

Role of vitamin D in the cardiac remodeling induced by tobacco smoke exposure[☆]

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Animal studies have shown that exposure to tobacco smoke (ETS) leads to inflammation and cardiac remodeling, characterized by heart hypertrophy, higher diastolic dimension of the left ventricle and impaired systolic function [1–3]. Although the precise mechanisms of smoking-induced alterations remain unclear, the evidence supports the hypothesis that oxidative stress and inflammation provide the pathophysiological link between ETS and heart alterations [4,5]. In recent years, vitamin D has emerged as an important nutrient for heart health and its deficiency has been linked to increased cardiovascular disease risk [6,7]. In heart aggression models, vitamin D (VD) supplementation attenuated the cardiac remodeling by influencing the contractility, hypertrophy, renin angiotensin system, fibrosis and inflammation [8–10]. Given that vitamin D may modulate cardiac alterations following different injuries, the objective of this study was to investigate the effect of vitamin D supplementation on cardiac remodeling induced by tobacco-smoke exposure in rats. Rats were allocated into six groups: 1) VD0-no ETS, without VD supplementation and no ETS, 2) VD1-no ETS, supplementation of 1000 IU VD/kg diet and no ETS, 3) VD3-no ETS, supplementation of 3000 IU VD/kg, 4) VD0-ETS, ETS without VD supplementation, 5) VD1-ETS, ETS with VD supplementation of 1000 IU, and 6) VD3-ETS, ETS with VD supplementation of 3000 IU. After two months of tobacco exposure and VD supplementation, the animals underwent blood pressure measure and echocardiography. Collagen volume fraction, myocyte cross-sectional area (MCSA), serum 25-hydroxycholecalciferol, oxidative stress and cytokine production in heart tissue were evaluated.

For both factors (VD and ETS), the groups did not differ significantly in final body weight, tibia length or food consumption.

As to echocardiographic data, no interaction was observed in all variables. Only the ETS factor presented differences, namely enlargement of the left chamber compared to the no ETS animals. The left ventricle end-diastolic diameter corrected for the tibia length (LVDD), left ventricle posterior wall (LVPW) and left ventricle mass (LVM) were increased in the ETS animals, with preserved relative wall thickness,

suggesting eccentric hypertrophy. No differences were observed in the other echocardiographic variables. For systolic pressure, no interaction was observed. A difference was shown only in the ETS factor, in which ETS animals had higher pressure values compared to their no-ETS counterparts.

The morphometric data revealed interaction between factors. The MCSA, which is an index of ventricular hypertrophy, was greater in the VD0-ETS group than in VD0-no ETS (Table 1). No difference was observed for interstitial collagen. In addition, there was no interaction between factors or differences in cardiac levels of IFN- γ , TNF- α and IL-10.

The ETS led to greater concentration of lipid hydroperoxide and lower activities of catalase and superoxide dismutase in group VD0-ETS compared to VD0-no ETS (Table 1).

Vitamin D supplementation produced no effect on echocardiographic variables among ETS animals. However, VD supplementation of 3000 IU/kg led to lower MCSA values in ETS animals.

With regard to oxidative stress enzymes, an interaction was observed between VD and ETS. Under VD treatment, lower lipid hydroperoxide and higher superoxide dismutase and catalase activity were observed in ETS animals. For glutathione peroxidase, differences were observed only in relation to the VD factor.

Vitamin D did not cause changes in the groups without exposure to tobacco smoke.

Exposure to tobacco smoke – Our study has found that exposure to tobacco smoke led to remodeling with eccentric hypertrophy and changes in oxidative status, in addition to significant increases in arterial blood pressure, compared to nonsmokers. These observations are consistent with previous studies that reported an increase in posterior wall thickness and LV mass, higher LV diastolic diameter, blood pressure elevation and reduced antioxidant activity after exposure to tobacco smoke [11,12].

In the present study, augmented oxidative stress might be involved in ETS-induced remodeling. Substantial evidence shows that cigarette smoke can induce increased production of reactive oxygen metabolites and species by augmenting oxidative stress. Besides the production of ROS, cigarette smoke weakens antioxidant defense system, such as antioxidant enzymes [13]. In agreement with these data, the present study found that ETS increased lipoperoxidation and decreased both catalase and superoxide dismutase activities, suggesting elevated oxidative stress status.

