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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Retinoic acid-induced ventricular non-compacted cardiomyopathy in mice

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Abstract

Background: Precise tissue concentration of retinoic acid (RA) is indispensable for proper interaction of second heart field cells with cardiac neural crest cells and induction of signalling pathways important for normal myocardial growth.

Aim: Since RA deficiency during embryogenesis induces noncompaction, we hypothesised that excess RA at the stage of heart tube elongation may cause thinning of the myocardial wall which leads to noncompaction.

Methods: RA was administered at 70 mg/kg b.w. on 8.5 days post coitus (dpc) to pregnant mice to elicit cardiac malformations in foetuses. We studied noncompaction development in RA-treated mouse offspring. The cardiac noncompaction was evaluated in different stages of heart development as the quotient of the distance between the epicardial surface and trabecular tips (represented by a) and the distance between the epicardial surface and trabecular recesses (represented by b) in RA-treated hearts compared to control non-treated.

Results: We demonstrated that apart from outflow tract defects such as double outlet right ventricle, transposition of the great arteries and tetralogy of Fallot in foetuses in mouse offspring, noncompaction occurs in about 42% of cases. At the stage of 13 dpc and later in development the ratio a/b was higher in RA-treated hearts exhibiting noncompaction compared to the control hearts. This cardiomyopathy was more evident in the right ventricle than in the left ventricle.

Conclusions: Noncompaction caused by RA overdose can be elicited in part of the mouse offspring by administering RA at the stage of cardiac tube elongation.

Key words: embryonic mouse heart, ventricular noncompaction, outflow tract malformations, secondary heart field

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INTRODUCTION

Left ventricular noncompaction (LVNC) or 'spongy myocardium' is considered to be the remnant of embryonic heart development, postulated to be caused by an arrest of the intrauterine development of the ventricular myocardium [1]. It is characterised by a pattern of prominent trabeculations and deep intertrabecular recesses communicating with the LV cavity. Occasionally these indentations occur also in the right ventricle (RV) [2]. According to the WHO classification, it belongs to undefined cardiomyopathy [3]. Two forms of LVNC have been classified: isolated LVNC and LVNC associated with other cardiac defect(s). In the latter case, LVNC can accompany ventricular septal defect, atrial septal defect, pulmonary stenosis, hypoplastic left heart syndrome, stenosis of the left or right ventricular outflow tract, complex cyanotic heart defects, origin of the left coronary artery from the pulmonary trunk, coronary artery fistula, and Di George anomaly [4–6]. Major complications of LVNC are heart failure, diastolic and systolic dysfunction, arrhythmias, thromboembolic events, and sudden cardiac death [7, 8].

Retinoic acid (RA) is an important morphogen playing a role in normal cardiac development [9]. Wilson and Warkany [10] observed for the first time that the myocardium of the ventricular walls was poorly developed in certain of the off-

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spring of vitamin A deficient mothers. Hearts thus affected had thinner, less compact walls than hearts from control foetuses of the same age apart from other cardiac (outflow tract malformations). Normal development of the compact myocardium depends on proper interactions between cardiomyocytes and epicardial-derived epithelial cells (EPDC) as well as extracellular matrix molecules. During and after the heart looping stage, EPDCs are the source of RA via endogenous activity of retinaldehyde dehydrogenase 2 (RALDH2), the major RA synthesising enzyme in the embryo. RA-responsive elements have also been demonstrated to be present in second heart field (SHF) cells and in cardiac neural crest cells (CNCCs) [11], both cellular populations contributing to the development of the heart. Either deficiency or overdose of RA during the embryonic stage of cardiac tube elongation and looping causes disturbed communication between CNCCs and SHF cells and delayed addition of SHF cells to the cardiac tube leading to various cardiac malformations, with predominance of the outflow tract defects [12, 13]. Since the precise level of RA is required for normal cardiac development, we hypothesised that this molecule might be involved in signalling pathways important for building the proper compact myocardium. Thus, RA overdose may cause a thinning of the myocardial wall similar to that in RA deficiency.

