Aus dem Institut für Physiologie

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DISSERTATION

Inhaled vasodilators as a new treatment strategy in pulmonary hypertension with left heart disease

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Inhalierte Vasodilatoren als neue Behandlungsstrategie der pulmonalen Hypertonie bei Linksherzerkrankung

Patienten mit kongestiver Herzinsuffizienz (CHF) entwickeln aufgrund eines Anstiegs des pulmonalen Gefäßwiderstands (PVR) eine pulmonale Hypertonie (PHT), und könnten daher von inhalierten Vasodilataren zur selektiven Senkung des PVR profitieren. In einem Rattenmodel der CHF untersuchten wir den Effekten inhalierter Vasodilatoren auf pulmonale und systemische Hämodynamik und Lungenödem. Da CHF Patienten eine verminderte Neigung zu Lungenödemen aufweisen, untersuchten wir zudem die Effekte einer CHF auf die alveoläre Flüssigkeitsreabsorption und deren Regulation durch die endotheliale NO Bildung. CHF wurde in Ratten durch eine partielle Aortenligatur induziert. Hämodynamik und Ödem wurden nach Inhalation der Vasodilatoren Milrinon, Iloprost oder NO in Ruhe sowie nach Iloprost bei erhöhter Lungenperfusion nach Gabe des β_1-Agonisten Dobutamin gemessen. Alveoläre Flüssigkeitsreabsorption und endotheliale NO-Produktion wurden an der perfundierten Rattenlunge mittels Doppelindikatorverdünnungsmethode und Fluoreszenz-Imagings pulmonaler Endothelzellen erfasst. Die Inhalation von Milrinon, Iloprost oder NO minderte den pulmonalarteriellen Druck (PAP) und den PVR. Repetitive Inhalation von Milrinon oder Iloprost bzw. kontinuierliche NO-Inhalation erzielten eine anhaltende pulmonale Vasodilatation, wobei sich Milrinon und Iloprost dem NO überlegen erwiesen. In Ruhe induzierten pulmonale Vasodilatoren kein Lungenödem, bei erhöhter Lungendurchblutung förderte inhaliertes Iloprost jedoch die Ödembildung. Dies ließ sich auf eine Hemmung des Kitajewreflexes, der eine Vasokonstriktion präkapillärer Sphinkter zum Schutz des pulmonalen Kapillarbettes vor hohen Drücken postuliert, zurückführen. CHF Ratten zeigten eine verbesserte alveoläre Flüssigkeits- reabsorption, was sich auf eine verminderte endotheliale NO Produktion zurückführen ließ. Diese Ergebnisse zeigen, dass inhalierte Vasodilatoren bei CHF selektiv den PVR reduzieren. Während eine gesteigerte alveoläre Flüssigkeitsreabsorption bei CHF in Ruhe vor Lungenödem schützt, können inhalierte Vasodilatoren bei erhöhter Lungenperfusion durch Hemmung des Kitajew-Reflexes Ödeme verursachen.

