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ORIGINAL CONTRIBUTION

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Transient pleural effusion in norepinephrine-stimulated rats

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Abstract Transient pleural effusions occurred in rats receiving continuous intravenous infusion of norepinephrine (NE, 0.1mg/kg/h). We hypothesized that these pleural effusions result from a NE-induced increase in right ventricular systolic pressure (RVSP) and total peripheral resistance (TPR). NE was administered over time intervals between 20 min and 72 h. It induced an immediate doubling in RVSP whereas LVSP remained at the control level. TPR increased with a delay of 6 h. At this time, pleural effusions occurred in NE-treated animals, reached their maximum after 8h and disappeared after 24 h of NE stimulation. Combining NE with the α-blocker prazosin normalized TPR and prevented pleural effusions. Therefore, we interpret the pleural effusion as a consequence of pulmonary venous congestion, mainly caused by an increased TPR. LV hypertrophy which developed after 24 h of NE stimulation is considered to compensate for the hemodynamic disturbance due to the NE-induced elevation in TPR. This is reflected in the disappearance of pleural effusion.

Key words Norepinephrine – total peripheral resistance – prazosin – pleural effusion – LV hypertrophy

Introduction

Norepinephrine (NE) has repeatedly been suggested to be involved in the pathogenesis of cardiac hypertrophy and congestive heart failure (23, 29). Enhanced activity of the sympathetic nervous system and increased NE release from the sympathetic nerve endings within the myocardium can be observed in a number of pathophysiological conditions leading to cardiac hypertrophy (23). Administration of catecholamines induced hypertrophy of the heart in rats and dogs (12, 24). Therefore, continuous intravenous (i.v.) infusion of NE is used as a model to study the pathogenetic mechanisms in the development of cardiac hypertrophy as well as the relationship between hypertrophy and the hemodynamic effects of NE treatment.

The effects of NE on the left (LV) and right ventricle (RV) are, however, discordant: hypertrophy develops only in the LV, but not in the RV (1, 15, 16, 20). Also the hemodynamic effects of NE on the two ventricles are different – in particular, the systolic pressure is elevated only in the RV; in the LV it remains at control level (1, 15, 16). In numerous experiments with i.v. NE stimulation, we observed pleural effusions in the NE-treated animals. The aim of the present study was to investigate the temporal relationship between the formation of pleural effusion and the hemodynamic effects of NE as well as the development of LV hypertrophy. This is supposed to elucidate the pathophysiological consequences of the discrepant response of the two ventricles to NE stimulation. In addition, we tested the hypothesis that the NE-induced increase in total peripheral resistance may be responsible for the formation of the pleural effusion.

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Materials and methods

All experiments were performed on female Sprague-Dawley rats supplied by Charles River (Sulzfeld, Germany). The body weight of the animals was 210 – 260 g at the beginning of the study. The experiments were approved by the appropriate Federal State Agency.

The animals received constant intravenous infusion with automatic pumps (Infors AG, Basel, Switzerland) at a rate of 4 ml/kg/h via an infusion catheter (Vygon, Aachen, Germany) placed in the left jugular vein. They were anesthetized with thiopental sodium (Trapanal®) 80 mg/kg i.p. (Byk Gulden, Konstanz, Germany) when hemodynamic parameters were to be measured between 20 and 90 min of infusion or with ether when longer stimulation intervals were studied. The depth of anesthesia was estimated by pinching the animal's paw. Up to 90min of infusion, the animals remained in anesthesia. Animals with longer periods of infusion were awake and moved freely in their cages with access to tap water and rat chow diet (Altromin C 100, Altromin GmbH, Lage, Germany) until they were examined. In these rats, the intravenous catheter was tunneled under the skin to the back of the animal. There it was shaped in a loop and fixed with 4-5 stitches to the skin. The catheter left the animal's body from the back. It was protected from biting by a hard PVC tube of about 25 cm of length that was also fixed to the skin. The loop guaranteed that the moving animal could not pull the catheter out of the vein. The cages were 25 cm long and 32 cm wide, and in this radius the animals could move without reaching the unprotected catheter. The pump was outside the cage.