The aim of this work was to study cardiac wall development by comparing the thickness of compact and trabeculated layer of the myocardium in mouse offspring after administering a single teratogenic dose of RA to pregnant mice.

METHODS

Experiments were performed on F1 cross of C57BL/6 and CBA mouse inbred strains. All procedures were approved by II Local Bioethics Committee of Medical University of Warsaw. Control groups consisted of foetal mice sacrificed at 9.5, 10, 11, 12.5, 13, and 16 days post coitus (dpc). Experimental groups were treated at 8.5 dpc with *all-trans* RA at a dose of 70 mg/kg body weight of pregnant mice to evoke the heart malformations in the offspring. Treated mice were sacrificed at 9.5, 10, 11, 12.5, 13, and 16 dpc. At least three hearts from each group were studied. The total number of hearts studied was 72. Hearts from embryos were fixed in 4% paraformaldehyde in PBS for 48 hours and subsequently processed for paraffin embedding. Hearts were oriented in paraffin blocks to cut cross sections. Serial sections were cut, and the slides were stained with haematoxylin-eosin.

Statistical analysis

Slides were evaluated with the use of the Multiscan system connected with the Nikon light microscope equipped with a digital camera and computer software for measuring the thickness of the compact myocardial layer and trabeculated myocardium. A total of 18 hearts from 13-dpc and from 16-dpc-stage groups were included for taking measurements (i.e. nine hearts from stage 13 dpc and nine hearts from stage 16 dpc). From every heart two slides were chosen for measurements: one slide from the middle section between the apex and the base of the heart (midventricular level), and the second slide at the level below the forming atrioventricular valves (subvalvular level). The values are presented as the quotient of the distance between the epicardial surface and a trabecular tip (value — a) and the distance between the epicardium and a trabecular recess (value — b). On each slide, 8–15 pairs of measurements (value a and value b) were taken. The mode of taking measurements is demonstrated in Figure 1 with white and blue lines.

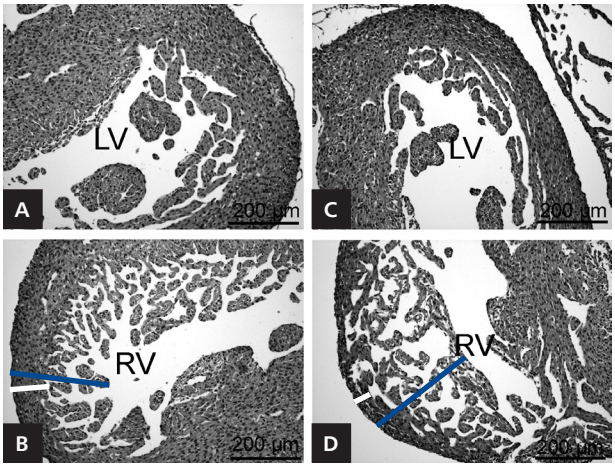

Figure 1. Selected histological sections from a 16 days post coitus control (**A**, **B**) and a retinoic acid (RA)-treated heart (**C**, **D**). The thickness of the compact and trabeculated myocardium (corresponding to value a) is marked with the blue line, and the thickness of the compact myocardium (corresponding to value b) is marked with the white line on panels **B** and **D**. The thickness of the left ventricular myocardial wall in the RA-treated heart is slightly diminished (**C**) compared to the myocardium of the control heart in panel **A**; LV — left ventricle; RV — right ventricle

Significant differences in a/b ratios between RA-treated and control hearts were determined with the nonpaired Student's t-test. A p value below 0.05 was considered statistically significant over controls.

RESULTS

The most important observation of our study was that exogenous RA administration to pregnant mice at 8.5 dpc induces noncompaction in a portion of offspring hearts during embryonic development. This noncompaction was identified by an increase of the ratio of compact and trabeculated layer to the compact layer of the myocardial wall compared to this ratio in control hearts from the same stage of development.