Abstract

Patients with congestive heart failure (CHF) develop pulmonary hypertension due to an increase in pulmonary vascular resistance (PVR). These patients may benefit from inhaled vasodilators to selectively reduce PVR. Here, we studied the effects of inhaled vasodilators on pulmonary and systemic hemodynamics and lung edema formation in a rat model of CHF. Since lungs of CHF patients are partially protected from lung edema formation, we further investigated the effect of CHF on alveolar fluid reabsorption and its regulation by endothelial-derived nitric oxide (NO). CHF was induced by aortic banding in rats. Pulmonary hemodynamics and edema formation were analyzed *in vivo* after inhalation of the vasodilators milrinone, iloprost or NO at rest, and inhaled iloprost at increased lung perfusion after administration of the β_1-agonist dobutamine. Alveolar fluid reabsorption and endothelial NO production in CHF were quantified in the isolated perfused rat lung by double indicator dilution technique and by fluorescence imaging of pulmonary endothelial cells *in situ*. Inhalation of milrinone, iloprost, or NO reduced pulmonary arterial pressure (PAP), PVR and the ratio of PVR over the systemic vascular resistance (SVR). Repetitive inhalation of milrinone or iloprost, or continuous inhalation of NO, respectively, caused prolonged pulmonary vasodilation, with milrinone and iloprost being superior to NO. At rest, inhaled vasodilators neither caused lung edema nor left ventricular overload, yet at increased lung perfusion inhaled iloprost promoted lung edema formation in CHF rats. This increase in lung edema was attributable to an inhibition of the Kitajew reflex which postulates a vasoconstriction of precapillary sphincters to protect the pulmonary capillary bed from excessive hydrostatic pressures. Rats with chronic CHF had a markedly increased alveolar fluid reabsorption at elevated left atrial pressure (P_{LA}). This protective effect was attributable to a reduced endothelial NO production in CHF. These results demonstrate that inhaled vasodilators selectively reduce PVR and decrease right ventricular afterload in CHF. While an increased alveolar fluid reabsorption in CHF protects the lung from edema at rest, inhalation of vasodilators at increased perfusion may cause lung edema due to an inhibition of the Kitajew reflex.

Introduction and aim

Congestive heart failure (CHF) results in a "passive" increase in pulmonary vascular pressure which causes pulmonary endothelial dysfunction. The reduced bioavailability of NO promotes vasoconstriction and vascular remodeling in the pulmonary circulation, and consequently results in an increase of PVR. Elevated PVR further aggravates pulmonary hypertension, increasing right ventricular afterload and the risk for right ventricular failure in CHF[1]. Therefore patients with left heart disease may benefit from vasodilatory approaches to reduce PVR and right ventricular afterload. However, intravenous or oral administration of vasodilators in CHF has been shown to increase mortality in several clinical trials[2]. By acting predominantly on the pulmonary circulation, inhaled vasodilators may circumvent the potential adverse effects of intravenously and/or orally administered vasodilators. Yet, inhalative adminstration of vasodilators for the treatment of pulmonary hypertension with left heart disease has not been methodologically studied so far. We hypothesized that inhalation of vasodilators may attenuate pulmonary hypertension in left heart disease. The main concern in this approach is the potential opening of lung precapillary sphincters which have been proposed to protect the lung capillary bed from excessive hydrostatic pressures by the so called Kitajew reflex[3]. Thus, inhalation of vasodilators could potentially exacerbate hydrostatic lung edema or left ventricular volume overload in CHF patients at rest or during exercise. Here, we studied the effects of the inhaled vasodilators milrinone, iloprost or NO on pulmonary hypertension and lung vascular resistance, as well as edema formation in a rat model of chronic CHF. Since CHF patients are less prone to lung edema, we further hypothesized that an increased alveolar fluid reabsorption may confer protection in CHF, and speculated that lack of endothelial-derived NO may provide a mechanistic basis for this phenomenon. Accordingly, we quantified alveolar fluid reabsorption and endothelial NO production in isolated perfused lungs of CHF and control rats by use of a two-compartmental double-indicator dilution technique and real-time fluorescence imaging.

Material and methods

Animals. Male Sprague-Dawley rats were obtained from Charles River Laboratories. All experiments were approved by the legislation of local government committee.

CHF animal model. CHF was induced in male juvenile rats (97±8g body weight) by supracoronary aortic banding as described[4]. The aorta was banded by implantation of a titanium clip with an internal diameter of 0.8 mm. Sham-operated rats which underwent the same operation, yet without clip implantation, served as controls.