NE (norepinephrine bitartrate, Sigma Chemical, München, Germany) was administered at an effective NE dose of 0.1 mg/kg/h dissolved in 0.9 % NaCl with 100 mg/l ascorbic acid added to prevent oxidation. Controls were infused with 0.9 % NaCl. 125 rats were treated with NE stimulation over time-intervals of 20, 45 and 90 min as well as 4, 6, 8, 12, 16, 24, 48 and 72 h each group containing between 8 and 19 animals; 104 rats served as time-matched controls (7-14 animals per group). Additionally, 17 animals were stimulated with NE combined with the α-blocker prazosin (P, 0.1 mg/kg/h) or with P alone over 6 (6 rats with NE+P, 3 with P) and 8 h (6 with NE+P, 2 with P), respectively. Prazosin is known as a potent vasodilator. Moreover, acute stimulation with prazosin decreases LVSP and the pressure-rate product of the LV (17).

Hemodynamic measurements

Hemodynamic parameters were measured in the anesthetized animal (Trapanal® 80 mg/kg i.p.). The RV and LV were catheterized with Millar® ultraminiature catheter pressure transducers (model SPR-249 and model SPR-291, 3 French; Millar Instruments, INC, Houston, TX, USA) (35, 36). The RV catheter was introduced via the right jugular vein to measure right ventricular systolic pressure (RVSP), right ventricular maximal rise in pressure (RV dP/dt_{max}) and heart rate (HR). After collecting the RV data, the LV catheter was inserted into the right carotid artery and advanced into the LV to measure LVSP, LV end diastolic pressure (LVEDP), LV dP/dt_{max} and HR. After withdrawal of the catheter tip into the aorta, the diastolic aortic pressure (DAP) was obtained. At last, the RV and LV catheters were replaced by a polyethylene tube (i.d. 0.58 mm) and a thermosensitive 1.5 F microprobe (Columbus Instruments, Columbus, OH, USA), respectively, to determine the cardiac output (CO) using the thermodilution method. The temperature curve was recorded with a Cardiomax II computer (Columbus Instruments). Total peripheral resistance (TPR) was calculated by dividing the mean aortic pressure (MAP) by CO. In animals with 20 min infusion periods, either RV (6 controls, 5 NE) or LV and CO (3 controls, 5 NE) measurements were performed.

Sampling of materials

After finishing the hemodynamic measurements, the animals were sacrificed. The hearts and the lungs were rapidly excised, the RV free wall was trimmed away, and all tissue samples were frozen in liquid nitrogen. Animals treated with NE for 6 to 16 hours showed remarkable amounts of liquid in the pleural space. The liquid was collected to measure its volume. The ventricles as well as pieces of the lungs were weighed separately. The right and left ventricular weights were normalized to body weight (RVW/BW, LVW/BW) and served as a parameter of hypertrophy. Lung pieces of 95 animals (53 NE, 42 controls) were then freeze-dried (Lyovac GT2, Leybold, Cologne, Germany) for 8 hours to remove all water from the tissue. No further weight reduction was achieved with longer periods of drying. From the lung pieces, lung wet-to-dry weight (W/D) ratio was determined as an indicator of pulmonary edema.

Northern blot analysis

Total RNA was isolated from LV and RV by a modification of the technique of Chomczynski and Sacchi (5), and separated by size by electrophoresis on a 1% agarose/5% formaldehyde gel (5 μg total RNA/lane). The RNA was transferred onto nylon membranes (Pall Gelman Sciences) and then crosslinked by UV Stratalinker®, 1800 (Stratagene). cDNAs of rat atrial natriuretic peptide (ANP) (1) and human glyceraldehyde-3-phosphate dehydrogenase (GAPDH; pGemGAPDH gift from Dr. E. Ueberham, Leipzig) were used. These cDNAs were

labeled by random priming with (α-^{32}P) dCTP (Amersham). Blots were prehybridized in 0.5 M phosphate buffer pH 7.2, 7% SDS, 1 mM EDTA (6) for 30 min at 65 °C and hybridized using the same buffer containing radioactive probes for 16 h at 65 °C, and washed with 0.1 x SSC and 0.1% SDS twice for 10 min at 65 °C. Quantification of hybridized bands was carried out using a PhosphorImager (Molecular Dynamics). The signals of specific mRNAs were normalized to those of GAPDH mRNA.

