



## Cardiac remodeling induced by 13-*cis* retinoic acid treatment in acne patients

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### ARTICLE INFO

#### Article history:

Received 10 February 2011

Received in revised form 22 March 2011

Accepted 13 May 2011

Available online 12 June 2011

#### Keywords:

Cardiac remodeling

Acne

13-*cis* retinoic acid

Vitamin A

### ABSTRACT

**Background:** Currently, 13-*cis*-retinoic acid (13-*cis*-RA) is the most effective therapy for acne. Isotretinoin, a first-generation synthetic 13-*cis*-RA compound, is associated with numerous adverse effects. To investigate the cardiac effects of 13-*cis*-RA, acne patients receiving 13-*cis*-RA were studied.

**Methods:** Twenty male patients with acne were enrolled in the study. Patients were treated with a dose of 0.5 mg/kg/d of isotretinoin. All participants were assessed prior to treatment and after 10 weeks of therapy with Doppler-echocardiogram.

**Results:** Patients showed reductions in right atrium vertical diameter, left atrium longitudinal diameter, left atrium volume and left ventricular diastolic diameter over the course of treatment. Significant increases in interventricular septum diastolic thickness, posterior wall diastolic thickness, relative wall thickness and left ventricle (LV) mass were observed. The LV mass index showed an increase in ventricular mass and a decrease in the cavity size. Examining LV systolic function, a decrease was observed for the cardiac index.

**Conclusion:** In this study, 10 weeks of 13-*cis*-RA therapy at a dose of 0.5 mg/kg/d was found to promote concentric-type heart remodeling due to the occurrence of two associated events: heart hypertrophy and hypovolemia.

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## 1. Introduction

Retinoic acid (RA) is the bioactive metabolite of vitamin A. It acts through nuclear retinoid receptors (RAR and RXR), alters protein synthesis in the heart and regulates embryonic development, tissue homeostasis and cellular differentiation and proliferation [1]. The effects of RA during adulthood are still poorly understood. Experimentally, it has been shown that all-*trans*-RA inhibits hypertrophy and fibrosis in spontaneously hypertensive rats [2], after myocardial infarction [3] and in aortic-banded rats [4]. In rats with no cardiovascular injury it was observed: 1) that a physiological dose of all-*trans*-RA caused cardiac remodeling with left ventricular hypertrophy, normal interstitial collagen and maintenance of cardiac geometry [5], and 2) that a deficiency vitamin A diet promoted a ventricular remodeling [6].

Some isomers of RA, including all-*trans*-RA, 9-*cis*-RA and 13-*cis*-RA are important to the heart with differing biological activities. All-*trans*-RA is a ligand for RARs, whereas 9-*cis*-RA is a high-affinity ligand for both the RXRs and the RARs [7–9]. Because 13-*cis*-RA has little or no binding affinity for RARs and RXRs [10,11], the effects of

13-*cis*-RA are thought to occur through the isomerization of 13-*cis*-RA to all-*trans*-RA and/or to 9-*cis*-RA [12].

For more than 25 years, 13-*cis*-RA has been used as an acne treatment [13], and it is the most effective systemic treatment option for severe acne. Isotretinoin is a first-generation synthetic retinoid that affects the skin and mucous membranes, the central nervous system, the gastrointestinal tract, and the musculoskeletal system [14].

Selcoki et al. used 24-h Holter electrocardiography monitoring for six months in isotretinoin therapy patients and did not find arrhythmic effects [15]. However, more studies are needed to obtain more precise results about the adverse cardiac effects of isotretinoin. Therefore, this study aimed to use Doppler-echocardiography to observe cardiac alterations in normal youth and adult subjects with acne vulgaris undergoing isotretinoin treatment.

## 2. Patients and methods

### 2.1. Subjects and treatment

This prospective study included twenty consecutive male adolescents and young adults aged 13 to 24 years (mean age of  $17.3 \pm 2.6$  years). Subjects were candidates to use 13-*cis*-RA (isotretinoin) at a single daily dose of 0.5 mg/kg. Subjects were followed at the Dermatology Outpatient Unit of the Botucatu School of Medicine University Hospital (FMB, UNESP). Exclusion criteria included being female, having diabetes mellitus, obesity, low weight, alcoholism, renal failure, previous hepatopathies, cardiopathies, dyslipidemias or inflammatory diseases of any etiology except acne

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itself, engaging in regular intense physical activity or using food supplements. All subjects provided informed consent, and the School of Medicine's Research Ethics Committee approved the study.