Hemodynamic monitoring and drug delivery. Nine weeks after aortic banding rats had developed manifest CHF. CHF and control rats were anesthetized, and catheters were introduced into the aorta and vena cava via the left carotid artery and right jugular vein, respectively. Following a median thoracotomy, catheters were placed into the left atrium and the pulmonary artery via the right ventricle. An ultrasonic flowprobe was positioned around the ascending aorta. Arterial (AP), central venous (CVP), pulmonary arterial (PAP), left atrial (LAP) and airway (AWP) pressure and aortic flow (AF) were continuously monitored using the software package DasyLab®32. Systemic and pulmonary vascular resistances were calculated as arteriovenous pressure differences over flow. The vasodilators milrinone (0.2-5mg/ml) and iloprost (1-5 µg/ml) or their solvent 0.9% NaCl were aerosolized by ultrasound and each inhaled for 3 min. NO was inhaled via a regulated flowmeter to yield inspiratory concentrations of 10-50 ppm.

Experimental protocol. Inhalation was performed as recently described[5]. Briefly, after surgical stabilization for 30 min, rats inhaled the respective test substance for 3 min. For prolonged inhalation, milrinone and iloprost were administered repetitively in intervals of 20 or 45 min, respectively, whereas NO was applied continuously. Hemodynamic data were measured before and immediately after inhalation. In a subset of experiments, lung perfusion was increased by intravenous infusion of the β_1-agonist dobutamine ($10\mu g \cdot kg^{-1} \cdot min^{-1}$). Pulmonary blood samples were obtained for determination of cyclic nucleotides and removed blood volume was replaced by hydroxyethyl starch. Fifteen minutes after the end of the experiment animals were killed by exsanguination, hearts and

lungs were removed and lung wet/dry weight ratio was determined.

Plasma cyclic nucleotides. Concentration of cyclic adenosine 3',5'-monophosphate (cAMP) and cyclic guanosine 3',5'-monophosphate (cGMP) was measured in 1.5 ml blood samples before and after inhalation of the test substances in CHF and control rats. Plasma aliquots were analyzed by an enzyme-linked immunosorbent assay (ELISA).

Fluorescence imaging of subpleural alveoli *in situ*. Alveolar delivery of aerosolized test substances was confirmed by inhalation of aerosolized fluorescein isothiocyanate (FITC) dextran and subsequent fluorescence imaging of subpleural alveoli *in situ*. After inhalation of FITC dextran or 0.9 % NaCl, lungs were excised, inflated with room air at 5 cmH_2O, and imaged under an upright fluorescence microscope with monochromatic illumination at λ=480 nm.

Lung vascular permeability. Pulmonary capillary leakage was assessed by the Evans blue technique as described previously[6]. Briefly, Evans blue albumin (EBA) (20 mg/kg) was injected into the internal jugular vein 30 min before termination of the experiment. After excision, lungs were perfused with phosphate-buffered saline (PBS) and homogenized in PBS (1 ml/100 µg tissue) at 4ºC. Next, lung homogenates were incubated with 2 volumes of formamide (60ºC, 18 hours). Samples were centrifuged at 5000 g for 30 min, and the optical density of the supernatant was determined by spectrophotometry at λ=620 nm.

Isolated perfused lung preparation. Lungs were excised *en bloc* from anesthetized CHF and control rats, continuously inflated and pump-perfused at 14 ml/min and 37ºC as reported[7]. Lungs were perfused with either BSA solution (for measurement of alveolar fluid reabsorption) or autologous heparinized blood (for imaging of endothelial NO production). At baseline, left atrial pressure (P_{LA}) was adjusted to 5 cmH_2O, yielding pulmonary artery pressures (P_{PA}) of 12±1 cmH_2O. P_{PA} and P_{LA} were recorded continuously.

Quantification of alveolar fluid reabsorption. Fluid fluxes into and out of the alveolar space were determined by a double-indicator dilution technique as described previously[7].

