

Received: 2010.01.21
Accepted: 2010.03.16
Published: 2010.08.01

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

Influence of lisinopril on cardiac remodeling induced by tobacco smoke exposure

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Source of support: Departmental sources

Background:
Material/Methods:

Results:

Conclusions:

key words:

Summary

To investigate the effect of lisinopril on cardiac remodeling induced by smoking.

Rats were allocated into 3 groups: group CON (n=8): control; group CSE (n=8): cigarette smoke exposure; group CSE-LIS (n=8): exposed to tobacco smoke and treated with lisinopril.

After 2 months, the tail systolic pressure was lower in CSE-LIS (CON=116 ±27 mm Hg, CSE=126±16, CSE-LIS=89±12; $P<.001$). CSE animals showed higher left ventricular systolic diameter (CON=8.25±2.16 mm/kg, CSE=11.5±1.3, CSE-LIS=9.27±2.00; $P=.009$) and myocyte cross-sectional area (CON=245±8 μm^2 , CSE=260±17, CSE-LIS=238±12; $P=.01$) than CON and CSE-LIS. The ejection fraction (CON=0.91±0.02, CSE=0.86±0.02, CSE-LIS=0.92±0.03; $P=.002$) and fractional shortening (CON=55.7±4.41%, CSE=48.7±3.43, CSE-LIS=58.2±7.63; $P=.006$) were lower in CSE group than CON and CSE-LIS. CSE and CSE-LIS animals showed higher collagen amounts (CON=3.49±0.95%, CSE= 5.01±1.58, CSE-LIS=5.27±0.62; $P=.009$) than CON. CON group showed a higher connexin 43 amount in the intercalated disc (CON=3.70±0.38, CSE=2.13±0.53; CSE-LIS=2.17±0.73; $P=.004$) than CSE and CSE-LIS. There were no differences in IFN- γ or TNF- α cardiac levels among the groups.

Lisinopril attenuated both morphologic and functional abnormalities induced by exposure to tobacco smoke. In addition, this effect was associated with diminished blood pressure, but not alterations in connexin 43 distribution, cytokine production or collagen amount.

ventricular function • smoking • hypertrophy • heart failure

Full-text PDF: <http://www.medscimonit.com/fulltxt.php?ICID=881098>

Word count: 2348

Tables: 2

Figures: –

References: 31

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BACKGROUND

Cardiac remodeling may be defined as changes in the size, geometry, shape, composition, and function of the heart. This process occurs in response to several stimuli including volume overload, hypertension, myocardial infarction, and genetic mutations. Importantly, ventricular remodeling is now recognized as a significant pathologic process that results in progressive ventricular dysfunction and cardiovascular death [1,2].

A significant issue is that strategies to reverse or prevent further remodeling are the key to improving prognosis following several injuries. Importantly, the renin-angiotensin system plays a pivotal role in modulation of pathological processes of the cardiovascular system. In addition, angiotensin converting enzyme (ACE) inhibitors can attenuate cardiac remodeling in different pathological models [3–6].

Recently, several studies have shown that exposure to tobacco smoke, or to its compounds, results in cardiac remodeling and compromised cardiac function [7–13]. This is an additional effect beyond those already well-known such as effects on the other tissues [14–16]. However, the exact mechanism involved in this phenomenon is not known. Considering that ACE inhibitors may attenuate cardiac alterations following different injuries, we hypothesized cardiac remodeling induced by exposure to tobacco smoke would be modulated by the renin-angiotensin system. Therefore, the objective of this study was to investigate the effect of lisinopril on cardiac remodeling induced by tobacco smoke exposure in rats.

MATERIAL AND METHODS

Groups and treatment

All experiments and procedures were performed in concordance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals and were approved by the Animal Ethics Committee of our Institution.

