Treatment of Ethanol-Induced Acute Pulmonary Hypertension and Right Ventricular Dysfunction in Pigs, by Sildenafil Analog (UK343-664) or Nitroglycerin.

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Short running title: Ethanol-Induced Acute Pulmonary Hypertension in Pigs
Summary

Background: In patients at risk for sudden ethanol (ETOH) intravascular absorption, prompt treatment of pulmonary hypertension (PHTN) will minimize the risk of cardiovascular decompensation. We investigated the haemodynamic effects of intravenous ETOH, and the pulmonary vasodilatory effects of a sildenafil analog (UK343-664) and nitroglycerin (NTG) during ETOH-induced PHTN in pigs.

Methods: We studied pulmonary and systemic haemodynamics, and right ventricular rate or time derivative of pressure rise during ventricular contraction = dP/dT as an index of contractility, in 23 pigs. ETOH was infused at a rate of 50 mg kg\(^{-1}\) min\(^{-1}\), titrated to achieve a twofold increase in mean pulmonary arterial pressure (MPAP), and then discontinued. The animals were randomized to receive an infusion of 2 ml kg\(^{-1}\) (n=7) normal saline, a 500 µg kg\(^{-1}\) bolus of UK343-664 (n=8), or NTG 1 µg kg\(^{-1}\) (n=8); each was given over 60 seconds.

Results: Following ETOH infusion, dP/dT decreased central venous pressure (CVP) and MPAP increased significantly, resulting in significantly increased pulmonary vascular resistance (PVR). Within 2 minute after treatment with either drug, CVP, heart rate (HR) and the systemic vascular resistance-to-pulmonary vascular resistance (SVR/PVR) ratio returned to baseline. However at that time, only in the UK343-664 group, MPAP and dP/dT partially recover and were different from the respective values at PHTN stage. NTG and UK343-664 decreased PVR within 2 minutes, from 1241(579) and 1224(494) dyne-cm-sec\(^{-5}\) which were 3-4 fold increased baseline values, to 672(308) and 538(203) dyne-cm-sec\(^{-5}\), respectively. However only in the UK343-664 group, changes from baseline PVR values after treatment, were significant compared to the maximal change during target PHTN. Neither drug caused a significant change in SVR.

Conclusions: In this model of ethanol-induced PHTN, both UK343-664 and NTG were effective pulmonary vasodilators with a high degree of selectivity. However, the changes from baseline values of PVR, and the partial recovery of systemic pressure and RV contractility
compared to the maximal change during target PHTN, were significant only in the sildenafil analog group.

**KEYWORDS:** Ethanol, sildenafil, nitroglycerin, pulmonary hypertension, right ventricular dysfunction

**Word Count:** 2999
**Introduction**

Absolute ethyl alcohol (ETOH) is used with increased frequency in the treatment of conditions such as percutaneous ablation of unresectable hepatic tumours, sclerotherapy of esophageal varices, ventricular septal ablation, and intravenous embolization of arteriovenous malformations.\(^1\)\(^3\) Although the incidence of complications with the use of ETOH is relatively low, episodes of cardiopulmonary collapse have been described.\(^4\)\(^7\) The postulated mechanism is severe pulmonary vasoconstriction from the sudden passage of ETOH into the pulmonary circulation,\(^7\)\(^8\) causing pulmonary hypertension (PHTN) and right ventricular (RV) strain.\(^9\)\(^10\) Under normal physiological conditions, the endothelium maintains a low pulmonary vascular resistance (PVR) by producing two potent vasodilators, an endothelium-derived relaxing factor, which is nitric oxide (NO), and prostacyclin.\(^11\) Pulmonary vasorelaxation can be achieved with drugs that increase pulmonary smooth muscle cAMP or cGMP.\(^12\)\(^13\) The predominant pathway for inactivation of these cyclic nucleotides in the pulmonary vasculature is via phosphodiesterase enzymes type III (PDEIII) and type V (PDEV).\(^14\)\(^15\) The oral PDEV inhibitor, sildenafil, has been shown to reduce PVR in patients with chronic PHTN.\(^16\)\(^20\) The NO-donor drugs, nitroglycerin (NTG) and sodium nitroprusside,\(^21\) have been used clinically to produce vasodilatation during the past 30 years. One purpose of this study was to investigate and suggest possible treatment in such catastrophes when intravenous administration of ETOH causes PHTN and alterations in pulmonary and RV haemodynamics. We hypothesized that the sildenafil analog (UK343-664), or NTG, would have clinically effective selective pulmonary vasodilatory effects during ETOH-induced pulmonary vasoconstriction, or will provide a greater contribution to the maintenance of vascular tone in the pulmonary circulation than the systemic circulation. In order to evaluate our hypothesis we used an established animal model creating PHTN with ETOH infusion.\(^22\)
Methods