Trabeculations in control hearts were first noted in these inbred mice at 9.0 dpc. They occurred at the outer curvature of the heart tube within the primitive ventricle. Between the 9 dpc and 12.5 dpc stages there was no difference in a/b ratio

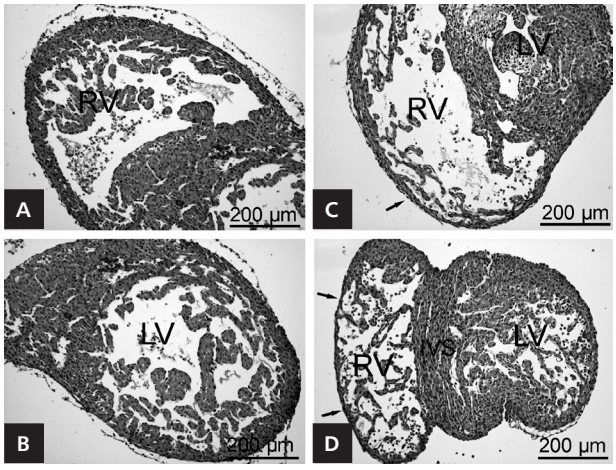

Figure 2. Selected histological sections (H&E stained) from serially cut 13 days post coitus hearts from control (**A**, **B**) and retinoic acid (RA)-treated (**C**, **D**) foetuses. Noncompaction of the right ventricle (RV) (**C**, **D**) has been diagnosed in RA--treated hearts. Of note is the bizarre shape of the heart with noncompacted right ventricle (cross section on panel **D**). The thinning of the compact myocardium is marked with arrows; LV — left ventricle; IVS — interventricular septum

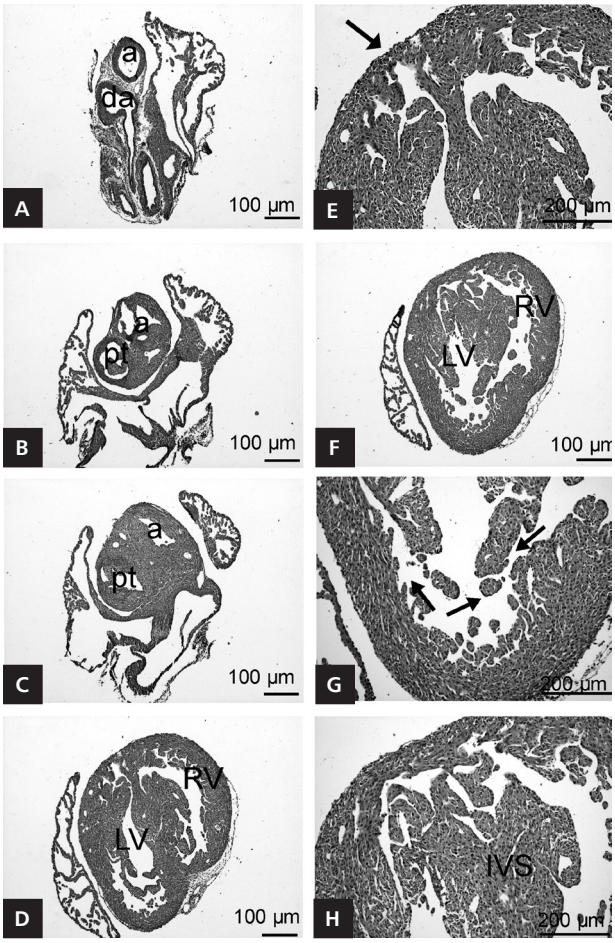

Figure 3. Selected histological sections of a serially (consecutively) sectioned 16 days post coitus heart treated with retinoic acid (RA). Transposition of the great arteries is evident in panels **A**–**C** in which the aorta arises from the right ventricle (RV) and the pulmonary trunk from the left ventricle (LV). Focal indentation (noncompaction) is demonstrated in panels **D** (low magnification) and **E** and marked with the black arrow. Swiss cheese-like ventricular septal defects are shown in panels **F** (small magnification), **G**, and **H** (high magnification). Panel **G** shows the upper part of the interventricular septum (IVS), **H** — the lower part of the IVS. Arrows in **G** point to slit-like defects in the IVS; ao — aorta; da — ductus arteriosus; pt — pulmonary trunk

