

Shared Endothelial Alterations in Cerebral and Cardiac Vessels in Rat Models of Ischemic Heart Disease and Prenatal Hypoxia[†]

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Abstract

Introduction: Endothelial dysfunction (ED) is a key pathogenetic mechanism underlying cardiovascular and cerebrovascular diseases and is increasingly recognized as a common link between ischemic heart pathology and cerebral vascular impairment. In addition to postnatal risk factors, adverse intrauterine conditions, particularly prenatal hypoxia (PH), may program long-term endothelial alterations. The aim of this study was to investigate the structural and molecular features of ED in the myocardial and cerebral vessels in experimental chronic heart failure (CHF) and PH, as well as to evaluate the endothelioprotective potential of pharmacological agents targeting the nitric oxide system. **Methods:** This study was conducted on Wistar rats using experimental models of CHF (doxorubicin administration, cumulative dose 15 mg/kg) and PH (sodium nitrite 50 mg/kg administered to pregnant females on gestational days 16–21). The endothelial status of cerebral and myocardial vessels was assessed using immunohistochemistry, ELISA, morphometric analysis, and real-time PCR. Key markers of endothelial function, inflammation, nitric oxide metabolism, oxidative stress, and angiogenesis were evaluated. The endothelioprotective potential of nitric oxide-modulating pharmacological agents was also evaluated. **Results:** CHF and PH induced pronounced structural and functional endothelial alterations in the microcirculatory and muscular-type vessels of the heart and brain. These changes were characterized by reduced endothelial cell density, suppressed eNOS expression, increased iNOS expression, nitric oxide deficiency, elevated nitrotyrosine levels, and activation of proinflammatory cytokines. VEGF levels were significantly decreased, while apoptotic features of endothelial cells were intensified. Angiotensin and Hypertril demonstrated the most pronounced endothelioprotective effects among the tested agents. **Conclusions:** CHF and PH induce persistent ED in cerebral and myocardial vessels through disruption of the nitric oxide system, oxidative stress, and inflammatory activation. PH may act as an early trigger increasing susceptibility to cardiovascular and cerebrovascular diseases later in life. These findings support the rationale for targeted endothelioprotective therapy in ischemic cardiovascular pathology.

Keywords: endothelial dysfunction; chronic heart failure; prenatal hypoxia; cerebral vessels; myocardial vessels; nitric oxide system; oxidative stress; vascular endothelial growth factor; inflammatory cytokines; endothelioprotection



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1. Introduction

Recent years have seen a significant rise in the prevalence of cardiovascular diseases, making them one of the leading causes of mortality in industrialized countries. The most serious complication—with a mortality rate ranging from 10% to 50% among patients with cardiovascular disease—is chronic heart failure (CHF). It is also known that the global progression of cardiovascular diseases is associated not only with lifestyle, diet, harmful habits, and socioeconomic upheavals, but also with suboptimal intrauterine conditions [1–3]. According to current understanding, endothelial dysfunction (ED) is one of the leading pathogenic links in cardiovascular diseases. The results of experimental and clinical studies in recent years have confirmed the concept of an important causal relationship between ED and the progression and/or development of arterial hypertension and hypertensive encephalopathy, atherosclerosis, chronic heart failure, diabetes mellitus, metabolic syndrome, chronic renal failure and their complications, pulmonary hypertension, dilated cardiomyopathy, obesity, hyperlipidemia, hyperhomocysteinemia, and chronic cerebral ischemia [4–6]. The presence of ED mechanisms was identified in cardiovascular pathologies following prenatal hypoxia (PH) [7,8]. The aim of this study was to investigate the structural and molecular features of ED in the myocardial and cerebral vessels in experimental CHF and PH, as well as to evaluate the endothelioprotective potential of pharmacological agents targeting the nitric oxide system.