Male Wistar rats weighing 200–250 g were allocated into 3 groups: group CON (n=8): control animals; group CSE (n=8): rats exposed to tobacco smoke (40 cigarettes/day); group CSE-LIS (n=8): rats exposed to tobacco smoke (40 cigarettes/day) and treated with lisinopril, 20 mg/kg/d in drinking water. The dose and route of lisinopril has been proved to attenuate ventricular remodeling [17]. The planned observation period was 2 months.

The CSE rats were exposed to cigarette smoke in a chamber (dimensions 95×80×65 cm) connected to a smoking device [7–11]. The smoke was drawn out of filtered commercial cigarettes (composition per unit: 1.1 mg of nicotine; 14 mg of tar; and 15 mg of carbon monoxide) with a vacuum pump and was exhausted into the smoking chamber. During the first week, the number of cigarettes was gradually increased from 5 to 10 cigarettes over 30 minutes, twice in the afternoon. After that, 10 cigarettes were used in each smoking trial, repeated 4 times/day, 2 in the morning and 2 in the afternoon.

This protocol has consistently shown that tobacco smoke exposure induces enlargement of the left ventricular chamber,

myocardial hypertrophy as well as reduction in left ventricular ejection indices such as systolic shortening fraction, fractional area change, and ejection fraction [7–11]. Considering the carboxyhemoglobin levels, this protocol is similar to 3–4 pack/day in human. On the other hand, this protocol did not result in hypoxia [8,10,18].

Systolic blood pressure

After 45 days of observation, the systolic pressures in the tail of the animals were measured by use of a tail plethysmograph with a polygraph (Byo-Sistem PE 300, NARCO), a sensor placed in the proximal region of the tail, and an electrospigmomanometer, to enable the recording of tail pressure. The animals were warmed in a wooden box at 37°C with the heat generated by 2 incandescent lamps for 4 minutes and were transferred to an iron support, where the tail was exposed. In the proximal region of the tail, a sensor (KSM-microphone) was placed and coupled to the plethysmograph. Blood pressure was recorded on paper with the polygraph at a 2.5-mm/s velocity.

Echocardiographic study

After 2 months, all animals were weighed and evaluated by a transthoracic echocardiographic examination. The examinations were performed using a commercially available echocardiographic machine (Philips model TDI 5500) equipped with a 12 MHz phased array transducer. Imaging was performed with a 60° sector angle and a 3 cm imaging depth. Rats were lightly anesthetized by intramuscular injection with a mixture of ketamine (50 mg/kg) and xylazine (1 mg/kg). All measurements were obtained according to the leading-edge method recommended by the American Society of Echocardiography/European Association of Echocardiography [19]. Measurements represented the mean of at least 5 consecutive cardiac cycles. Left ventricle (LV) end-diastolic dimension (LVEDD) and posterior wall thickness (LVWT) were measured at maximal diastolic dimension, and the end-systolic dimension (LVESD) was taken at the maximal anterior motion of the posterior wall. The left atrium (LA) was measured at its maximal diameter and the aorta at the end of diastole. The LV systolic function was assessed by calculating the fractional shortening $\{(LVDD-LVSD)/LVDD \times 100\}$, and the ejection fraction $\{(LVDD^3-LVSD^3)/LVDD^3\}$. The E/A ratio were used as an index of LV diastolic function.

Morphometric analysis

At the completion of the functional study, the right (RV) and left ventricles (including the interventricular septum) were dissected, separated, and weighed.

The morphometric analysis of the myocardium was performed as described previously [7–11]. Myocyte cross-sectional area (CSA) was determined for at least 100 myocytes per slide stained with hematoxylin-eosin. The measurements were performed using a Leica microscope (magnification lens ×400) attached to a video camera and connected to a personal computer equipped with image analyzer software (Image-Pro Plus 3.0, Media Cybernetics, Silver Spring, MD). Interstitial collagen volume fraction (IC) was determined for the entire picrosirius-red-stained cardiac section through an automated image analyzer (Image-Pro Plus 3.0, Media

Table 1. Echocardiographic data.