Statistical analysis

The data are expressed as mean ± S.E.M. A multiple-sample comparison (ANOVA and multiple range test using the criterion of the least significant differences) was applied to test the differences between the groups representing the different kinds and time intervals of infusion for significance. A value of $P < 0.05$ was considered to be significant.

Results

With the beginning of the infusion, NE caused a significant increase in HR as well as in RVSP. HR was about 25% higher than in control animals (Table 1). RVSP and RV dP/dt_{max} rose more than twofold from 33 to 70 mmHg and from 2112 to 4453 mmHg/s, respectively, after only 20 min of NE infusion. Within three days, these values remained nearly constant or further increased slightly (Table 2). In contrast, LVSP, LVEDP, DAP and MAP were not significantly elevated compared to controls. After 8 h of NE infusion, a depression in LVSP and LV dP/dt_{max} as well as in CO was observed (Tables 1 and 2). Throughout all stimulation intervals, LVEDP varied between 1 and 7 mmHg both in NE (mean ± SEM: 3.0 ± 0.27) and control animals (3.3 ± 0.23). NE treatment induced a significant elevation in TPR from 0.47 to 0.78 mmHg · min · kg/ml after 6 h of NE infusion. With continuous NE stimulation, TPR reached a maximum after 8 h with 0.83 mmHg · min · kg/ml. After 72 h, however, TPR returned to a value of 0.53 mmHg · min · kg/ml being only slightly higher than the time-corresponding control value (Fig. 1A).

In animals treated with NE for 6 to16 h, between 1.5 and 3.3 ml of fluid were found in the pleural space. Control animals showed only minute amounts of fluid (< 0.5 ml) in their chest. After 24 h of NE infusion, the pleural effusion disappeared (Fig. 1B). Lung W/D ratios of NE-stimulated rats were in the same range as the controls (NE: 5.1 ± 0.2, controls: 4.8 ± 0.1). Only 9 NE-treated animals (17%) exceeded the critical value of 6 which is considered to discriminate between interstitial and severe lung edema (22). All these animals had received NE infusion for at least 6 h. Five of them died from apnea with foam in the tracheal canula during anesthesia.

Combination of NE with the α-blocker prazosin for 6 and 8 h, respectively, normalized TPR (Fig. 2A). RVSP decreased slightly (to 55 mmHg) but remained significantly elevated compared to controls ($P < 0.001$) whereas LVSP was unaltered (135 mmHg, $P > 0.05$). None of these animals exhibited pleural effusions exceeding an amount of 0.5 ml (Fig. 2B). The effects of prazosin alone did not differ from those of sodium chloride (data not shown). In animals infused for 6 and 8 h with NE, NE plus prazosin

Table 1 Hemodynamic effects of continuous infusion of sodium chloride (Control) and of norepinephrine (NE, 0.1 mg/kg/h) over various time intervals between 20 min and 72 h on heart rate (HR), cardiac output (CO), mean aortic pressure (MAP) and diastolic aortic pressure (DAP)