Patients were evaluated prior to the beginning of treatment (initial moment—IM) and after 10 weeks of treatment (final moment—FM). Clinical evaluation, Doppler-echocardiogram and measures of serum total protein and fractions (TP and albumin), C-reactive protein (CRP) and alpha-glycoprotein were performed on the same day.

## 2.2. Clinical evaluation

The same physician examined all individuals. The following parameters were recorded: weight, height, arterial blood pressure and cardiac frequency. Clinical signs and symptoms of medication toxicity were also investigated.

## 2.3. Dietary intake

The food intake evaluation included a 24-h dietary recall and a food frequency questionnaire (FFQ) [16]. The FFQ consisted of a list of 62 food types, preparations and drinks. The home measurements described by the patients were converted into grams or milliliters, according to Pinheiro et al.[17]. The data were changed into retinol equivalents, numbers of calories and grams of proteins, lipids and carbohydrates.

## 2.4. Doppler-echocardiographic evaluation

All exams were performed by the same cardiologist (BBM) following standard procedures for image recording and measurements [18]. Ultrasounds were performed with an HDI® 5000 SONOCT (Philips, Andover, MA). Left ventricle (LV) mass was estimated from linear dimensions as:  $LV\ mass\ (g) = 0.8 \times \{1.04 [(LVDD + PWT + IVSDT)^3 - (LVDD)^3] + 0.6\}$ , where LVDD, PWT and IVSDT represent the diastolic LV diameter, posterior wall thickness and septal wall thickness, respectively. LV mass was normalized for body surface area (LVMI, g/m<sup>2</sup>). Relative wall thickness (RWT) was calculated as  $2PWT/LVDD$ . LV systolic function was assessed by ejection fraction (EF) using the modified Simpson's rule and Doppler-derived stroke volume (SV), cardiac output (CO) and indexed CO (CI). Diastolic function was evaluated using pulsed Doppler recordings of mitral inflow velocities E and A waves (cm/s), deceleration time (DT, ms), isovolumic relaxation time (IRVT, ms), and also tissue Doppler-derived septal diastolic mitral annular motion (E', cm/s) and left atrial volume indexed to body surface area (LAVI, ml/m<sup>2</sup>). The dimensions of the left atrium were also evaluated by measuring the maximum diameter (LA, cm) in the parasternal view, the short axis in the mono-dimensional image and longitudinal (LA<sub>1</sub>) and cross-sectional (LA<sub>2</sub>) diameters (cm) obtained in the two-dimensional four-chamber apical view. Right ventricular chamber dimensions were evaluated using the same view by measuring the longitudinal and cross-sectional diameters of the right atrium (RA<sub>1</sub> and RA<sub>2</sub>, respectively) and systolic and diastolic right ventricular areas. Doppler-derived lateral tricuspid annular motion was recorded for right ventricular function analysis.

## 2.5. Biochemical evaluation

Albumin, C-reactive protein (CRP) and alpha-glycoprotein were measured from serum. Testing was performed using dry chemistry methodology on a Vitros 950 device (Johnson & Johnson, Rochester, NY).

## 2.6. Statistical methods

Differences between values at the initial and final moments were compared using the paired sample *t*-test or the Wilcoxon signed-rank test. SigmaStat for Windows v3.5 (SPSS Inc, Chicago, IL) was used. All values are expressed as mean ± SD, or median (quartile 1–quartile 3). The statistically significant level was set at 0.05 for all calculations.

## 3. Results

There were no significant differences over time in relation to weight, height, body mass index, food ingestion, systolic arterial pressure, diastolic arterial pressure or heart rate (data not shown). There was no difference in the serum albumin [IM = 4.70 (4.52–4.87) g/dl, FM = 4.70 (4.60–5.00) g/dl; *p* = 0.818], in the CRP [IM = 0.10 (0.00–0.70) mg/dl, FM = 0.20 (0.07–0.40) mg/dl; *p* = 0.426] or in the alpha-glycoprotein [IM = 92.5 ± 27.9 mg/dl, FM = 70.0 ± 20.4 mg/dl; *p* = 0.220].