Variables	CON (n=8)	CSE (n=8)	CSE-LIS (n=8)
HR (beats/min)	284 (273–292)	265 (257–291)	261 (253–294)
LA (mm)	3.88±0.65	4.06±0.76	3.93±0.42
LVEDD (mm)	6.92±0.99	7.87±0.58*	7.90±0.56*
LVEDD/BW (mm/kg)	18.4±3.57	22.9±1.98*	22.1±1.30*
LVESD (mm)	3.09±0.67	4.03±0.35*	3.32±0.72
LVESD/BW (mm/kg)	8.25±2.16	11.7±1.20* [#]	9.27±2.00
LVWT/LVEDD	0.20 (0.18–0.23)	0.15 (0.14–0.18)	0.14 (0.14–0.18)*
E/A	1.60±0.36	1.66±0.23	1.85±0.42
EF	0.91±0.02	0.86±0.02* [#]	0.92±0.02
FS (%)	55.7±4.41	48.7±3.43* [#]	58.2±7.63

CON – control animals; CSE – animals exposed to tobacco smoke; CSE-LIS – animals exposed to tobacco smoke and treated with lisinopril; HR – heart rate; LA – left atrium; LV – left ventricle; LVEDD – LV end-diastolic dimension; BW – body weight; LVESD – LV end-systolic dimension; LVWT – LV posterior wall thickness; EF – ejection fraction; FS – fractional shortening; E – peak velocity of early ventricular filling; A – peak velocity of transmitral flow during atrial contraction. Data are expressed as mean ±SD or medians (including the lower and upper quartiles). **P*<.05 versus CON; [#]*P*<.05 versus CSE-LIS.

Cybernetics). On average, 35 microscopic fields were analyzed with an ×40 lens. Perivascular collagen was excluded from this analysis.

Immunohistochemistry for connexin 43

Immunohistochemistry experiments were performed as described by Saffitz and associates [20]. All hearts were transversally cut and fixed, successively, in 10% buffered formaldehyde solution for 24 hours, running water for 24 hours and 70 percent alcohol for 24 hours. After fixation, tissues were embedded in paraffin and cut into 3-μm sections. Before immunolabeling, tissue characterization and orientation was recorded by hematoxylin-eosin staining.

Immunolabeling of Cx43 was examined by epi-fluorescent microscopy (Carl-Zeiss, Inc. North America) equipped with a WG filter cube (excitation =550 nm and emission =650 nm) connected to a video camera and compatible computer (AxioPlan 4.1; Carl-Zeiss Inc.). All images were recorded on the same day as labeling and the tissues were coded and examined blindly by the same person. From each heart, as described by Kostin and associates [21], 10 optical fields were recorded and analyzed and the sections were evaluated by intensity scores (+++: strong, ++: moderate, +: weak) and by the localization of connexin 43 in the intercalary disc (+++: totally, ++: majority, +: half in and half out, -: minority).

Evaluation of cytokine production

Briefly, 60 mg of cardiac tissue samples was homogenized and solubilized in 50 mM potassium phosphate buffer, pH 7.4; 0.3 M sucrose; 0.5 mM DTT; 1mM EDTA, pH 8.0; 0.3 mM PMSF; 10 mM NaF, and 1:100 protease inhibitor. Cytokine levels in cardiac homogenate were evaluated by ELISA according to manufacturer instructions (R & D Systems, Minneapolis, MN, USA). Sensitivities of ELISA for IFN-γ and TNF-α were 19 and 31 pg/mL respectively.

Statistical analysis

The comparisons between groups were made by ANOVA test complemented by the Tukey test, when the data were normally distributed. When the data presented an abnormal distribution, the Kruskal-Wallis test was complemented by the Dunn test. Data analysis was carried out with Sigma Stat for Windows (version 2.03, Chicago, IL). The significance level was 5%.