2. Materials and Methods

The experiments were performed on Wistar rats weighing 190–220 g, obtained from the vivaria of the Institute of Pharmacology and Toxicology and the A.A. Bogomolets Institute of Physiology of the Academy of Medical Sciences of Ukraine. Animals underwent a 14-day quarantine and acclimatization period, during which their general condition, behavior, morbidity, and mortality were monitored daily. Before the start of the study, animals that met the inclusion criteria in the experiment were divided into groups using the randomization method. Throughout the experiment, the animals were observed, death was recorded, and their appearance was described. All procedures complied with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes. The study protocol was approved by the Bioethics Committee of ZSMU (Protocol No. 3, 22 March 2021).

CHF was modeled by administering doxorubicin (50 mg/25 mL; EBEWE Pharma Ges.m.b.H Nfg. KG, Unterach am Attersee, Austria) for 14 days at a cumulative dose of 15 mg/kg. The administration of doxorubicin according to this regimen leads to a decrease in the contractile function of the left ventricle, its eccentric remodeling, and the development of progressive heart failure in rats. All drugs were administered intragastrically once daily as a 1% starch slurry for 30 days following a 14-day course of doxorubicin “Hypertril” (1-(β -phenylethyl)-4-amino-1,2,4-triazolium bromide; Scientific and technological complex “Institute of Single Crystals” of the National Academy of Sciences of Ukraine, certificate №2, series 020213) at an experimentally validated dose of 3.5 mg/kg, and nebivolol in the same regimen at a dose of 10 mg/kg. In this experimental series, each group comprised 20 animals: the intact group, the control group with CHF without treatment, experimental group 1 with CHF treated with Hypertyl, and experimental group 2 with CHF treated with nebivolol.

PH was induced by administering sodium nitrite at a dose of 50 mg/kg to pregnant females from day 16 to day 21 of gestation. Sodium nitrite administration to pregnant females induces hemic hypoxia through methemoglobin formation and disrupts oxidative phosphorylation, resulting in impaired oxygen transport, reduced uteroplacental blood

flow, and fetal or embryonic hypoxia. PH modeling leads to the development of postnatal heart defects.

The offspring were divided into six groups. Group 1 included healthy pups born to females with physiologically normal pregnancies and treated with saline. Group 2 served as the control group and included pups born after partial gestational hypoxia that received daily saline administration from birth. Groups 3–6 included pups born after partial gestational hypoxia that received daily pharmacological treatment from postnatal day 1 to day 30: group 3, thiotriazoline (morpholinium 3-methyl-1,2,4-triazolyl-5-thioacetic acid; 2.5% injectable solution, Arterium, Kyiv, Ukraine) at 50 mg/kg i.p.; group 4, angiolin ([S]-2,6-diaminohexane acid 3-methyl-1,2,4-triazolyl-5-thioacetate; substance, NPO Farmatron, Zaporozhye, Ukraine) at 50 mg/kg i.p.; group 5, L-arginine, an NO precursor (42% injectable solution, Tivortin, Yuria-Pharm, Kyiv, Ukraine), at 200 mg/kg i.p.; and group 6, mildronate, a metabolic modulator (2-(2-carboxyethyl)-1,1,1-trimethylhydrazinium; 10% injectable solution, Grindeks, Riga, Latvia), at 100 mg/kg i.p.

Rats from all experimental groups were removed from the experiment under thiopental anesthesia (40 mg/kg). The apical portion of the heart and brain regions containing the hippocampus were placed in Buena's fixative; following standard tissue dehydration and impregnation with chloroform and paraffin, the myocardium was embedded in paraplast. Serial histological sections 15 µm thick were prepared on a rotary microtome and subsequently used for real-time PCR and immunohistochemistry. Some of the samples, after homogenization in liquid nitrogen, were subjected to ultracentrifugation, and mitochondrial and cytosolic fractions were isolated. The endothelial status of cerebral and myocardial vessels was assessed using immunohistochemical, enzyme-linked immunosorbent assay, morphometric, and real-time polymerase chain reaction methods. The analysis included the evaluation of ED markers, inflammatory mediators, angiogenic factors, nitric oxide system components, oxidative stress indicators, and morphological signs of endothelial cell damage and apoptosis. In addition, the potential endotheliotropic effects of pharmacological agents influencing the nitric oxide system were assessed. All statistical calculations were done by «STATISTICA® for Windows» (version 14.4.0). The evaluation of differences between groups was done by using one-way ANOVA or ANOVA for repeated measurements with post hoc Bonferroni correction or Kruskal–Wallis criterion with post hoc Dunn correction. A significant difference was considered at $p < 0.05$.