### 3.1. Doppler-echocardiographic evaluation

Over the treatment period, there was a reduction in RA<sub>1</sub>, LA<sub>1</sub> diameter, LA volume and LVDD. Significant increases in IVSDT, PWT,

**Table 1**  
Data for cardiac morphometric variables.

Variables	IM	FM	<i>p</i> value
LA (cm)	3.3 ± 0.4 <sup>a</sup>	3.3 ± 0.3	0.389
LA <sub>1</sub> (cm)	4.5 ± 0.6	4.2 ± 0.7	<b>0.033</b>
LA <sub>2</sub> (cm)	3.9 ± 0.4	3.9 ± 0.5	0.600
LA volume (ml)	31.3 ± 7.9	28.3 ± 9.1	<b>0.023</b>
RA <sub>1</sub> (cm)	4.3 ± 0.5	4.1 ± 0.5	<b>0.019</b>
RA <sub>2</sub> (cm)	4.0 ± 0.5	3.7 ± 0.9	0.137
LVDD (cm)	5.0 ± 0.4	4.9 ± 0.4	<b>0.019</b>
LVSD (cm)	3.10 (2.88–3.30) <sup>b</sup>	3.10 (2.80–3.35)	0.761
RVAd (cm <sup>2</sup> )	20.22 ± 4.19	22.12 ± 5.88	0.149
RVAs (cm <sup>2</sup> )	11.42 ± 3.20	12.27 ± 3.01	0.247
IVSDT (cm)	0.70 (0.70–0.80)	0.85 (0.80–0.90)	<b>0.001</b>
PWT (cm)	0.73 (0.70–0.80)	0.81 (0.80–0.90)	<b>0.007</b>
RWT	0.29 ± 0.03	0.34 ± 0.05	<b>0.002</b>
LVM (g)	124.2 ± 25.5	143 ± 36.7	<b>0.007</b>
LVMI (g/m <sup>2</sup> )	68.8 ± 11.1	78.6 ± 16.7	<b>0.033</b>

IM and FM: Initial and final moments; LA: Left atrium diameter; LA<sub>1</sub> and LA<sub>2</sub>: Left atrium longitudinal and cross-sectional diameters; RA<sub>1</sub> and RA<sub>2</sub>: Right atrium vertical and cross-sectional diameters, respectively; LVDD and LVSD: Left ventricular diastolic and systolic diameters, respectively; RVAd and RVAs: Diastolic and systolic right ventricle areas, respectively; IVSDT: Interventricular septum diastolic thickness; PWT: Posterior wall diastolic thickness; RWT: Relative wall relative thickness; LVM: Left ventricle mass; LVMI: Left ventricle mass index.

Bold values indicates statistical significance (<0.05).

<sup>a</sup> Means and standard deviations.

<sup>b</sup> Medians and quartile 1 and quartile 3.

RWT, LVM and LVMI were observed, with increases in ventricular mass and decreases in cavity size, as shown in Table 1.

Table 2 shows the echocardiographic variables that evaluate LV systolic and diastolic function. A decrease was observed between the initial and final moments in the cardiac index for LV systolic functioning.

There was a decrease in the left ventricle fast filling maximum velocity, left ventricle late filling maximum velocity, the ratio between peaks of flow velocity and mitral annulus movement at the beginning of diastole and LA variation fraction. The peak of the displacement velocity for the septal portion of the mitral annulus increased during atrial contraction (Table 2).

## 4. Discussion

Cardiac remodeling is defined as an alteration in protein synthesis, which results in molecular, cellular and interstitial cardiac changes. Such alterations can clinically manifest as changes in cardiac volume,

**Table 2**  
Data for left ventricle systolic and diastolic function variables.

Variables	IM	FM	<i>p</i> value
EF	0.59 ± 0.06 <sup>a</sup>	0.62 ± 0.05	0.127
%ΔD	38.2 ± 6.2	36.4 ± 4.7	0.116
SV (ml)	67.7 ± 15.0	63.7 ± 15.9	0.084
CO (L/min)	4.50 ± 1.18	4.08 ± 0.99	0.061
CI (L/min/m <sup>2</sup> )	2.50 ± 0.60	2.24 ± 0.43	<b>0.044</b>
E (cm/s)	91.8 ± 15.1	82.4 ± 16.4	<b>0.004</b>
A (cm/s)	47 ± 9.2	39.8 ± 8.9	<b>0.006</b>
E/A ratio	2.0 ± 0.5	2.2 ± 0.8	0.289
DT (ms)	187 ± 53.7	178 ± 53.1	0.455
IRT (ms)	77.1 ± 17.7	77.4 ± 12.7	0.932
E' (cm/s)	14.0 ± 3.6	15.2 ± 4.5	0.196
A' (cm/s)	7.4 ± 2.4	9.1 ± 3.1	<b>0.016</b>
E/E'	6.9 ± 1.7	5.7 ± 1.3	<b>0.004</b>