Exposure to tobacco smoke and vitamin D supplementation – In the present study, VD supplementation attenuated cardiac hypertrophy after ETS. VD supplementation in salt-sensitive Dahl rats was associated with lower heart weight and LV mass reduction, lower posterior wall thickness and end diastolic pressure and increased shortening fraction [14]. Kong et al. reported a reduction in the thickness of the LV posterior wall by echocardiogram and LV cross-sectional histology, and reduction of the diameter of cardiomyocytes in spontaneously hypertensive rats after treatment with vitamin D [10]. Clinical trials in hemodialysis patients treated with vitamin D showed reduced LV hypertrophy [6]. In the present study, vitamin D supplementation attenuated hypertrophy, expressed by lower values of MCSA.

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Table 1

Myocyte cross-sectional area and cardiac oxidative stress measurements.

ETS	Vitamin dose	n	MCSA q(μm^2)	Lipid hydroperoxide (nmol/g tissue)	Catalase ($\mu\text{mol}/\text{mg}$ protein)	Glutathione peroxidase (nmol/mg tissue)	Superoxide dismutase (nmol/mg protein)
No ETS	VD0	8	182 $\pm$ 12.1 ^{a,A,C}	337 $\pm$ 25.8 ^{a,A}	1.1 $\pm$ 0.06 ^a	37.8 $\pm$ 2.9	4.02 $\pm$ 0.20 ^a
No ETS	VD1	8	233 $\pm$ 12.1 ^A	439 $\pm$ 25.8 ^{b,A}	0.9 $\pm$ 0.06	36.8 $\pm$ 2.9	4.12 $\pm$ 0.20
No ETS	VD3	8	237 $\pm$ 12.1 ^C	359 $\pm$ 25.8	0.9 $\pm$ 0.06	46.2 $\pm$ 2.9	3.89 $\pm$ 0.20
ETS	VD0	12	267 $\pm$ 10.8 ^{a,F}	716 $\pm$ 22.1 ^{a,D,F}	0.6 $\pm$ 0.05 ^{a,D,F}	29.9 $\pm$ 2.5	2.42 $\pm$ 0.17 ^{a,D,F}
ETS	VD1	10	251 $\pm$ 10.8	519 $\pm$ 25.8 ^{b,D,E}	0.8 $\pm$ 0.06 ^D	42.6 $\pm$ 2.9	3.79 $\pm$ 0.20 ^D
ETS	VD3	8	222 $\pm$ 10.8 ^F	426 $\pm$ 28.0 ^{E,F}	0.8 $\pm$ 0.05 ^F	41.3 $\pm$ 3.2	3.94 $\pm$ 0.22 ^F
P1 (ETS)			0.005	<0.001	<0.001	<0.001	<0.001
P2 (VD)			0.331	<0.001	0.969	0.006	<0.001
P3 (ETSxVD)			<0.001	<0.001	<0.001	0.056	<0.001

Data are expressed as mean $\pm$ standard error of mean. n = number of rats. VD0 = diet with no supplementation; VD1 = diet supplemented with 1000 IU/kg of vitamin D; VD3 = diet supplemented with 3000 IU/kg of vitamin D; ETS = exposed to cigarette smoking; no ETS = not exposed to cigarette smoking; MCSA = myocyte cross-sectional area. P1 = p value of ETS effect; P2 = p value of vitamin D effect; P3 = p value of interaction. Equal letters are showing differences in the comparisons.

Comparisons for factor ETS: (^a – ETS $\neq$ no ETS within VD0; ^b – ETS $\neq$ no ETS within VD1; ^c – ETS $\neq$ no ETS within VD3). Comparisons for factor Vitamin D: (^A – VD0 $\neq$ VD1 within no ETS; ^B – VD1 $\neq$ VD3 within no ETS; ^C – VD0 $\neq$ VD3 within no ETS) and (^D – VD0 $\neq$ VD1 within ETS; ^E – VD1 $\neq$ VD3 within ETS; ^F – VD0 $\neq$ VD3 within ETS).

In addition to hypertrophy, there is evidence that vitamin D participates in the modulation of other factors in cardiac remodeling, such as oxidative stress [15]. There are reports on the role of vitamin D as an antioxidant agent in tissues such as liver, kidney and pancreas [16,17]. More recently, treatment with vitamin D improved the oxidative stress in uremic rats by preventing the depletion of SOD and GSH-Px [18].

Therefore vitamin D modulates cardiac remodeling induced by exposure to tobacco smoke by the action of its antioxidant capacity on cardiac hypertrophy.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (Shewan and Coats 2010; 144:1–2).

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