3. Results

The modeling of CHF and PH resulted in significant structural and functional alterations of the endothelium in muscular-type vessels and the microcirculatory bed of both the heart and brain. Alongside preserved areas of the aortic intima and endocardial endothelium, pronounced zones of endothelial injury were observed, in some cases leading to desquamation of endothelial cells. These changes were particularly evident in the heart, especially in regions of local edema of the aortic media, where marked disorganization of elastic membranes and the appearance of large fibroblast-like cells were also detected in rats with CHF and in two-month-old offspring after PH.

Laboratory studies revealed elevated levels of C-reactive protein in animals with these pathological conditions, indicating the development of an inflammatory response in CHF and following PH, as well as the onset of ED. Enzyme-linked immunosorbent assay analysis (ELISA) of myocardial and brain cytosol in animals with CHF and after PH revealed a decrease in vascular endothelial growth factor (VEGF) compared to the corresponding value in intact animals. Further ELISA of the cytosol of the myocardium and brain in animals with CHF and after PH revealed an increase in molecular markers of ED and CHF—tumor necrosis factor (TNF- α) and gamma-interferon (IFN- γ). These inflammatory

mediators are known to reduce endothelial nitric oxide synthase (eNOS) expression and nitric oxide (NO) production, enhance oxidative modification of NO, converting it into peroxynitrite [9–11] (Table 1). TNF- α and IFN- γ suppress VEGF expression and induce apoptosis in endothelial cells [12,13].

Table 1. Molecular markers of endothelial dysfunction in the atrial myocardium and blood serum of animals with CHF on day 35 of the experiment.

Indicator	Intact (n = 20)	CHF (Control) (n = 20)	CHF + Hypertyl (n = 20)	CHF + Nebivolol (n = 20)
VEGF, pg/mL	33.8 $\pm$ 4.19	18.8 $\pm$ 8.41 *	55.1 $\pm$ 7.22 ^{*1}	21.5 $\pm$ 4.11 *
TNF- α , pg/mL	4.18 $\pm$ 0.71	28.7 $\pm$ 3.66 *	10.2 $\pm$ 1.78 ^{*1}	27.1 $\pm$ 4.87 *
C-reactive protein, g/L	4.21 $\pm$ 0.31	14.13 $\pm$ 0.87 *	5.32 $\pm$ 0.28 ^{*1}	10.11 $\pm$ 0.78 ^{*1}
IFN- γ , ng/mL	11.82 $\pm$ 2.8	32.28 $\pm$ 2.26 *	18.21 $\pm$ 2.31 ^{*1}	36.67 $\pm$ 4.11 *
eNOS, pg/mL	22.11 $\pm$ 0.86	8.46 $\pm$ 0.29 *	68.21 $\pm$ 6.26 ^{*1}	54.34 $\pm$ 0.75 ^{*1}
eNOS mRNA, u.e.	1.00 $\pm$ 0.01	0.27 $\pm$ 0.02 *	4.39 $\pm$ 0.01 ^{*1}	2.88 $\pm$ 0.02 ^{*1}
iNOS mRNA, u.e.	1.00 $\pm$ 0.01	6.43 $\pm$ 0.04 *	2.07 $\pm$ 0.05	3.48 $\pm$ 0.03 ^{*1}
Density of eNOS-positive cells	512.7 $\pm$ 38.4	210.5 $\pm$ 20.2 *	412.5 $\pm$ 34.2 ^{*1}	211.4 $\pm$ 22.4 *
Density of iNOS-positive cells	114.6 $\pm$ 12.0	276.3 $\pm$ 21.4 *	122.5 $\pm$ 12.2 ^{*1}	280.2 $\pm$ 14.4 *

*—significant changes compared to the intact group ($p < 0.05$); ¹—significant changes compared to the control group ($p < 0.05$).