This study was designed as a prospective animal study. The protocol was approved by the University of Florida Institutional Animal Care and Use Committee. Animals were handled in accordance with guidelines established by the National Institutes of Health (NIH publication 85-23, revised 1985).

Twenty-three of 30 domestic pigs (45-50 kg), were studied to completion. The animals were premedicated with intramuscular ketamine (50 mg kg\(^{-1}\)) and anesthetized with isoflurane in 50% O\(_2\). A tracheostomy was performed and the animals were mechanically ventilated using 12 breaths min\(^{-1}\), and tidal volumes of 12 ml kg\(^{-1}\) to maintain an end-tidal CO\(_2\) between 32 and 36 mmHg. Mechanical ventilation was maintained with the use of a Narkomed 4 anaesthesia machine (North American Drager, Telford, Pennsylvania). Pancuronium was used for muscle relaxation during the surgical preparation. A 7-French (Fr), pressure-tipped, flotation pulmonary artery catheter (Millar Instruments Inc, Houston, Texas) was inserted via the right internal jugular vein into the main pulmonary artery through an 8-Fr Cordis introducer (Arrow International, Reading, PA). A 7-Fr, triple lumen, central venous catheter was placed through the left internal jugular vein. The left carotid artery was exposed, and a 5-Fr pressure-tipped catheter (Millar Instruments Inc, Houston, Texas) was placed and advanced into the ascending aorta for continuous arterial pressure monitoring. A median sternotomy was then performed and the heart placed in a pericardial cradle. A 5-Fr pressure-tipped catheter (Millar Instruments Inc, Houston, TX) was inserted via a small stab wound into the RV cavity for measurement of RV pressure and RV dP/dT. Cardiac output (CO) was measured with a 10 mm perivascular ultrasound probe placed in the main pulmonary artery. All transducers were connected to a biomedical amplifier (Grass model 7D, Grass Instruments Co, Quincy, Massachusetts). The signals were digitized and continuously recorded at 200 Hz on a personal computer (Sonometrics Corp, London, Ontario, Canada) for later analysis.
Maintenance of intravascular volume was accomplished with lactated Ringer’s solution administered by continuous infusion through a peripheral vein at a rate of 10 ml kg\(^{-1}\) h\(^{-1}\). Normothermia (pulmonary artery temperature of 37°C) was maintained by the application of a warming blanket. All animals were allowed to stabilize for 60 minutes following the surgical preparation prior to data collection.

**Haemodynamic Measurements**

Haemodynamic measurements included systemic mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), RV pressure (RVP), central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), and CO. Pulmonary and systemic haemodynamics and RV dP/dT, as an index of contractility, were measured. PVR and systemic vascular resistance (SVR) were calculated using standard formulas (MAP-CVP/CO \(\times 80 = SVR\); MPAP-PAOP/CO \(\times 80 = PVR\)).

**Experimental Protocol**

Undiluted ETOH was infused via a central venous catheter at a rate of 2 ml min\(^{-1}\) (approximately 50 mg kg\(^{-1}\) min\(^{-1}\)) until a twofold increase in MPAP was reached or a maximum of 20 ml were infused. Two previous animals (not included in this study) suffered from acute RV failure when a dose of 5 ml of ETOH was administered as a rapid intravenous bolus (as is frequently administered for ablation procedures) and could not be resuscitated. Therefore, we decided to proceed with the slower infusion of ETOH. When the target MPAP was reached, the infusion was discontinued and the animals observed until haemodynamics returned to within 10% of baseline.