in the LV and the RV between RA-treated and control hearts. In 13 dpc hearts, the wall of the compact myocardium thickened moderately at the expense of the trabecular layer (Fig. 2A–D). On histological examination, the hearts demonstrating noncompaction exhibited longer trabeculae and a thinner compact myocardial wall compared to control hearts of the same stage of development (Fig. 2C, D as compared to 2A, B). In hearts from the 13 dpc and 16 dpc embryonic stages exhibiting noncompaction, defects in the outflow tract, such as transposition of the great arteries (TGA) or double-outlet right ventricle (DORV) were diagnosed (Fig. 3A–D). In most affected hearts, the noncompaction was restricted to the wall of the RV, leaving the LV with a normal appearance. However, in other hearts noncompaction was present in both ventricles. The ratio of the thickness of the compact and trabeculated layer (value a) to the compact layer (value b) was lower in the LV of control compared to the RA-treated hearts (Table 1). In 16 dpc hearts, this ratio decreased markedly in LVs of control hearts due to an increase in thickness of the compact myocardium at the expense of trabeculae length during development. These differences in structure of the myocardial wall between control and RA-treated 16 dpc hearts were easily demonstrable on histological examination (Fig. 1 compares B with D and A with C). In the RV, the a/b ratio was higher compared to this value in the LV (Table 1). Another finding observed in some malformed and/or noncompacted hearts was the presence of multiple ventricular septal defects similar in appearance to Swiss cheese (Fig. 3G, arrows).

In our experimental model, this cardiomyopathy occurred at a frequency of about 42% of all RA-treated animals and was accompanied by outflow tract malformations such as DORV, TGA, and tetralogy of Fallot (Table 2).

DISCUSSION

Our study indicates that vitamin A overdose causes myocardial wall underdevelopment leading to a noncompacted appearance of the myocardial wall. Noncompaction in our experimental model was presented as an increased a/b ratio i.e. the ratio of the thickness of the trabeculated and compact myocardial wall to the thickness of compact myocardium. A similar observation of thinning or poorly developed myo-

Table 1. The a/b ratio in the left and the right ventricles of control (three hearts from each group) and noncompacted hearts after retinoic acid (RA) treatment (nine hearts from each group). Measurements were made at mid-ventricular and at subvalvular positions

Stage of development	Experimental group	a/b (mid-ventricular)	P	a/b (subvalvular)	P
13 days post coitus	Left ventricle, RA-treated	6.33 ± 3.21	< 0.05	5.76 ± 2.34	< 0.05
	Left ventricle, control	3.42 ± 1.39		3.60 ± 1.15	
	Right ventricle, RA-treated	7.98 ± 4.67	< 0.05	7.60 ± 4.63	< 0.05
	Right ventricle, control	3.44 ± 1.2		3.25 ± 1.17	
16 days post coitus	Left ventricle, RA-treated	2.88 ± 0.75	< 0.05	2.95 ± 1.65	< 0.05
	Left ventricle, control	2.25 ± 0.53		2.09 ± 0.81	
	Right ventricle, RA-treated	4.76 ± 5.05	< 0.05	3.32 ± 2.04	< 0.05
	Right ventricle, control	2.3 ± 0.72		2.57 ± 0.73	

The numbers in Table 1 represent mean values (M) of the quotient of the thickness of trabeculated and compact layer (value a) to the thickness of compact layer (value b) with standard deviation (M ± SD). A p value below 0.05 proved to be statistically significant.

Table 2. An incidence of noncompaction with outflow tract and other cardiac malformations in hearts of retinoic acid-treated mice at stages 13 and 16 days post coitus

Malformation	No. of cases (%)
Transposition of the great arteries	13 (30.24%)
Double outlet right ventricle	10 (23.25%)
Persistent truncus arteriosus	2 (4.65%)
Transposition of the great arteries and noncompaction	8 (18.6%)
Double outlet right ventricle and non-compaction	10 (23.25%)
Total number of hearts	43 (100%)

cardial wall has been reported in an early study by Wilson and Warkany [10] in certain of the offspring of a vitamin A-deficient rat, although the authors did not perform a more detailed study of this malformation. Noncompaction of the myocardial wall has been recently confirmed in knockout mice devoid of RA-synthesising gene *Raldh2* [14, 15]. Since RALDH2 is the major RA-synthesising enzyme during embryonic development, these mice can be considered as vitamin A-deficient [16].