Immunohistochemical analysis of the myocardium demonstrated a significant decrease in the density of eNOS-positive cells, accompanied by a moderate increase in iNOS-positive cells (Table 1). This was associated with reduced eNOS mRNA expression, increased iNOS mRNA expression, and elevated oxidative stress markers in the cytosol of the myocardium and brain (Table 2). A decrease in eNOS protein concentration was detected in the brain cytosol of rats with CHF and after PH. Morphometric analysis revealed that in rats with CHF and after PH, there was a decrease in the density of muscle-type vascular endothelial cells and the microcirculatory bed of the heart and brain, a decrease in RNA content in endothelial cell nuclei, and an increase in cells with morphological signs of apoptosis.

Table 2. Molecular markers of endothelial dysfunction in the atrial myocardium of animals after PH and its pharmacological correction on day 30 of life.

Indicator	Intact (n = 10)	PH (Control) (n = 10)	PH + Angiolin (n = 10)	PH + Thiotriazoline (n = 10)	PH + L-Arginine (n = 10)
VEGF, pg/mL	44.7 $\pm$ 1.01	32.1 $\pm$ 1.02 *	47.80 $\pm$ 0.89 ^{*1}	36.81 $\pm$ 1.17 ^{*1}	34.73 $\pm$ 1.49 *
eNOS, pg/mL	37.41 $\pm$ 0.88	14.60 $\pm$ 0.26 *	54.73 $\pm$ 1.02 ^{*1}	25.63 $\pm$ 1.31 ^{*1}	32.39 $\pm$ 1.08 ^{*1}
eNOS mRNA, u.e.	1.00 $\pm$ 0.003	0.15 $\pm$ 0.001 *	4.88 $\pm$ 0.021 ^{*1}	2.30 $\pm$ 0.009 ^{*1}	0.79 $\pm$ 0.001 ¹
iNOS mRNA, u.e.	1.00 $\pm$ 0.011	7.22 $\pm$ 0.031 *	1.89 $\pm$ 0.016 ^{*1}	3.88 $\pm$ 0.002 ^{*1}	4.82 $\pm$ 0.005 ^{*1}

*—significant changes compared to the intact group ($p < 0.05$); ¹—significant changes compared to the control group ($p < 0.05$).

A substantial disruption of the nitrgenic system in the myocardium and brain was identified after the modeling of CHF and PH (Figure 1). This disruption was characterized by an altered eNOS/iNOS expression ratio, NO deficiency, and increased nitrotyrosine levels. These findings suggest impaired myocardial tolerance to ischemia/reperfusion, disturbed cerebral oxygen supply, and damage to endothelium-dependent mechanisms of vasodilation/ vasoconstriction, which further contribute to the development of ED.

We evaluated the potential endotheliotropic effects of drugs affecting the nitric oxide system: L-arginine, Angiolin, Thiotriazolin, Hypertril, Nebivolol, and Mildronate (Figure 2). It was found that the most pronounced endothelioprotective effects were exhibited by Angiolin (a metabolite-based cardio- and neuroprotector) [8,14] and Hypertril (a cardioselective beta-blocker with an NO-mimetic effect) [15]. Angiolin exerts a protective effect on NO and also increases its bioavailability. Due to its chemical structure, angiolin acts as a spin trap and can form a complex with NO. Angiolin positively affects the state of the myocardial