Data were collected at baseline, when the target MPAP was achieved, and after discontinuation of the infusion. The animals were randomized to receive an infusion of 2 ml kg\(^{-1}\) (n=10) of normal saline (NS), 500 µg kg\(^{-1}\) bolus of UK343-664 over 60 seconds with NS infusion (N=10), or NTG 1 µg kg\(^{-1}\) over 60 seconds (N=10). The control group treated
with NS was essential to evaluate the changes related to the insult (PHTN) without drug effect = sham group. Otherwise, changes post-PHTN could be related to time effect (without drugs), rather to treatment (= drug effect).

The size of the experimental groups was similar to previous and similar experiments.\textsuperscript{21,23-25} The treatment dose of \textit{UK343-664} was decided based on previous studies were it was given intravenously in 0.3-0.5 mg kg\textsuperscript{-1} boluses over 1-2 minutes every 4 hours.\textsuperscript{17 -19, 24} Data were continuously recorded until haemodynamics returned to within 10\% of baseline. Statistical analysis was performed with ANOVA. A p<0.05 was considered significant.

At the end of the experiment, the animals were euthanased with an intravenous injection of potassium chloride to achieve asystole, and the general anaesthesia was discontinued.

\textit{Drugs}

Sildenafil Analog (UK343-664) (provided by Pfizer Pharmaceuticals, Sandwich, Kent England).

\textit{Statistical Analysis}

Values were expressed as mean (standard deviation). A two-way analysis of variance (ANOVA) by repeated measure design was used, followed by Student Newman-Keuls test for multiple comparisons to determine significant variability within groups. The control group was used to test the effect of insult (PHTN) alone without any drug intervention. Data from control and intervention groups were compared statistically by nonpaired \textit{t} test with Bonferroni correction. A one-way ANOVA was used for baseline measurements to determine whether the 3 groups were comparable prior to the interventions. A p<0.05 was considered significant. The distributions of % change within and between groups, was compared by SAS.
Results

Twenty-three of 30 pigs were studied to completion; the number of subjects lost to study was similar for all 3 groups studied. Three control animals did not survive the entire experiment; in 2 animals in each of the 2 treatment groups, due to technical problems in cannulation and preparation it was not possible to complete the protocol. Thus, 7 pigs were excluded from data analysis, and the number of animals studied to completion was 23: n=7 in control group, n=8 in the UK343-664 group, and n=8 in the NTG group.

Measured haemodynamic data (Table 1), calculated LV and RV performance data (Table 2) and changes during PHTN following ETOH, were similar in all 3-treatment groups. Two minutes following treatment with either drug (UK343-664 and NTG, but not with NS), CVP and HR (Table 1), and SVR/PVR ratio (Table 2) returned to baseline. However, MPAP remained increased [from 38(6) and 36(3) before treatment to 30(5) and 30(5) mmHg after treatment, respectively; Table 1], and dP/dT remained decreased [from 187(20) and 203(35) before treatment to 252(29) and 252(20) mmHg sec\(^{-1}\) after treatment, respectively; Table 2] from baseline. The differences were significant with p< 0.001 for all values compared to baseline values of 20(3) and 19(2) mmHg for MPAP and 351(42) and 361(51) mmHg sec\(^{-1}\) for dP/dT, respectively. Only in the UK343-664 group did MPAP and dP/dT partially recover (still significantly different from baseline) and were different (p=0.03) from the respective values immediately following ETOH infusion (PHTN stage). However, there were no significant differences in the values of MPAP and dP/dT, between the three groups.

The changes in PVR and SVR induced by either treatment, are presented in Figure. The infusion of NTG and UK343-664 decreased PVR significantly, within 2 min after the treatment drug was administered [from 1241(579) and 1224(494) to 672(308) and 538(203) dyne-cm-sec\(^{-5}\), respectively] (p=0.03 for both). Nitroglycerin and UK343-664 decreased
MPAP by 16% and 23% (Table 1) and PVR by 40% and 53% (Figure) respectively, within 2 minutes after the drug was infused. Changes in SVR with either treatment drug (Figure) were non-significant. Thus, the decreases in PVR and SVR induced by treatment, expressed as a percentage of the value recorded during the PHNT stage, demonstrated relative selectivity in PVR decrease (compared to SVR decrease) with NTG and UK343-664. However, we found significant difference between the groups measuring PVR post-treatment in the sildenafil-analog group, when compared to the control group (p< 0.05; Figure). The changes in PVR in the UK343-664 groups 2 min after treatment were significant compared to the maximal change during target PHTN. This difference along time (2 minutes post treatment) from the maximal change during PHTN was not apparent in the NTG or the NS group.