Thus, RA deficiency in pregnant mice causes noncompaction cardiomyopathy in the offspring. Our analysis was based on an experimental model with RA overdose and represents the first detailed histological study on noncompaction in mice after RA treatment. We presented experimental evidence that a dose of 70 mg/kg of body weight of pregnant mice administered exactly at 8.5 dpc causes noncompaction in about 42% of the offspring. The dose of 70 mg/kg body weight was selected as having the most 'potent' teratogenic and less 'lethal' effect based on our studies and previous literature reports [13]. Additionally, our observations were: 1. the earliest stage of development of noncompaction that could be classified based on histomorphometric analysis of the myocardial wall is 13 dpc; 2. the noncompaction in this experimental model has been observed mostly in the RV, in some cases in the interventricular septum, and also in the LV, or in both ventricles; 3. in some hearts, the noncompaction occupied the whole myocardial wall and in others noncompaction has been observed to be present only in one section of the ventricle (the right or the left ventricle).

Referring to recent literature reports, we propose a mechanism of noncompaction caused by RA overdose. RA is upstream of various signalling pathways involved in heart development [17], i.e. it stimulates FGF8 signalling within the SHF and activates downstream genes of Hox family, and Wnt/beta-catenin family [12, 18, 19].

Activation of Wnt/beta-catenin regulates several processes during heart development including differentiation and proliferation of cardiac myocytes. One of these pathways is a canonical activation of different molecules like Frizzed, Dishevelled, or Vang responsible for planar cell polarity (PCP) [18, 20]. Disturbed PCP causes cardiomyocytes to remain round (i.e. without established cellular polarity) and elicits noncompaction of the heart [20]. We postulate that RA overdose might disturb the proper PCP pathway of cardiomyocyte development causing noncompaction.

In our experimental model of RA overdose, we observed that noncompaction of the RV was more affected than that of the LV. Since cells of the SHF, which are sensitive for RA signalling, contribute markedly to the RV and the outflow tract development [21, 22], it is accepted that a lack of addition of SHF cells to the heart tube during development causes shortening of the outflow tract and leads to outflow tract malformations [23]. The abnormal migration of SHF cells to the heart tube may also cause the thinning of the RV myocardial wall.

In humans, LVNC is usually an isolated malformation. The reports on human noncompaction are always case studies. Usually in such reports we do not have information about the mother's exposure to different environmental factors at various stages of development, except for one study [24].

Based on the mechanism of RA action on the developing heart, however, we cannot exclude the possibility that RA overdose during pregnancy might contribute to the development of noncompaction in human embryos, since it also causes the outflow tract malformations [24, 25]. In spite of this, there are no direct literature reports on this cardiac malformation (noncompaction) in the foetuses of women who overdose on retinoids.

In our experimental model, we noted that RA overdose causes outflow tract and heart malformations such as DORV, TGA, tetralogy of Fallot, persistent truncus arteriosus, uneven level of the pulmonary trunk roots to the aortic roots, ventricular septal defect, and hypoplastic aorta. Similar observations have been presented by Kalter, Warkany and Yasui et al. [13]. However, our study yielded different results since we demonstrated the presence of noncompaction in some hearts with DORV, tetralogy of Fallot, or TGA.

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CONCLUSIONS

Noncompaction caused by RA overdose can be elicited in part of the mouse offspring by administering RA at the stage of cardiac tube elongation.

Conflict of interest: *none declared*

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Kardiomiopatia gąbczasta u myszy indukowana kwasem retinowym

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Wszyscy autorzy w równym stopniu przyczynili się do powstania niniejszego artykułu.