IM and FM: Initial and final moments; EF: Ejection fraction; %ΔD: Left ventricular fractional shortening; SV: Stroke volume; CO: Cardiac output; CI: Cardiac index; E: Early peak transmitral flow velocity; A: Late peak transmitral flow velocity; DT: E-wave deceleration time; IRT: Left ventricle isovolumetric relaxation time; E': Early peak velocity of mitral annular motion; A': Late peak velocity of mitral annular motion.

Bold values indicates statistical significance (<0.05).

<sup>a</sup> Means and standard deviations.

mass, constitution, geometry and/or function [19,20]. The main findings in our study were an increase in ventricular mass and a decrease in the size of the chambers. Together, these results lead us to assume that the patients developed cardiac hypertrophy, although the absolute values did not surpass the upper limits of normality for any of the measured variables.

Several mechanisms could explain this finding of myocardial growth, including nutritional status improvement, body growth, physical exercise, pressure overload, inflammation status and retinoid acid action.

#### 4.1. Nutritional status

Acne is a disease characterized by dermal inflammation, and inflammation is a possible cause of protein-energy malnutrition (PEM). In the present study, the subjects showed normal weight and height for their age [21]. These observations allowed us to exclude nutritional status as a determinant for myocardial growth.

#### 4.2. Growth

When analyzing weight and height values, it was also important to note that the initial and final moment measurements were not significantly different. This lack of change led us to disfavor physical development as a variable that could be associated with cardiac structural alterations.

#### 4.3. Physical exercise

Physical exercise could be associated with cardiac enlargement, but was ruled out by the exclusion criteria.

#### 4.4. Pressure overload

The ventricular remodeling process is influenced by various stimuli, including mechanical factors like hemodynamic pressure overload [22].

At the time the study began, our patients were normotensive, with a mean SAP value of 112 mm Hg and a median DAP of 70 mm Hg. None of them showed arterial pressure values that would indicate systemic arterial hypertension, according to the V Brazilian Guidelines for Arterial Hypertension (2006) [23]. Even so, significant variations within the normal limits could justify a gain in myocardial mass during the protocol period. However, subjects maintained constant systolic and diastolic arterial pressure values without significant variations between our first and last evaluations of them, which led us to discard such variables as the cause of myocardial mass increase. Also, Karadag et al. did not show an increase in blood pressure in patients receiving isotretinoin during a period of 3 months [24].

#### 4.5. Inflammation

Acne vulgaris is a disease that affects pilosebaceous follicles, and it is characterized by sebaceous hyperproduction, follicular hyperkeratinization, bacterial colonization and periglandular dermal inflammation [25]. Severe acne can also cause pain, fever, arthralgia and anorexia. It can also cause a humoral inflammatory response mediated by keratinocytes to occur, interleukin 1 (IL-1) as well as tumor necrosis factor (TNF- $\alpha$ ) to be produced and reactive oxygen species to form [25]. Therefore, patients may face cutaneous and systemic inflammatory processes.

In the present study, CRP was used as an inflammation marker. Our patients did not show high levels of this marker prior to treatment with 13-*cis*-RA, and no change was observed between the two evaluations. This was also true for the acid alpha-glycoprotein, another inflammation marker that was within normal values at the

beginning of our study and did not significantly change over the course of our study. Using routine analytical methods, the CRP detection limit is 0.5 mg/dl, but using ultra-sensitive methods, it is possible to detect CRP levels as low as 0.08 mg/dl. Recent studies have shown that even slightly increased CRP is a cardiovascular risk factor. We did not use the ultra-sensitive method in our study; hence, we may have failed to detect atherosclerotic or similar inflammatory processes, in which CRP levels above 0.3 mg/dl are associated with higher cardiovascular risk.