The percent changes in PVR and SVR from baseline after each treatment in all groups are presented in Table 3. Both treatment drugs decreased the PVR from 3-4 fold-increased values of 353(230) and 444(169) %change to 1-2 fold of 156(103) and 110(51) %change, respectively (p<0.0.5 compared with pretreatment value, only for UK343-664). Thus, the changes in PVR in the UK343-664 groups 2 min after treatment were significant compared to the maximal change during target PHTN. This difference along time (2 minutes post treatment) from the maximal change during PHTN was not apparent in the NTG or the NS group. The latter represents the control group with time effect only, and no-drug effect. Neither NTG nor UK343-664 caused a significant change in SVR (Table 3).

**Discussion**

In this model of ETOH-induced PHTN, both the sildenafil analog and NTG were effective pulmonary vasodilators with a high degree of selectivity. However, the changes from baseline values of PVR, and the partial recovery of systemic pressure and RV contractility
compared to the maximal change during target PHTN, were significant only in the sildenafil analog group.

**Treatment of ETOH-Induced PHTN: NTG (NO-donor)**

The sildenafil analog and low-dose NTG both have selective pulmonary vasodilatory effects during ETOH-induced pulmonary vasoconstriction. The NO-donor drugs, nitroglycerin (NTG) or sodium nitroprusside, have long been used clinically to produce pulmonary vasodilation.\(^{21,25}\) All agents presently used as NO donors are precursor drugs, with NO being the essential product that ultimately promotes the pulmonary vasodilatation. NTG is preferred clinically because it influences the preload, rather than the afterload, of the cardiovascular system, and thus the reason we chose to use it in our study. Interestingly, most of these pro-drugs displayed nearly identical dose-effect relationships with respect to onset, extent, and duration of pulmonary vasodilatation, whether administered via inhalation or infused into the pulmonary artery of the isolated lungs. Unfortunately, high levels of NTG will cause systemic and pulmonary vasodilation.\(^{26}\)

**Treatment of ETOH-Induced PHTN: Sildenafil (PDEV-Inhibitor)**

Prostacyclin is the other intravenous drug that is widely used to treat primary or secondary PHTN in adults and children.\(^{27}\) It represents a group of compounds that stimulate adenylate cyclase,\(^{13}\) thus increasing cAMP concentrations as PDEII inhibitors will do. However, we chose to study a sildenafil analog (a PDEV inhibitor that enhances intracellular cGMP levels and affects the pulmonary circulation), because we recently demonstrated its interaction with PDEIII inhibitors during acute PHNT.\(^{24}\) This sildenafil analog was found to have additive effects on pulmonary vasodilatation without the risk of increased systemic vasodilation.\(^{24}\) The efficacy of sildenafil in achieving pulmonary vascular relaxation has been also demonstrated in the acute and chronic setting.\(^{16,28}\) Although the negative inotropic effects of increased cGMP have been described, there is little evidence that sildenafil causes decreased contractility. In fact, recent data suggest a cardioprotective effect of sildenafil against myocardial ischemia and reperfusion injury.\(^{29}\) Partial or no improvement in RV
contractility was documented in our present or previous studies with sildenafil, and negative inotropic effects were not found.\textsuperscript{24}

It is important to note that we,\textsuperscript{24} like others,\textsuperscript{30} observed a relative degree of \textit{pulmonary selectivity} after the administration of sildenafil. In the present study, neither low dose (1 µg kg\textsuperscript{-1} min\textsuperscript{-1}) NTG nor the sildenafil analog caused a significant change in SVR, but both caused a significant change in PVR. Also, the SVR/PVR ratio was restored from the low PHTN levels within 2 min after treatment with the sildenafil analog or low dose NTG. Thus, in this model of ETOH-induced PHTN, the sildenafil analog or low dose NTG were effective pulmonary vasodilators with a high degree of selectivity.