Streszczenie

Wstęp: Badania z ostatnich lat wskazują, że precyzyjne lokalne stężenie kwasu retinowego (RA) w tkankach zarodka jest niezbędne do prawidłowego rozwoju komórek wtórnego pola sercotwórczego (SHF). Komórki SHF stanowią populację, która jest dodawana do wydłużającej się cewy serca podczas jej zapętlania, co jest istotne do prawidłowego jej dalszego rozwoju i pogrubiania ściany miokardium. Wykazano, że deficyt RA (np. u myszy, których matki utrzymywano na diecie ubogiej w RA lub u myszy transgenicznych pozbawionych najważniejszego genu, tj. *Raldh2*, produkującego lokalnie RA z jego aldehydu) powoduje ścieńczenie ściany miokardium.

Cel: Celem pracy była weryfikacja hipotezy, że nadmiar RA w czasie zapętlania się cewy serca może być również przyczyną ścieńczenia ściany miokardium (tzw. niescalenia mięśnia sercowego).

Metody: Kwas retinowy (*all-trans*) podano dootrzewnowo w dawce 70 mg/kg mc. samicom ciężarnym w stadium 8,5 dni po zapłodnieniu (dpc), tj. w okresie odpowiadającym wydłużaniu się i zapętlaniu cewy serca u zarodków. Analizie poddano serca płodów prawidłowych (niepoddanych działaniu RA) i badanych (po jednorazowej dawce RA), z których przygotowano skrawki histologiczne o orientacji poprzecznej. Niescalenie mięśnia sercowego oszacowano morfometrycznie, mierząc odległość między powierzchnią nasierdzia i szczytem beleczek sięgających w głąb jamy komory (wartość a) oraz między powierzchnią nasierdzia a wgłębieniem beleczek (wartość b). Iloraz a/b porównano w tych samych stadiach rozwojowych serc prawidłowych i serc płodów traktowanych RA.

Wyniki: Wykazano, że u ok. 42% płodów traktowanych RA pojawia się niescalenie miokardium, wyrażone znacznie większą wartością a/b w porównaniu z sercami prawidłowymi. Niescalenie można najwcześniej zaobserwować u płodów w stadium 13 dpc, na wysokości podzastawkowej (tj. w poziomie przekroju poprzecznego tuż poniżej tworzących się zastawek przedsionkowo-komorowych) oraz w połowie odległości między podstawą serca a koniuszkiem. Niescalenie utrzymuje się do końca życia płodowego, tj. do stadium 16 dpc. Ścieńczenie ściany miokardium występuje w tym modelu doświadczalnym częściej w prawej komorze niż w komorze lewej, choć w niektórych przypadkach jest obecne w obu komorach. Ponadto zaobserwowano, że serca te mają wady drogi odpływu, takie jak transpozycja wielkich naczyń, dwuujściowa prawa komora, tetralogia Fallota. Częstsze występowanie niescalenia w komorze prawej niż w lewej oraz wady drogi odpływu można wyjaśnić wrażliwością komórek SHF na lokalne zmiany stężenia RA oraz tym, że komórki te budują składniki komory prawej i drogi odpływu. Autorzy dyskutują nad prawdopodobnym mechanizmem powstawania niescalenia w wyniku nadmiaru RA poprzez zaburzenie aktywacji genów znajdujących się w dół drogi sygnałowej RA i odpowiedzialnych za tzw. płaszczyznową polaryzację kardiomiocytów (*planar cell polarity*). Retrospektywne dane kliniczne o wpływie przyjmowania wysokich dawek RA przez kobiety w ciąży (np. w leczeniu niektórych schorzeń skórnych) na wady serca u potomstwa są dostępne w literaturze, ale brak danych na temat niescalenia mięśnia sercowego u płodów w tych przypadkach.

Wnioski: Nadmiar RA w okresie wydłużania i zapętlania się cewy serca powoduje niescalenie u części płodów. Jest to pierwsze doniesienie o wpływie nadmiaru RA na niescalenie miokardium.

Słowa kluczowe: serce prenatalne myszy, niescalenie komory, wady drogi odpływu, wtórne pole sercotwórcze

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