Texas red dextran (TRD) was instilled into the alveolar space for measurement of alveolar net fluid shift, while a low molecular weight tracer, Na^+ fluorescein (NaF), was added to the perfusate to allow for differentiation between alveolar fluid influx and alveolar fluid reabsorption. Samples were drawn at different time points from the alveolar and the vascular compartments, and alveolar fluid reabsorption, alveolar fluid influx, and net fluid shift were calculated under the assumption of a two-compartmental distribution model.

Imaging of endothelial NO production. Isolated perfused rat lungs were positioned under an upright fluorescence microscope as described[7]. A microcatheter was advanced via the left atrium and wedged into the pulmonary vein, draining a capillary area on the lung surface. The NO-sensitive dye 4-amino-5-methylamino-2'-7'- difluoro-fluorescein (DAF-FM) was infused for 20 min via the microcatheter. Endothelial DAF-FM fluorescence was imaged at λ=480 nm by monochromatic illumination.

Statistical analysis. Data are presented as mean ± SEM. Data were analyzed by Wilcoxon or Friedman tests for intragroup comparisons and Kruskal-Wallis test or Mann-Whitney U-tests for intergroup comparisons. Statistical significance was assumed at $p < 0.05$.

Results

Cardiovascular and hemodynamic characteristics of CHF rats. After 9 weeks of supracoronary aortic banding, rats had manifest CHF and pulmonary hypertension evident as biventricular cardiac hypertrophy and elevated PAP, LAP and PVR. However, systemic hemodynamic parameters, i.e. AP, CVP, AF and SVR, did not differ significantly between CHF and control rats (data presented in refs. 4, 5 & 7).

Alveolar deposition of inhaled test substances. In order to verify alveolar delivery of aerosolized drugs in our experimental setup, fluorescence microscopy of lungs was performed after inhalation of aerosolized FITC dextran or 0.9 % NaCl. Strong and homogeneous fluorescence was evident in all imaged alveoli after inhalation of FITC dextran. No intra-alveolar fluorescence was observed after inhalation of 0.9% NaCl (data presented in ref. 4).

Single inhalation of vasodilators in CHF. Pulmonary and systemic hemodynamic

responses to inhalation of milrinone (0.2, 1, and 5 mg/ml), iloprost (1, 2.5, and 5 µg/ml) and NO (10, 20, and 50 ppm) were determined in CHF rats. Doses of 1 mg/ml milrinone, 2.5 µg/ml iloprost or 20 ppm NO resulted in a maximal reduction of PAP in the absence of detectable effects on AP, and accordingly, in a decrease of both PVR and the PVR/SVR ratio demonstrating pulmonary selectivity of the vasodilatory effect. No pulmonary or systemic hemodynamic effects were detected in control rats inhaling equal doses of vasodilators. The reduction in PAP, PVR and the PVR/SVR ratio was more pronounced after inhalation of milrinone or iloprost as compared to NO. Baseline cAMP concentrations did not differ significantly between CHF and control rats, yet baseline cGMP levels were significantly lower in CHF rats. Milrinone and iloprost inhalation increased plasma cAMP levels, whereas NO inhalation increased plasma cGMP levels. Lung wet/dry weight ratios were slightly higher in rats with aortic banding as compared to control rats indicating the presence of moderate lung edema in CHF. However, inhalation of a single dose of either milrinone, iloprost or NO did not result in a further increase in lung water content (data presented in refs. 4 & 5).

Prolonged inhalation of vasodilators in CHF. For prolonged inhalation, milrinone (1mg/ml) and iloprost (2.5µg/ml) were administered repetitively in 20 and 45 min intervals according to their biological half lives, while NO (20 ppm) was inhaled continuously. All vasodilators, but not inhalation of 0.9% NaCl caused a prolonged reduction in PAP. Yet, pulmonary vasodilation was more sustained during repetitive inhalation of milrinone or iloprost as compared to continuous NO inhalation. Prolonged inhalation of none of the tested vasodilators resulted in an increased lung wet/dry weight ratio indicating that inhaled vasodilators do not induce lung edema in CHF at rest. Rather, a reduction in lung wet/dry weight ratios was noted after repetitive inhalation of milrinone or iloprost (the latter just missing the level of significance with $p=0.058$) but not NO, suggesting that the foremost vasodilators actually reduced lung edema in CHF (data presented in refs. 4 & 5).