This suggests that during acute PHTN (such as that induced by ETOH), a PDEV inhibitor may provide significant pulmonary vasorelaxation, without a significant risk for systemic hypotension. The perioperative treatment of acute PHTN with traditional agents, such as nitrosodilators, beta adrenergic agonists, and PDEIII inhibitors, is limited by the risk of hypotension as a result of their systemic vasodilatory effects.\textsuperscript{31,32} Patients with preexisting PHTN seem to be at higher risk because they frequently require high doses of these drugs. Although inhaled NO is a potent selective pulmonary vasodilator, it has several limitations: the delivery system, rebound PHTN upon withdrawal, and monitoring for toxicity.\textsuperscript{33} Reports have recently described the use of oral sildenafil in cardiac surgical patients to facilitate the withdrawal of NO during placement of ventricular assist devices or in the postoperative period,\textsuperscript{17,34} suggesting a possible role for sildenafil in the treatment of perioperative pulmonary hypertension. It should be noted that the changes in PVR with the sildenafil analog and NTG were significant, but were not apparent with the control (NS) group, which was effected only by time and not by any drug.\textsuperscript{2}

We did not have another or separate control group, \textit{with treatment without insult}. However, other researchers studied the drug effect of sildenafil and/or NTG on SVR, with or without insult. A dose response study with sildenafil (0.4-3mg kg\textsuperscript{-1}) in the presence and absence of an insult (acute lung injury), was conducted in piglets\textsuperscript{35}. 
The effect on PVR and MPAP (30% decline) was achieved at the lowest dose in the injured and non-lung-injured animals. Sildenafil reduced SVR at the lowest dose (similar to the dose used in our study) in lung injured animals, but this occurred only at higher doses in the non-lung-injured animals. Another study in sheep which evaluated the effect of higher doses of sildenafil (0.7 mg kg\(^{-1}\) with continuous infusion) before and after insult (fat embolization), found a significant change (50%) in SVR before the insult, but no significant changes in any systemic variable after the insult in the sildenafil group\(^{36}\). Sildenafil in doses 0.06-2.0 mg kg\(^{-1}\) per hour in injured (hypoxic) neonatal piglets\(^{37}\), did not cause a decrease of SAP and SVR in the low-medium doses (lower than 2mg kg\(^{-1}\)), and had a better pulmonary selectivity (PAP/SAP ratio) in a relatively low (0.2 mg kg\(^{-1}\)) dose, which is closer to the dose we used. In conclusion, sildenafil should be administered with caution in the presence of lung injury because of a dose related increase in systemic vasodilatation. The knowledge about NTG effect on systemic haemodynamics with an intact lung is very clear. Unfortunately, high levels of NTG will cause systemic and pulmonary vasodilation.\(^{26}\)

Another limitation is the issue of using dp/dt a measurement that on one hand (being less affected by increases in afterload) represents a considerable RV dysfunction caused by the ethanol prior to any drug effect, but on the other hand (since it is load-dependent) will not represent acute changes in loading conditions. Acknowledging this limitation, our data for dp/dt over time suggests that there is no significant recovery in RV function, except with sildenafil when compared to the insult (ETOH) value (table 2). It is important to mention that we, similar to others, observed a relative degree of stability in RV contractility and of pulmonary selectivity after administration of sildenafil\(^{30,38-41}\).
Also, we did not evaluate any haemodynamic effect of drug combination of sildenafil and NO donor compound (like NTG). This combination was recently studied in a dog model, which demonstrated that sildenafil alone produced maximum attenuation of pulmonary-injury-induced PHTN as far as NO-cGMP pathway is concerned. In another study pretreatment with high dose sildenafil (1mg kg$^{-1}$ followed by 0.3 mg kg$^{-1}$ h$^{-1}$) decreased SVR and MPAP and increased plasma cGMP concentrations, which was further increased by SNP but not affected by NTG in low-to-high (2-32 µg kg$^{-1}$ min$^{-1}$) doses.

