary venous return to a poorly compliant left ventricle may result in an acute pulmonary edema.[19,31] This finding has not been confirmed by other authors. Sablotzki et al.[17] found no increase of PCWP during NO inhalation. To the contrary, they observed a falling trend in wedge pressure with NO inhalation. In their study, the main disadvantage of NO inhalation was an increase in PA pressure and PVR in four patients (28.6%). However, in the pooled analysis, some increase in PCWP by inhaled NO transformed into dramatic decrease in TPG calculated as difference between MPAP and PCWP.

Not surprisingly, the combination of agents resulted in more profound hemodynamic changes than in using separate drugs. Combinations of sildenafil and inhaled NO[12] and NO and dipyridomole[12] were well-tolerated and resulted in more profound favorable changes than each of the individual drugs.

Some comparisons were made in retrospective studies which were not included in our main analysis. In recipients of heart and lung transplantations, inhaled NO and inhaled prostacyclin decreased pulmonary arterial pressure similarly,[32] but prostacyclin lowered PVR better than with nitroglycerin, and comparable to sodium nitroprusside.[33]

In another retrospective study, there was no difference in hemodynamic effects between inotropes (dopamine or dobutamine), venodilators (nitroglycerin or sodium nitroprusside), and intravenous prostacyclin. The amount of patients who became eligible for heart transplant was also similar: 50% of patients on inotropes, 45.5% patients on vasodilators, and 50% of patients on prostacyclin.[34]

It is known that patients with a PVR greater than 2.5 WU have early post-transplant mortality, which is tripled when compared with patients without PH. However, their survival improves dramatically if their PVR can be decreased to the levels below 2.5 WU.[35] In order for the patients to be listed as transplant candidates, their PH has to be reversible. It appears that a decrease in PVR is the most important hemodynamic gain that can be obtained from multiple pulmonary vasodilators.

In HF, elevation of pulmonary arterial pressure initially occurs because of increase in left ventricular end diastolic pressure and is proportionate to PCWP. However, if congestion persists, patients develop vasoconstriction of pulmonary vasculature which causes further increase in PASP. The first component is reversible with normalization of intracardiac filling pressures which is traditionally achieved with diuresis and vasodilators like nitroglycerin or nitroprusside. Their use is frequently limited by a concomitant decrease in systemic vascular resistance and systemic pressure. Inotropes like milrinone decreases PCWP to a lesser extent (Table 6 and Fig. 5). Optimization of PCWP is a routine target during patient

management, including the pre-transplant period. Increased TPG and PVR reflect the next stage of PH in HF when pulmonary arterial pressure increases out of proportion to PCWP. Because the goal of pulmonary reversibility testing is to reverse this component of PH, prostacyclin and PGE1 are preferable agents to be used in this setting.

Some prior findings were in concert with our results. Inhaled prostacyclin effectively reversed PH in patients resistant to sodium nitroprusside,[27] and caused a significantly greater reduction in pulmonary arterial pressure and an increase in CO than with inhaled NO.[11,17] Other data have indicated that patients unresponsive to NO may be responsive to PGE1.[18] In another study, all patients with PH experienced a successful reduction in PVR by using PGE1 or prostacyclin; their 30-day and 10-year survival rates after orthotopic cardiac transplantation were similar to patients without PH.[36]

In a more chronic setting, continuous infusion of PGE1 for six to eight days resulted in decrease of PVR (initially elevated up to 13.9 WU) in all 11 patients, and eight of them proceeded to heart transplant, with no right ventricular failure after the surgery.[7] Unfortunately, results from the first trial where prostacyclin was associated with bad outcomes in HF patients, effectively stopped any large scale testing of prostaglandins in HF with elevated pulmonary pressure.[37] Meanwhile, PH was not an inclusion criterion in that trial, and therefore results are not applicable to patients with advanced HF and severe PH.

It is unclear whether the results of acute testing can be extrapolated to chronic management, but based on our results prostacyclin and PGE1 and perhaps sildenafil (Table 4 and Fig. 3, data on TPG) may be considered the agents of choice for pre-transplant management of patients with high PVR.

Limitations

This meta-analysis is based on small studies and they vary in protocols. Additionally, the bias and limitations in the individual studies themselves become part of this analysis. Effects of studied drugs in the setting of reversibility testing may or may not sustain long-term. However, this is the first meta-analysis in this field and conducting bigger, well-planned studies—where an effective sample size will be the only way to overcome this inherent limitation—is needed.

In conclusion, different drugs used for testing of reversibility of PH in advanced HF provided significant effects on hemodynamic parameters. Our meta-analysis shows that nitroglycerin and sodium nitroprusside cause the most profound effect on PCWP, MPAP, and SPAP. Sildenafil is good but not as effective as other drugs for reduction of PVR. Prostacyclin, PGE1, and inhaled nitric oxide appear to be superior to other drugs in their effects on PVR. Sildenafil produces higher increase in CI than prostaglandins. Although no single drug appears to be superior to others in all respects, prostaglandins and sildenafil might be considered the drugs of choice for pre-transplant management of patients with high PVR. Further research is needed to test whether acute hemodynamic effects of the drugs sustain in chronic setting.

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