Prolonged inhalation of vasodilators in CHF at increased lung perfusion. The effects of a repetitive iloprost inhalation (2.5µg/ml in 45 min intervals) on pulmonary

hemodynamics and lung edema formation in CHF were furthermore assessed under conditions of increased lung perfusion. Cardiac output was raised *in vivo* by intravenous infusion of the β_1-agonist dobutamine ($10\mu g \cdot kg^{-1} \cdot min^{-1}$), resulting in an increase of aortic blood flow by ~70% (Fig. 1A). Repetitive inhalation of iloprost yet not inhalation of 0.9% NaCl decreased PAP in CHF but not control rats (Fig. 1B). Dobutamine infusion decreased PVR in both control and CHF rats, but additional inhalation of iloprost only reduced PVR further in animals with CHF (Fig. 1C).

Figure 1

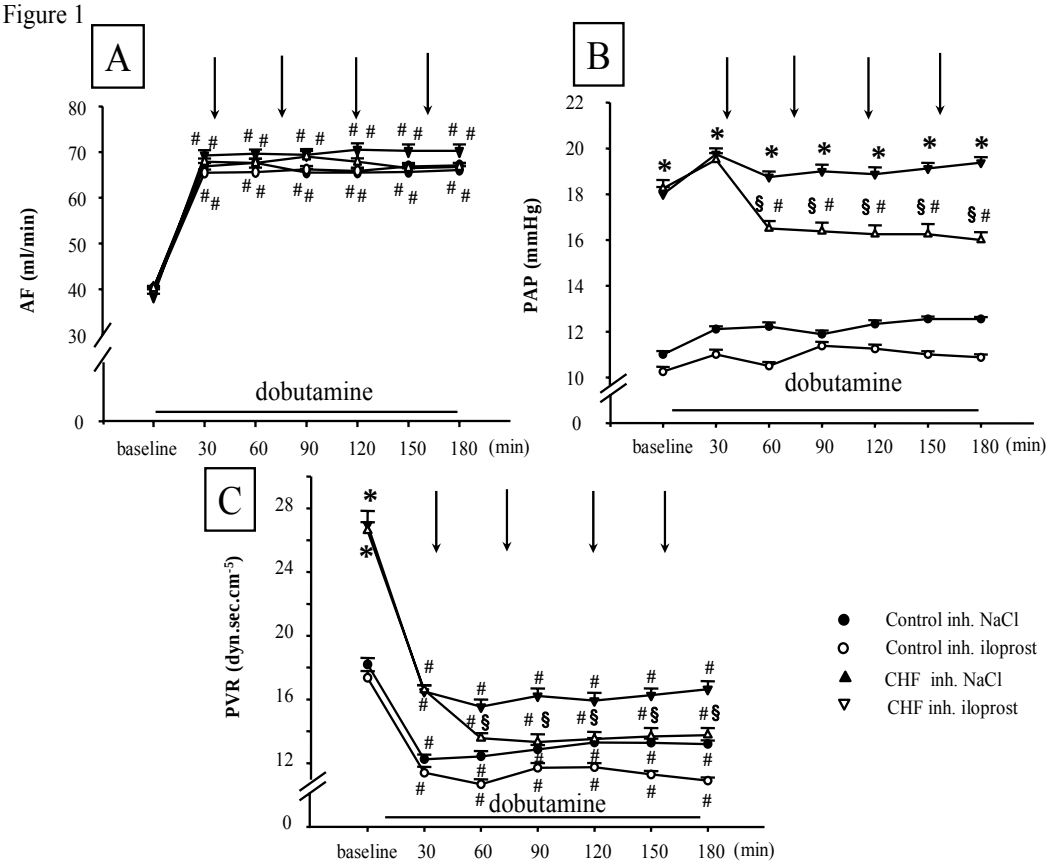

Figure 1. Hemodynamic effects of inhaled iloprost in CHF rats during increased lung perfusion. Group data show aortic flow (AF; A), pulmonary arterial pressure (PAP; B) and pulmonary vascular resistance (PVR; C) prior to and during infusion of dobutamine ($10\mu g \bullet kg^{-1} \bullet min^{-1}$) and during repetitive inhalation of iloprost (2.5 µg/ml; open) or 0.9% NaCl (filled) in 45 min intervals as indicated by arrows in CHF (triangles) and control (circles) rats. Data from n = 8 rats in each group. * P<0.05 vs. control; # P<0.05 vs. baseline; § P<0.05 vs. inh. NaCl.