We did found some advantages to the use of sildenafil-analog in the treatment of acute PHTN. Only in the UK343-664 group did MPAP and dP/dT partially recover (still significantly different from baseline) and were different from the respective values immediately following ETOH infusion (PHTN stage). Also, the changes in PVR in the UK343-664 groups 2 min after treatment were significant compared to the maximal change during target PHTN. This difference along time (2 minutes post treatment) from the maximal change during PHTN was not apparent in the NTG or the NS group. We found significant difference between the groups measuring PVR post-treatment in the sildenafil-analog group, when compared to the control group. When we combine these findings to the knowledge that high levels of NTG will cause systemic and pulmonary vasodilation, our preference is sildenafil-analog treatment.

In conclusion, this study demonstrated effective treatments for significant pulmonary vasoconstriction and RV dysfunction that may occur with intravenous ETOH. In patients at risk for sudden intravascular absorption of ETOH, an increased level of awareness for this
potential complication, together with prompt treatment of PHTN with the sildenafil analog or with a low dose of a NO-donor drug will minimize the risk of cardiovascular decompensation, and may be the treatment of choice in such catastrophes.
References


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### Table 1. Measured Haemodynamic Data Before and After ETOH Administration

<table>
<thead>
<tr>
<th>Group</th>
<th>CVP (mm Hg)</th>
<th>PAOP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>MPAP (mm Hg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>8.6 (2.0)</td>
<td>9.9 (3.6)</td>
<td>10.0 (3.1)</td>
<td>68.1 (5.3)</td>
<td>21.1 (2.1)</td>
</tr>
<tr>
<td>UK</td>
<td>9.9 (1.1)</td>
<td>8.6 (1.7)</td>
<td>8.6 (1.7)</td>
<td>75.4 (8.4)</td>
<td>19.9 (3.3)</td>
</tr>
<tr>
<td>NTG</td>
<td>10.0 (3.1)</td>
<td>8.6 (1.7)</td>
<td>8.6 (1.7)</td>
<td>79.1 (7.0)</td>
<td>19.1 (2.0)</td>
</tr>
<tr>
<td><strong>Target PHTN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>12.7 (1.8)</td>
<td>14.3 (3.1)</td>
<td>12.6 (1.7)</td>
<td>75.7 (12.5)</td>
<td>38.0 (2.9)</td>
</tr>
<tr>
<td>UK</td>
<td>*</td>
<td>*</td>
<td>9.3 (2.7)</td>
<td>75.9 (10.0)</td>
<td>*</td>
</tr>
<tr>
<td>NTG</td>
<td>13.1 (2.6)</td>
<td>*</td>
<td>9.3 (2.7)</td>
<td>86.4 (13.3)</td>
<td>*</td>
</tr>
<tr>
<td><strong>Post Drug</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2 min after</td>
<td>13.2 (2.4)</td>
<td>11.6 (2.3)</td>
<td>12.3 (3.3)</td>
<td>65.3 (7.4)</td>
<td>35.1 (2.3)</td>
</tr>
<tr>
<td>ETOH)</td>
<td>*</td>
<td>*</td>
<td>10.9 (1.5)</td>
<td>72.8 (3.3)</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10.3 (1.8)</td>
<td>83.6 (8.9)</td>
<td>*</td>
</tr>
</tbody>
</table>

UK343-664 Group (n=8), NS Group (n=7), and NTG Group (n=8)

*\( p<0.001 \) compared to baseline.

† \( p<0.05 \) compared to ETOH effect. Values represent mean (S.D.)

CVP = central venous pressure; PAOP = pulmonary artery occlusion pressure; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; \( \frac{dP}{dT} \) = first time derivative of ventricular pressure; HR = heart rate; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; ETOH = absolute ethanol; UK343-664 = Sildenafil analog; PHTN = pulmonary hypertension (when target MPAP was achieved).
Table 2. Measured and Calculated Haemodynamic Data (LV/RV performance) Before and After ETOH Administration