nitric oxide system during experimental ischemia—it increases NO synthesis by upregulating eNOS expression, enhances NO bioavailability, and reduces parasitic reactions by decreasing iNOS hyperactivity. The mechanism of action on eNOS expression can be explained in terms of Angiotensin's effect on HSP70 and HIF-1 α . Angiotensin prolongs the “lifespan” of HIF-1 α via HSP70 mechanisms. Angiotensin also has a positive effect on the glutathione-thiol-disulfide system, which is coupled with the NO system. The effect of Hypertril on the myocardial nitric oxide system in doxorubicin-induced CHF, as demonstrated in this study, combined with its β_1 -blocking effect, leads not only to ECG normalization but also to improved myocardial metabolism and the inhibition of oxidative stress. The positive modulation of eNOS expression by Hypertril, confirmed by PCR, immunoenzymatic, and immunohistochemical methods, is based on its antioxidant effect, since according to the “kindling radicals” or “bonfire” hypothesis, ROS and peroxynitrite are active mechanisms of eNOS inactivation. The targets for Hypertril's antioxidant modulation of eNOS may include: oxidative depletion of tetrahydrobiopterin, oxidative modification of the zinc–sulfur complex of the eNOS dimer, glutathione deficiency, ROS-dependent oxidation of cysteine residues and phosphorylation of Thr495/Tyr657, ROS-dependent increase in asymmetric dimethylarginine [16–18].

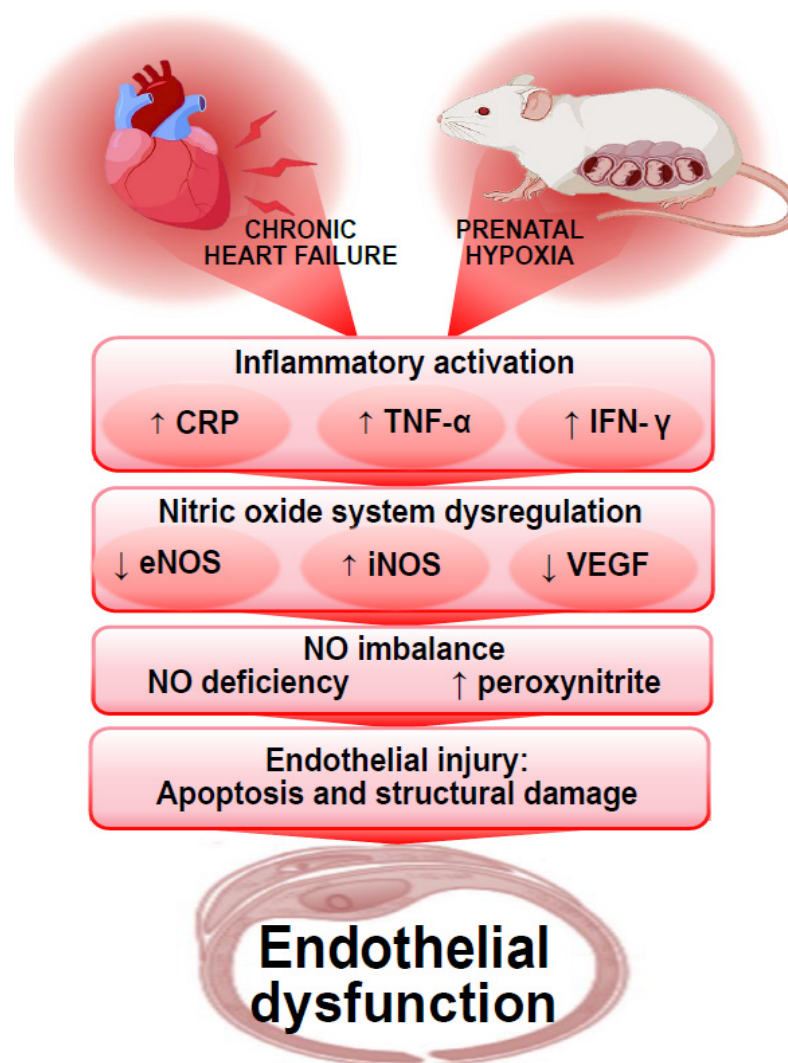


Figure 1. Pathogenetic mechanisms of endothelial dysfunction in chronic heart failure and prenatal hypoxia. ↑ indicates an increase in level/concentration, and ↓ indicates a decrease in level/concentration of molecular markers.