RESULTS

Considering the final body weight, there are no differences among the groups (CON=381±46 g, CSE=345±42 g, CSE-LIS=358±14 g; *P*<.001). The tail systolic pressure was lower in CSE-LIS rats than in CON and CSE (CON=116±27 mm Hg, CSE=126±16 mm Hg, CSE-LIS=89±12 mm Hg; *P*<.001).

The echocardiographic data are shown in Table 1. CON animals showed lower left ventricular diastolic diameter adjusted by body weight (*P*=.006) compared with CSE and CSE-LIS. CSE animals showed higher left ventricular systolic diameter than CON and CSE-LIS (*P*=.009). The ejection fraction (*P*=.002) and fractional shortening (*P*=.006) were higher in CON and CSE-LIS than in CSE animals. Also, CSE group showed significantly increased myocyte cross-sectional area (*P*=.01). CSE and CSE-LIS groups showed higher collagen amounts (*P*=.009), whereas CSE-LIS showed decreased values for normalized left ventricular mass in relation to CON and CSE (*P*<.001) as showed in Table 2.

CON animals showed a higher connexin 43 amount in the intercalated disc (CON=3.70±0.38, CSE=2.13±0.53; CSE-LIS=2.17±0.73; *P*=.004) than CSE and CSE-LIS. On the other hand, there was no difference in the intensity of total connexin 43 among the groups.

In relation to cytokine production, there were no differences in IFN-γ (CON=335±73 pg/mg protein, CSE=323±164

Table 2. Morphologic data.

Variables	CON (n=8)	CSE (n=8)	CSE-LIS (n=8)
BW(g)	381±46	345±42	358±14
LVW/BW(mg/g)	1.96±0.10	2.03±0.12 [#]	1.68±0.14*
RVW/BW(mg/g)	0.53±0.05	0.55±0.09	0.53±0.05
CSA (μm ²)	245±8	260±17* [#]	238±12
IC (%)	3.49±0.95	5.01±1.51*	5.27±0.62*

CON – control animals; CSE – animals exposed to tobacco smoke; CSE-LIS – animals exposed to tobacco smoke and treated with lisinopril; BW – body weight; LVW – left ventricular weight; RVW – right ventricular weight; CSA – cross-sectional area; IC – interstitial collagen volume fraction. Data are expressed as mean ±SD. **P* < .05 versus CON; [#]*P* < .05 versus CSE-LIS.

pg/mg protein, CSE-LIS=247±91 pg/mg protein; *P*=.45) or TNF-α (CON=356±178 pg/mg protein, CSE=418±292 pg/mg protein, CSE-LIS=393±223 pg/mg protein; *P*=.23) cardiac levels among the groups.

DISCUSSION

The objective of this study was to analyze the effect of the renin-angiotensin system on ventricular remodeling induced by smoking. Our results showed that lisinopril attenuated both morphologic and functional abnormalities induced by exposed to cigarette smoke. In addition, this effect was associated with diminished blood pressure, but not alterations in connexin 43 distribution, cytokine production, or collagen amount.

Previous experimental studies have shown that exposure to tobacco smoke induces morphologic and functional irregularities [7–13]. However, the mechanisms involved in the morphologic and functional cardiac alterations induced by exposed to cigarette smoke are still incompletely understood.

The noteworthy finding in the present study was that treatment with lisinopril decreased cardiac remodeling associated with cigarette smoking. In fact, smoking rats presented higher left ventricular area, increased myocyte cross-sectional area and left ventricular mass, smaller ejection fraction and fractional shortening in comparison with smoking animals treated with lisinopril. Therefore, our data strongly support the participation of the rennin-angiotensin system in ventricular remodeling induced by exposed to cigarette smoke.