	HR [min^{-1}]		CO [ml min^{-1} kg^{-1}]		MAP [mmHg]		DAP [mmHg]	
Time interval of stimulation	Control	NE	Control	NE	Control	NE	Control	NE
20 min	413 ± 14.6	494 ± 10.2 *	447 ± 24.0	423 ± 49.1	141 ± 2.8	155 ± 1.2	126 ± 2.6	134 ± 1.7
45 min	421 ± 13.5	490 ± 14.2 *	354 ± 32.4	383 ± 70.0	113 ± 8.1	134 ± 9.2	102 ± 7.4	121 ± 4.3
90 min	411 ± 24.6	396 ± 27.3 *	384 ± 19.2	278 ± 11.5 *	123 ± 7.1	133 ± 7.0	107 ± 8.3	116 ± 6.2
4 h	393 ± 12.7	471± 16.5 *	281 ± 6.3	182 ± 44.8	96 ± 5.7	109 ± 7.0	80 ± 6.0	94 ± 8.2
6 h	395 ± 8.9	492 ± 16.4 *	229 ± 19.8	186 ± 26.7	109 ± 7.6	125 ± 5.9	86 ± 9.6	110 ± 5.9
8 h	408 ± 16.4	504 ± 9.7 *	251 ± 9.8	145 ± 17.7 *	114 ± 6.8	111 ± 7.9	99 ± 6.4	97 ± 7.3
12 h	379 ± 11.2	486 ± 9.5 *	306 ± 15.6	240 ± 21.3 *	117 ± 4.6	132 ± 0.8	102 ± 5.3	116 ± 7.2
16 h	424 ± 13.0	487 ± 11.3 *	265 ± 20.9	207 ± 18.0	124 ± 5.2	106 ± 9.1	109 ± 6.6	89 ± 9.7
24 h	404 ± 17.1	528 ± 9.4 *	367 ± 44.8	186 ± 29.7 *	130 ± 5.0	124 ± 5.9	115 ± 4.4	103 ± 6.9
48 h	413 ± 13.6	488 ± 10.1 *	315 ± 17.9	230 ± 28.8 *	129 ± 10.5	118 ± 7.9	110 ± 10.1	96 ± 5.7
72 h	407 ± 8.7	460 ± 10.1 *	265 ± 13.2	246 ± 12.2	120 ± 6.1	123 ± 7.0	100 ± 6.2	103 ± 6.7

Values are presented as mean ± S.E.M. * $P < 0.05$ vs. time-corresponding controls.

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Table 2 Hemodynamic effects of continuous infusion of sodium chloride (Control) and of norepinephrine (NE, 0.1 mg/kg/h) over various time intervals between 20 min and 72 h on left and right ventricular systolic pressures (LVSP, RVSP) and on maximal rise in left and right ventricular pressure (LV dP/dt_{max}, RV dP/dt_{max})

	LVSP [mmHg]		LV dP/dt_{max} [mmHg s^{-1}]		RVSP [mmHg]		RV dP/dt_{max} [mmHg s^{-1}]	
Time interval of stimulation	Control	NE	Control	NE	Control	NE	Control	NE
20 min	157 ± 4.0	176 ± 2.9	10880 ± 790	29066 ± 1024 *	33 ± 1.5	70 ± 2.8 *	2112 ± 249	4453 ± 435 *
45 min	125 ± 4.9	154 ± 6.1 *	8630 ± 325	23024 ± 2503 *	32 ± 1.0	55 ± 3.9 *	2377 ± 183	6500 ± 919 *
90 min	140 ± 6.1	149 ± 8.0	10338 ± 717	21700 ± 2028 *	37 ± 1.0	57 ± 2.7 *	2848 ± 237	4517 ± 381 *
4 h	111 ± 6.0	125 ± 5.9	6789 ± 732	16106 ± 2495 *	33 ± 2.0	63 ± 3.9 *	1981 ± 218	4629 ± 398 *
6 h	131 ± 6.7	141 ± 6.2	9079 ± 716	16224 ± 2127 *	33 ± 1.3	65 ± 3.3 *	2330 ± 214	5248 ± 524 *
8 h	129 ± 7.8	126 ± 8.8	8309 ± 879	12300 ± 1741	34 ± 1.6	64 ± 2.6 *	2297 ± 260	4491 ± 411 *
12 h	132 ± 4.4	148 ± 7.2	9276 ± 451	18447 ± 1124 *	29 ± 1.8	66 ± 2.8 *	1927 ± 207	5614 ± 564 *
16 h	138 ± 4.2	123 ± 8.7	11425 ± 874	17267 ± 2722 *	35 ± 1.4	66 ± 6.1 *	2625 ±122	6000 ± 686 *
24 h	143 ± 5.5	144 ± 6.5	9912 ± 631	16686 ± 1211 *	33 ± 1.0	77 ± 3.9 *	2115 ± 162	5455 ± 399 *
48 h	148 ± 11.1	137 ± 8.3	10584 ± 1150	15989 ± 2106 *	33 ± 1.1	73 ± 4.2 *	2450 ± 210	5056 ± 538 *
72 h	134 ± 6.5	144 ± 7.4	9465 ± 906	16160 ± 696 *	34 ± 1.2	78 ± 2.8 *	2391 ± 225	4900 ± 335 *