<table>
<thead>
<tr>
<th></th>
<th>CO (Lit min⁻¹)</th>
<th>RV dP/dT (mm Hg sec⁻¹)</th>
<th>SVR/PVR Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NS</td>
<td>UK</td>
<td>NTG</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>2.9 (0.3)</td>
<td>3.4 (0.6)</td>
<td>3.7 (1.2)</td>
</tr>
<tr>
<td></td>
<td>360.7 (54.9)</td>
<td>350.5 (42.3)</td>
<td>361.3 (51.4)</td>
</tr>
<tr>
<td><strong>Target PHTN</strong></td>
<td>3.4 (0.5)</td>
<td>2.9 (0.8)</td>
<td>2.9 (1.1)</td>
</tr>
<tr>
<td></td>
<td>360.7 (54.9)</td>
<td>350.5 (42.3)</td>
<td>361.3 (51.4)</td>
</tr>
<tr>
<td><strong>Post Treatment</strong></td>
<td>2.4 (0.3)</td>
<td>3.0 (0.5)</td>
<td>2.7 (0.9)</td>
</tr>
<tr>
<td>(2 min)</td>
<td>360.7 (54.9)</td>
<td>350.5 (42.3)</td>
<td>361.3 (51.4)</td>
</tr>
</tbody>
</table>

UK343-664 Group (n=7), NS Group (n=8), and NTG Group (n=8).

* p<0.001 compared to baseline.

† p<0.05 compared to ETOH effect. Values represent mean (S.D.)

CO = cardiac output; RV= right ventricle; dP/dT= first time derivate of ventricular pressure; SVR=systemic vascular resistance; PVR=pulmonary vascular resistance; ETOH = absolute ethanol; UK343-664= Sildenafil analog; PHTN = pulmonary hypertension (when target MPAP was achieved).
Figure:

Changes in PVR and SVR after ETOH-Induced Pulmonary Hypertension, and Post Treatment with UK343-664 or NTG

<table>
<thead>
<tr>
<th></th>
<th>SVR</th>
<th>PVR</th>
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<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK343-664</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Control**: Baseline, Post Treatment

**NTG**: Baseline, Post Treatment

**UK343-664**: Baseline, Post Treatment

**PVR** and **SVR** values are presented in dynes·cm⁻⁵·sec⁻¹.
*p<0.001 compared to baseline value.
†p<0.05 post treatment value, compared to target pulmonary hypertension (PHTN) values
‡p<0.05 compared to control group value, in the same time period.

Values represent mean (S.D.); ETOH = absolute ethanol; PVR=pulmonary vascular resistance; SVR=systemic vascular resistance; NTG= nitroglycerin; Control = treatment with NS (normal saline). Post Treatment = post UK343-664 500 μg kg⁻¹ bolus over 60 seconds, or post NTG 1 μg kg⁻¹, or infusion of NS 2 ml kg⁻¹, 2 minutes after treatment.
Table 3. PVR and SVR Percent Changes From Baseline, After ETOH and Treatment Administration, All Groups (n=23)

<table>
<thead>
<tr>
<th>% Change</th>
<th>PVR % Change</th>
<th></th>
<th>SVR % Change</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>NS</td>
<td>NTG</td>
<td>UK343-664</td>
<td>NS</td>
</tr>
<tr>
<td>Target PHTN</td>
<td>301.1 (153.4) *</td>
<td>352.9 (230.6)*</td>
<td>444.0 (168.6)*</td>
<td>20.1 (32.2)</td>
</tr>
<tr>
<td>Post Treatment</td>
<td>169.9 (71.5)</td>
<td>156.2 (103.1)</td>
<td>109.6 (51.3) †</td>
<td>6.9±19.4</td>
</tr>
<tr>
<td>(2 min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05 compared to baseline (0% change).

† p<0.05 compared to target pulmonary hypertension (PHTN) value=ETOH effect.

Values represent mean (S.D.).

NS= normal saline; NTG= nitroglycerin; ETOH = ethyl ethanol; SVR=systemic vascular resistance; PVR=pulmonary vascular resistance; Post Drug = UK343-664 500 µg kg⁻¹ bolus over 60 seconds, or NTG 1 µg kg⁻¹, or infusion of NS 2 ml kg⁻¹, 2 minutes post treatment; PHTN = pulmonary hypertension (when target MPAP was achieved).