However, iloprost inhalation during dobutamine infusion concomitantly increased lung wet/dry weight ratios (Fig. 2A) and Evans blue extravasation (Fig. 2B), demonstratig that inhaled vasodilators may promote lung edema in CHF under conditions of increased lung

perfusion.

Figure 2

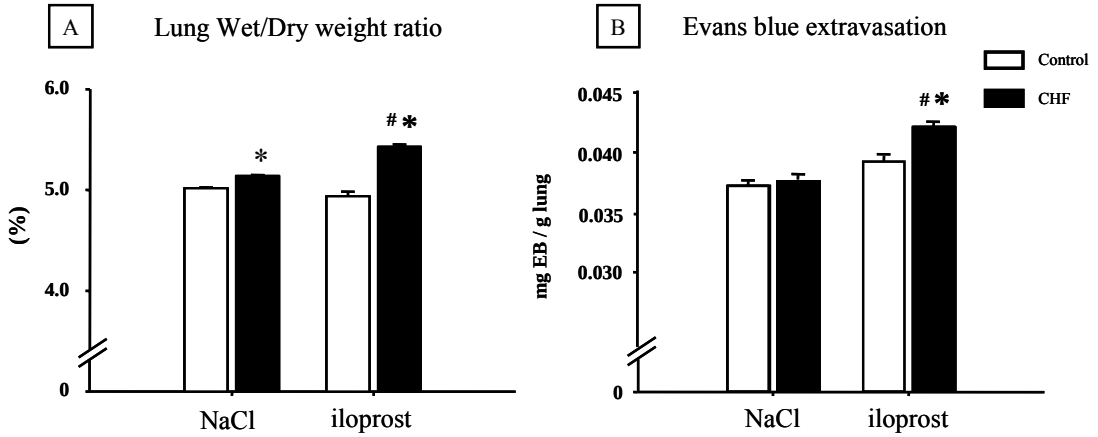

Figure 2. Effects of inhaled iloprost on lung edema formation in CHF rats during increased lung perfusion. Group data show lung wet/dry weight ratio (A) and extravasation of Evans blue (B) after 180 min of dobutamine infusion (10µg•kg^{-1}•min^{-1}) and repetitive inhalation of either iloprost (2.5 µg/ml) or 0.9% NaCl in CHF (filled bars)and control (open bars) rats. Data from n = 8 rats in each group. * P<0.05 vs. control; # P<0.05 vs. 0.9% NaCl.

Alveolar fluid reabsorption in CHF. Measurement of alveolar fluid fluxes in CHF and control rats by a double-indicator dilution technique revealed that alveolar fluid absorption is inhibited by an acute elevation of hydrostatic pressure in control lungs, while intact fluid clearance is preserved in lungs of CHF rats. Administration of the exogenous NO donor *S*-nitroso-glutathione (GSNO) equally blocked alveolar fluid clearance in CHF and control lungs, indicating that lack of endothelial NO production may contribute to the preservation of an intact alveolar fluid reabsorption in CHF (data presented in ref. 7).