Values are presented as mean ± S.E.M. * $P < 0.05$ vs. time-corresponding controls.

and NaCl, respectively, TPR and the amount of pleural fluid were in significant positive correlation ($r = 0.83$, $p < 0.001$).

Throughout all stimulation intervals, NE did not affect the RVW/BW ratio. In contrast, the LVW/BW ratio was moderately elevated after 8 h stimulation by 16% from 2.2 to 2.5 mg/g. After 24 h it reached 2.6 mg/g, which was significantly higher than after shorter stimulation intervals, and increased further to 2.8 mg/g at 72 h (32% over the control values, Fig. 3A). In control animals, both

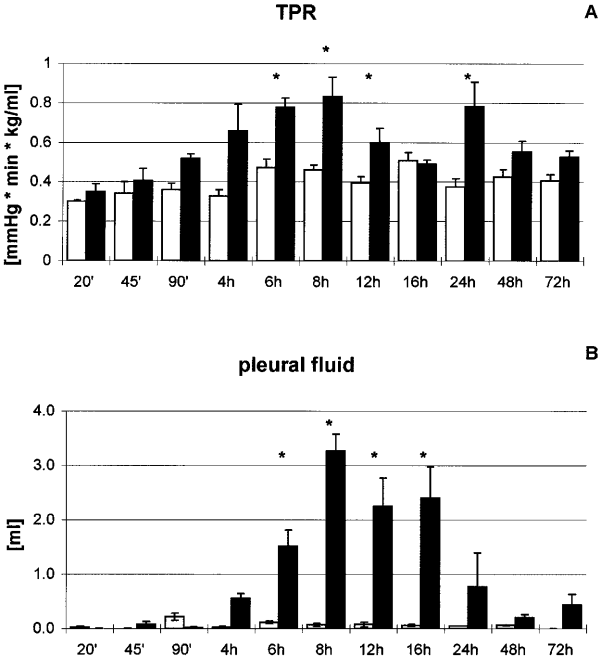

Fig. 1 **A** Total peripheral resistance (TPR, mean ± S.E.M.) after continuous infusion of norepinephrine (NE, 0.1 mg/kg/h, black columns, n = 60) over various time intervals between 20 min and 72 h compared with saline-treated controls (white columns, n = 60). * $P < 0.05$ vs. time-corresponding controls. **B** Volume of pleural fluid (mean ± S.E.M.) after 20 min up to 72 h infusion of NE (black columns, n = 53) and saline (control, white columns, n = 41). * $P < 0.05$ vs. time-corresponding controls.