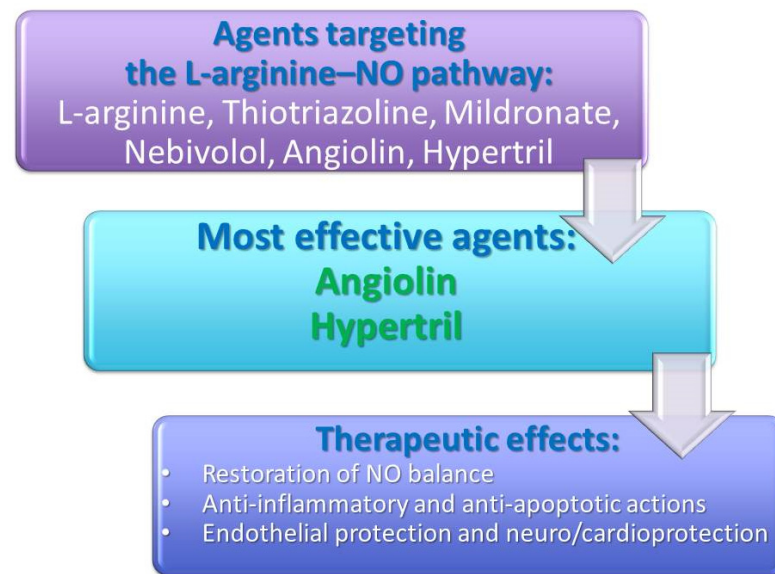


Figure 2. Endothelioprotective pharmacological strategies.

4. Conclusions

In the present experimental models, CHF and PH were associated with persistent endothelial dysfunction in cerebral and myocardial vessels, accompanied by alterations in nitric oxide system parameters, oxidative stress, and inflammatory markers. These observations suggest a possible relationship between prenatal hypoxia and long-term alterations in vascular endothelial function. These findings provide a rationale for further investigation of the mechanisms underlying brain injury in ischemic heart pathology and support the potential use of endothelioprotective therapy in cardiovascular and cerebrovascular disorders.

5. Study Limitations

Several key limitations should be noted:

Methodological Limitations: Single-dose testing: In the study, Angiolin and Hypertril were tested at only a single dose, which limits our understanding of the dose–response relationship and therapeutic windows. This hinders the determination of optimal dosing regimens or potential toxicity at higher doses.

Limitations of tissue-based endothelial marker assessment: Endothelial dysfunction markers were assessed in collected tissue samples and therefore do not fully reflect dynamic in vivo hemodynamic conditions, including blood flow-dependent wall shear stress [19].

Limited time frame: The duration of the pharmacological effects of Angiolin and Hypertril and the potential for sustained benefits remain unexplored.

Single-animal model: Relying solely on the CHF and PH models may limit the generalizability of the results to other types of cerebral and cardiac vascular endothelial dysfunction. Validation in additional models (e.g., traumatic brain injury, ischemia, or aging) would enhance the potential for translational medicine.

Incomplete pathway analysis: The endothelioprotective study focused on specific molecular and genetic markers but did not conduct a comprehensive analysis of all potential pathways involved in the mechanisms underlying cardiac and cerebral endothelial dysfunction caused by PH and CHF.

Limitations Related to Translational Medicine:

Uninvestigated sex differences: The study does not address potential sex differences in the response to Hypertril and Angiolin, which limits the generalizability of the results.

Species limitation: The use of rats alone limits extrapolation to human conditions without additional testing in other animal species or human cell models.

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Institutional Review Board Statement: The experimental studies were carried out in accordance with the “Regulations on the Use of Animals in Biomedical Research” and with the European Convention on the Protection of Animals Used for Scientific and Other Purposes. The experiment was approved by the Bioethics Committee of Zaporizhzhia State Medical and Pharmaceutical University (Protocol No. 3, 22 March 2021).

Informed Consent Statement: Not applicable.

Data Availability Statement: The data are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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