With regard to the potential mechanisms involved in the lisinopril actions, some studies provide evidence that exposure to tobacco smoke results in impaired vasodilatory function, and increased blood pressure [8,22]. An important point is that, in a previous study, propranolol administration did not decrease blood pressure in smoking animals [23]. In our study, the beneficial effects of lisinopril on the morphologic and functional variables were associated with decreased systolic blood pressure. Therefore, we could deduce that the rennin-angiotensin system, but not the sympathetic system, contributes to the increased blood pressure in this model. However, the follow-up period in our study was short and associated with blood pressure levels that are not as high in smoking rats. For these reasons, we believe that reduced blood pressure may contribute to the beneficial effects of lisinopril, but is not a critical mechanism involved.

It is widely accepted that ventricular remodeling may be associated with alterations in the structure of the interstitial matrix. Different models of cardiac remodeling have revealed collagen accumulation, associated with myocardial dysfunction and poor prognosis. In addition, this collagen accumulation can be modulated by the renin-angiotensin system [24]. Interestingly, in our study, ACE inhibitors did not change the collagen amount in comparison to exposure to tobacco smoke in male Wistar rats. Thus, our data suggest that collagen amount is not involved in the protective effect of lisinopril in this model.

Another potential mechanism involved in the lisinopril action is the gap junctions. Gap junctions are clusters of transmembrane channels that connect the cytoplasmic compartments to neighboring cells. The component proteins of gap junction channels are termed *connexons*. There are many types of connexons, but the predominant isoform in the heart, mainly in the ventricle, is connexin 43 [25,26].

A major role of gap junctions in the myocardium is to coordinate electrical excitation. However, gap junction can also facilitate intercellular change of small proteins such as signal transduction proteins. Therefore, gap junctions can be an important modulator of ventricular remodeling induced by several cardiac injuries and is a potential target to therapeutic interventions [25–27]. The normal gap junction functions are related to normal expression and distribution of connexin 43 given that connexin 43 is mainly located in the intercalated disc of cardiomyocytes. In different models of cardiac injuries, there is a decreased intensity of connexin 43. Additionally, alterations occur in the distribution of connexin 43, including a decreased amount in the intercalated disc, referred to as connexin 43 lateralization [25–27].

In our study, CSE was associated with a decreased connexin 43 amount in the intercalated disc, suggesting connexin 43 lateralization, but did not change the intensity of total connexin 43. Importantly, lisinopril did not change connexin 43 lateralization. Therefore, in this model, we infer that the protective effect of ACE inhibitor is not modulated by alterations in connexin 43 distribution.

Another important issue is that, in some heart failure models, cytokine production can modulate left ventricular remodeling. Indeed, increased IFN-γ, and especially TNF-α levels, are associated with left ventricular dysfunction, cachexia,

activation of foetale gene programs, apoptosis, hypertrophy, and fibrosis [28]. In this study, the remodeling attenuation induced by lisinopril was not associated with altered IFN- γ or TNF- α levels. However, we did not analyze the potential role of other cytokines. Therefore, at this point, the exact participation of inflammation in the lisinopril effect remains to be investigated.

Finally, we should consider the potential implications of this study. Clinical studies also have analyzed the cardiac effects of smoking. Indeed, acute inhalation of cigarette smoke was accompanied by disorders in diastolic function [29]. Furthermore, in the MESA trial including over 1100 subjects, the results demonstrated regional myocardial dysfunction assessed by magnetic resonance imaging in smokers, compared with nonsmokers, despite the absence of clinically manifest disease [30]. In the observational CARDIA study, smokers had a greater left ventricular mass when compared with nonsmokers assessed by echocardiogram [31], suggesting that smoking may induce cardiac alterations. Importantly, this effect is additional to the already well-known effects, such as those on the vascular endothelium and lungs. Therefore, our study indicates that ACE inhibitors could be an attractive strategy in the management of cardiac remodeling induced by exposed to cigarette smoke.

CONCLUSIONS

Lisinopril decreased both morphologic and functional abnormalities induced by exposed to cigarette smoke. In addition, this effect was associated with diminished blood pressure, but not alterations in connexin 43 distribution, cytokine production or collagen amount.

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