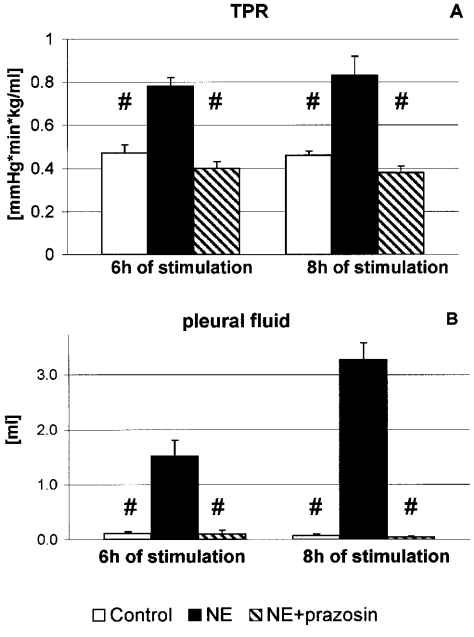

Fig. 2 **A** Total peripheral resistance (TPR, mean ± S.E.M.) after continuous infusion of norepinephrine (NE, 0.1 mg/kg/h, black columns, n = 6), NE combined with prazosin (0.1 mg/kg/h, NE+P, hatched columns, n = 11) and saline (control, white columns, n = 10) for 6 and 8 h. # $P < 0.001$ vs. stimulation with NE alone. **B** Volume of pleural fluid (mean ± S.E.M.) after continuous infusion of norepinephrine (NE, 0.1 mg/kg/h, black columns, n = 13), NE combined with prazosin (0.1 mg/kg/h, NE+P, hatched columns, n = 12) and saline (control, white columns, n = 7) for 6 and 8 h. # $P < 0.001$ vs. stimulation with NE alone.

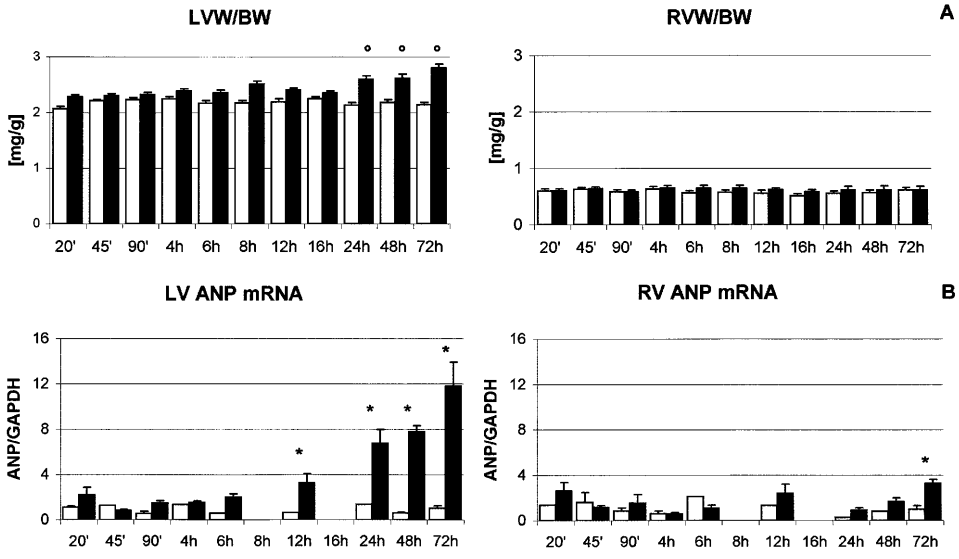

Fig. 3 **A** (upper panels) Development of left and right ventricular weight related to body weight (LVW/BW and RVW/BW) after continuous infusion of norepinephrine (NE, 0.1 mg/kg/h, black columns, n = 125) and saline (control, white columns, n = 104) over various time intervals between 20 min and 72 h. Values are presented as mean values ± S.E.M. Columns marked by ° represent significantly higher values than in all shorter NE stimulation periods, except for 8 h ($P < 0.05$). **B** (lower panels) Expression of atrial natriuretic peptide (ANP) mRNA in the left (LV) and right ventricle (RV) after 20 min up to 72 h infusion of NE (black columns) and saline (control, white columns). The analyses were performed on 42 LV and 34 RV of NE-stimulated as well as 21 LV and 21 RV of control animals. Values are normalized to GAPDH mRNA and presented as mean values ± S.E.M.
* $P < 0.05$ vs. time-corresponding controls.

the RVW/BW and LVW/BW ratios remained constant over time. The development of the asymmetric ventricular hypertrophy was also reflected in the expression of ANP mRNA. We found a significant increase in the LV starting after 12 h of NE stimulation. After 24 and 72 h, ANP mRNA reached 7- and 11-fold, respectively, of the control values. In the RV, only a moderate increase was observed after 72 h (Fig. 3B).