Endothelial NO production in CHF. By *in situ* fluorescence imaging, we could demonstrate that NO production in lung endothelial cells of control lungs is increased in response to acute hydrostatic pressure, which contributes critically to the inhibition of alveolar fluid clearance and thus, the formation of cardiogenic lung edema. In CHF rats, endothelial NO production in response to hydrostatic stress is abrogated, suggesting that endothelial dysfunction may actually constitute a protective mechanism in CHF in that it preserves intact alveolar fluid clearance and thus, minimizes lung edema (data presented in ref. 7).

Discussion

In the present study, we applied an experimental model of chronic left heart failure that is characterized by biventricular cardiac hypertrophy, lung vascular remodelling, endothelial dysfunction and moderate lung edema. Inhalation of the vasodilators milrinone, iloprost or NO reduced pulmonary arterial pressure and thus, right ventricular afterload in this model of pulmonary hypertension with left heart disease. Vasodilator inhalation specifically targeted the pulmonary vasculature, and showed no side effects with respect to systemic hemodynamics. Prolonged inhalation of vasodilators maintained stable long-term pulmonary vasodilation. Over the tested dose range, milrinone and iloprost showed a higher potency to reduce both PAP and PVR as compared to inhaled NO. Lungs of CHF rats were found to be protected from hydrostatic lung edema by a preservation of intact alveolar fluid clearance which could be attributed to a lack of endogenous NO production due to endothelial dysfunction. At rest, vasodilators did not promote lung edema, but rather tended to reduce lung water content when inhalation was prolonged. However, when pulmonary blood flow was elevated, inhaled vasodilators increased both lung edema and protein extravasation.

Inhaled vasodilators in left heart disease. Chronic left heart disease frequently results in secondary pulmonary hypertension due to a passive increase in lung vascular pressures which causes pulmonary endothelial dysfunction, thus increasing pulmonary vascular tone and promoting vascular remodeling. Substitution of deficient endogenous vasodilators or downstream second messengers by inhaled vasodilators such as milrinone, iloprost or NO may present a novel and effective treatment strategy to reduce PVR and right ventricular afterload in patients with CHF. Inhaled vasodilators selectively improved pulmonary hemodynamics in CHF without systemic side effect. Concomitantly, LAP decreased indicating that inhaled vasodilators did not cause left ventricular volume overload. Quantification of cyclic nucleotide levels in plasma indicate that inhaled milrinone and iloprost acted predominantly via the adenylate cyclase/cAMP pathway, while NO stimulated primarily the guanylate cyclase/cGMP pathway.

Lung edema in left heart disease and the risk of inhaled vasodilators. The observed

moderate edema in our rat model of left heart disease and the protection from cardiogenic edema are in line with the clinical situation where CHF patients frequently tolerate high pulmonary capillary pressures in the absence of overt lung edema. In the present study, we could attribute this protection to a preservation of intact alveolar fluid clearance in CHF. The fact that endothelial-derived NO production blocks alveolar fluid reabsorption in the intact control lung, but is impaired in CHF gives rise to the somewhat counterintuitive notion that lung endothelial dysfunction may actually present a protective mechanism in CHF in that it prevents the formation of alveolar edema. Furthermore, our results demonstrate that chronic elevation of lung vascular pressure in CHF results in an increase in PVR that can be rapidly reversed by administration of vasodilators. This increase in pulmonary vascular tone in response to hydrostatic stress has previously been postulated in the concept of the so called Kitajew reflex which was also suggested to constitute an intrinsic rescue mechanism by protecting the pulmonary capillary bed from excessive hydrostatic pressures. Yet, in CHF rats at rest, inhaled vasodilators reduced lung edema, demonstrating that the Kitajew reflex does not constitute a protective mechanism under these conditions. However, at increased blood flow the Kitajew reflex becomes a critical delimiter of lung capillary pressure and thus, edema formation. Accordingly, inhaled vasodilators may present a powerful therapeutic option for the reduction of right ventricular afterload in pulmonary hypertension due to left-sided heart disease in patients at rest. Yet, care is warranted in ambulating or exercising patients, when vasodilator therapy may cause serious adverse effects by promoting the formation of lung edema.