The relationship between inflammation and cardiac hypertrophy is well established in the literature. In type 2 diabetes mellitus, Palmieri et al. showed that the higher the CRP, the greater the risk of hypertrophy in the left ventricle [26]. This was also observed in a cross-sectional study [27]. Additionally, experimental studies have shown that inflammatory cytokines, such as TNF- $\alpha$  and interleukin-1b among others, can contribute to the development and progression of cardiac failure, since they promote cardiac hypertrophy by activating cellular matrix metalloproteinases, causing contractile dysfunction and inducing apoptosis [28]. In the present study, no alterations in inflammatory activity markers were observed. Additionally, since RA attenuates inflammation, treatment would tend to reduce ventricular mass; however, cardiac hypertrophy was found.

#### 4.6. Concentric remodeling or “pseudohypertrophy”

In a model of bleeding hypovolemia in pigs, Di Segni et al. [29] used echocardiography to observe an increase in the left ventricle posterior wall and interventricular septum, a decrease in the left ventricle diastolic and systolic diameter, an increase in the left ventricular wall relative thickness and maintenance of left ventricular mass. The authors called such alterations “pseudohypertrophy” [29]. Another study involving hypovolemia and echocardiographic measurements was conducted by Boussuges et al. [30] on healthy volunteers who were submitted to hyperbaric exposure and hyperoxia through the performance of a fasting physical activity session. In addition to a reduction in the heart's left chambers, a decrease in ventricular systolic function indexes (percentage of ventricular diameter shortening and cardiac output) was observed while heart rate was maintained [30].

Some of these previously published data are consistent with the present study, i.e. increased left ventricle wall thickness, chambers reduction and decreased heart rate. Taken together, these would suggest a hypovolemic state. However, in the studies by Di Segni et al. [29] and Boussuges et al. [30], LVM remained unchanged by the proportionality between the increase in the left ventricle walls (IVSDT and PWT) and cavity reduction. However, in our study, LVM and LVMI increased.

RA has effects that can explain our findings of cardiac hypertrophy and cavity reduction: direct action on the heart and peripheral action on the renin–angiotensin–aldosterone system.

Our finding of LV mass increase can be explained by the direct action of vitamin A on the heart. We have previously shown that Wistar rats receiving a standard diet plus a low dose of RA for 90 days show an increased LV mass [5]. Also, light microscopy revealed that myocyte sectional area was increased without collagen fraction volume variation, indicating hypertrophy without interstitial fibrosis.

This cardiac hypertrophy could be explained by an effect of vitamin A on growth and cellular differentiation, as well as by the fact that RAR and RXR receptors act as DNA transcription factors, similar to receptors for cortisol, vitamin D and thyroidal hormone [31]. Additionally, the activation of the RXR-PPAR $\gamma$  complex has been described as a cause of cardiac hypertrophy. RXR $\beta$  activation by the supply of in normotensive rats for 90 days resulted in a 10% increase in left ventricular mass [32].

RA acts on the renin–angiotensin–aldosterone system, and it is an important regulator for cardiovascular and renal structure and function, in addition to providing salt and water balance [33].

Treatment with RA increases expression of the angiotensin-converting enzyme 2 (ACE2) at both the mRNA and protein levels, resulting in blood pressure reduction and attenuation of myocardial damage [34]. Thus, the vasodilating action of ACE2 and its participation in the salt and water balance could lead to hypovolemia and reduced chambers and blood flow velocities. All-*trans*-RA can inhibit the renin–angiotensin–aldosterone system under experimental conditions [4]. Therefore, our patients may have been under conditions of lower salt and water retention during the study period. We observed a reduction in mitral transvalvular blood flow velocity, thus supporting this hypothesis. In individuals without cardiovascular disease, these indicators are closely associated with the circulating volume. That is, in situations of smaller venous return, there would be a reduction in diastolic flow velocity through the atrioventricular valves. The observation of a lower cardiac index at the final time point of our study reinforces this hypothesis.

A potential limitation of this study is that it is not a randomized clinical trial and no control groups were included.

We conclude that a ten week 13-*cis*-RA treatment promotes concentric-type heart remodeling due to the occurrence of two associated events: heart hypertrophy and hypovolemia.

#### Acknowledgements

This work was supported by Botucatu Medical School. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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