Discussion

The new finding in this study was the transient accumulation of fluid in the pleural space of NE-treated animals. Besides malignant and inflammatory diseases, cardiogenic disorders belong to the most important causes in the pathogenesis of pleural effusion in humans (9, 13, 14, 18, 21). In our experiments, NE stimulation was associated with an immediate increase in RVSP and in RV dP/dt_{max}. The NE effects on the LV were much less pronounced so that a mismatch in the pumping force of the two ventricles can be assumed. Additionally, TPR began to rise after 4 – 6 h. The decrease in LVSP, LV dP/dt_{max} and in CO after 8h of NE stimulation indicated that the LV did not cope with the burden resulting from the elevated RVSP and TPR. Systemic vasoconstriction is one of the main causes of increased pulmonary blood volume (11). Norepinephrine also increases the pulmonary venous tone (30). This might explain the reduced cardiac output and the absence of increase in LVEDP and LVSP. These hemodynamic changes might have caused congestion in the pulmonary circulation and increase in the pulmonary venous and capillary pressures (Fig. 4).

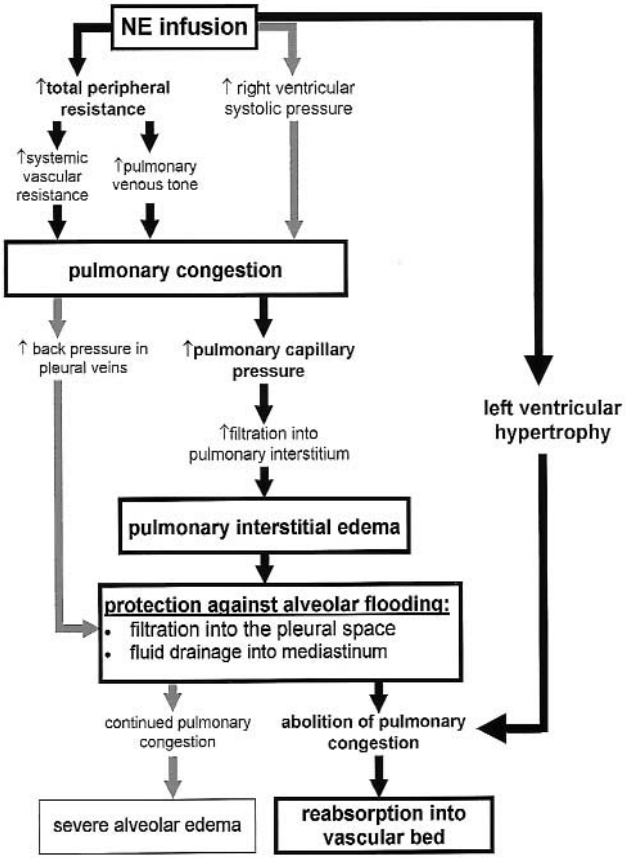

Fig. 4 Pathogenetic concept for the build-up and disappearance of pleural effusions as a putative mechanism of the transient pleural effusion observed in norepinephrine-stimulated rats. The main pathway is indicated by black arrows, factors and developments of minor relevance by grey arrows. A detailed explanation is given in the discussion.

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As a consequence of pulmonary congestion, more fluid can be filtrated from the capillaries into the pulmonary interstitium (25, 28). An interstitial pulmonary edema develops which can be drained via the pulmonary and parietal pleural lymph vessels (3, 10, 28, 32). Negrini et al. demonstrated in rabbits that the pulmonary interstitium takes up relatively large amounts of fluid while the pulmonary interstitial pressure rises from subatmospheric values of about –10 cmH_2O to positive values with a maximum of +4 cmH_2O (22). During this period, the pulmonary W/D ratio remains within the normal range that is between 4.5 and 5 according to data ascertained in rabbits and in sheep (22, 26). The alveoli are still free from fluid at this stage.