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Curriculum Vitae

CV is not available online for private reason.

Publication List

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1.T.Hentschel[*], **N.Yin**[*], A.Riad, H.Habazettl, J.Weimann, A.Koster, C.Tschope, H.Kuppe, W.M.Kuebler. Inhalation of the phosphodiesterase 3 inhibitor milrinone attenuates pulmonary hypertension in an experimental model of congestive heart failure. *Anesthesiology* 2007;106:124-31 Impact Factor: 4.596

2.**N.Yin**[*], S.M.Kaestle[*], J.Yin, T.Hentschel, A.R.Pries, H.Kuppe, W.M. Kuebler. Inhaled nitric oxide versus aerosolized iloprost for the treatment of pulmonary hypertension with left heart disease. *Critical Care Medicine* 2009; 37: 980-986 Impact Factor: 6.283

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Congress Abstract and Poster

1.T.Hentschel, **N.Yin**, H.Habazettl, J.Weimann, A.Koster, H.Kuppe, W.M.Kuebler. Inhalation vasodilativer Substanzen-eine neue therapeutische Alternative bei pumonalvenöser Hypertonie(PVH). Germany Anesthesiology Congress, April ,2005, Munich, Germany.(Abstract)

2.**N.Yin**, H.Habazettl, J.Weimann, A.Koster, H.Kuppe, W.M.Kuebler, T.Hentschel. Inhaled vasodilators-A new treatment option in pulmonary venous hypertension (PVHT)? Der Hauptstadtkongress für Anästhesiologie und Intersivtherapie mit pflegesymposium (HAI). Berlin Journal für Anästhesia und Intersivbehandlung. Nr.2-2005-s.198 (Abstract)

3.**N.Yin**, H.Habazettl, J.Weimann, A.Koster, H.Kuppe, T.Hentschel ,W.M.Kuebler. Attenuation of pulmonary venous hypertension by inhalation or intravenous infusion of a phyosphodiesterase III inhibitor. Annual Meeting Gesellschaft für Mikrozirkulation und Vaskuläre Biologie .Sep. 15-17 , 2005. Rostock. Germany. P.97(Abstract)

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5.**N. Yin,** S.M Kaestle, H Kuppe, R Hetzer, W.M Kuebler. Kitajew reflex protects lung from hydrostatic edema in chronic heart failure. Deutsche Physiologische Gesellschaft 87th Annual Meeting March 2-5, 2008 Cologne.P143 (Abstract)

Presentation

1. **N.Yin.** Inhaled vasodilators as a treatment for pulmonary venous hypertension caused by congestive heart failure. Presentation in the Institut für Physiologie. Charite Campus Benjamin Franklin 2005.4.25

2. **N.Yin.** Inhaled nitric oxide versus aerosolized iloprost in a rats model of pulmonary-venous hypertension caused by congestive heart failure. Presentation in the Institut für Physiologie.Charite Campus Benjamin Franklin 2007.2.26

3. **N.Yin.** Relevance of Kitajew reflex in β1 -stimulated heart failure rats. Presentation in the Institut für Physiologie. Charite Campus Benjamin Franklin 2007.4.12

4. **N.Yin.** Kitajew reflex protects lung from hydrostatic edema in chronic heart failure. Presentation in the Institut für Physiologie. Charite Campus Benjamin Franklin 2008.2.11

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Erklärung

„Ich, [Yin, Ning], erkläre, dass ich die vorgelegte Dissertationsschrift mit dem Thema: [Inhaled vasodiators as a new treatment strategy in pulmonary hypertension with left heart disease] selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.“

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