Besides the capacity of the pulmonary interstitium, two mechanisms mainly contribute to prevent the transition to alveolar edema. Interstitial fluid can be soaked up by the peribronchovascular tissue and drained into the mediastinum or it can be filtrated into the pleural space (3, 28, 33). The latter could occur because the pressure in the pleural space is less than in the lung tissue beneath the pleura (2). Pulmonary venous hypertension also increases the back pressure in the visceral pleural veins that are drained into the pulmonary veins. An increased fluid filtration from the pleural capillaries additionally contributes to the formation of the pleural effusion (33). Only if all these reservoirs are overloaded does leakage of the alveolo-capillary membrane develop, and the alveoli are flooded according to the all-or-none law (27). At this stage, the pulmonary W/D ratio reaches values greater than 6 indicating a severe edema (22). In the majority of the NE-treated rats, the pulmonary W/D ratio was at the control level; this means that these animals had not formed a severe alveolar edema. Only in a few animals (17%) which were stimulated with NE for at least 6 h did severe edema occur as indicated by external symptoms such as foam in the trachea. In these rats, the pulmonary W/D ratio exceeded the critical value of 6. More than half of them died from the edema. This finding demonstrates clearly the importance of the pleural effusion in preventing alveolar flooding.

Two hemodynamic factors induced by NE infusion are considered to produce pulmonary congestion and the formation of pleural effusion: the increase in RVSP and the elevated TPR. Normalization of the NE-induced TPR increase by the α-adrenergic blocker prazosin prevented the development of pleural effusions. Prazosin also reduced RVSP, but it remained significantly above control level. From this, we conclude that increased TPR plays a pivotal role in the pathogenesis of the pleural effusions in NE-stimulated rats. A study of Chen and Chai revealed that NE stimulation in rats caused pulmonary edema which proved to be mainly due to systemic, but not pulmonary vasoconstriction (4). The same pathogenetic mechanism is assumed to be responsible for the neurogenic pulmonary edema (7, 31) which in its initial phase is characterized by a massive sympathetic discharge with an intense generalized vasoconstriction causing a shift of blood into the pulmonary circulation. The hydrostatic effect of the increased pulmonary capillary pressure results in the formation of pulmonary edema (31).

However, the fluid can be reabsorbed into the lung and into the vascular bed if the cause of the congestion is abolished and the pleural membranes are still intact (19). As indicated by the progressive increase in ANP mRNA, a marker gene for hypertrophy (8), and an increase in the LVW/BW ratio, NE stimulation induced isolated LV hypertrophy (see Fig. 3). This is also confirmed by previous studies on NE effects on the rat heart (1, 15, 34). The time course of the increase in the LVW/BW ratio demonstrates that LV hypertrophy became manifest after 24 h of NE stimulation. At the same time, pleural effusion disappeared and was entirely absent in all animals examined with longer periods of NE stimulation. This coincidence led us to the assumption that LV hypertrophy compensates for the hemodynamic disturbances resulting from the increased RVSP and particularly, from the increased TPR. As a consequence, the congestion in the pulmonary vascular bed and the fluid filtration into the lung interstitium might have been attenuated. Also, the filtration into the pleural space would cease so that the pleural effusion could be reabsorbed into the vascular system (Fig. 4). Additionally, the later decrease of TPR might contribute to the reabsorption of the pleural effusion.

In summary, the transient occurrence of pleural effusion following NE infusion over several hours indicates substantial disturbances in pulmonary circulation which probably result from the different NE effects on the LV and RV systolic pressures and in particular, from the increase in TPR. These changes might have caused congestion in the pulmonary circulation and increased filtration of fluid into the pulmonary interstitium and into the pleural space. Normalization of TPR by the α-antagonist prazosin prevented the formation of pleural effusions. LV hypertrophy which developed after 24 h of continuous NE administration is considered to compensate for the mismatch between LV and RV that is preferentially due to the elevated TPR, and to restore the pulmonary circulation. This is reflected in the disappearance of the pleural effusion at this time.

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