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Ω-3 PUFA supplementation decreases nuclear factor κB activity and attenuates pressure overload-induced cardiac dysfunction**

Suplementacja wielonienasyconymi kwasami tłuszczowymi ω-3 obniżająca aktywność czynnika transkrypcyjnego κB i zapobiegająca dysfunkcji serca indukowanej przeciążeniem ciśnieniowym

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Key words

diet, ω-3 polyunsaturated fatty acids, heart failure, left ventricular remodeling, NF-κB

Słowa kluczowe

dieta, wielonienasycone kwasy ω-3, niewydolność serca, przebudowa lewej komory serca, czynnik transkrypcyjny NFκB

Summary

Introduction. Supplementation with ω-3 polyunsaturated fatty acids (ω-3 PUFA) exerts cardioprotective effects in heart failure patients, however the mechanism is not well know. The present study assessed the effect of DHA+EPA on the activation of nuclear factor (NF)-κB and on the left ventricular (LV) response to pressure overload.

Aim. The present study assessed the effect of DHA+EPA on the activation of nuclear factor (NF)-κB and on the left ventricular (LV) response to pressure overload.

Material and methods. Male Wistar rats were fed a standard chow or DHA+EPA supplemented diet. After 1 week rats underwent abdominal aortic banding or sham surgery (n = 6-7/group). LV function was assessed by echocardiography after 12 weeks. In addition, we studied the effect of ω-3 PUFA on the cardiac NF-κB activity and expression of NF-κB target genes.

Results. Male Wistar rats were fed a standard chow or DHA+EPA supplemented diet. After 1 week rats underwent abdominal aortic banding or sham surgery (n = 6-7/group). On the standard diet, 12 weeks of pressure overload induced significant LV hypertrophy, remodeling and contractile dysfunction, and increased cardiac (NF)-κB activity. Dietary DHA+EPA attenuated pressure overload induced cardiac pathology and inhibited (NF)-κB activity. DHA+EPA decreased mRNA expression of NF-κB-depended genes encoding proteins involved in regulation of inflammation (TNFα and IL-1β), apoptosis (Bcl2), and fibrosis (TGF-β1).

Conclusions. Dietary supplementation with DHA+EPA attenuated pressure overload induced LV hypertrophy, remodeling and contractile dysfunction, which was associated with decreased cardiac (NF)-κB activity and switched expression of NF-κB target genes.

Streszczenie

Wstęp. Istnieją dowody, że suplementacja diety wielonienasocynymi kwasami ω-3 ma korzystne działanie u pacjentów z niewydolnością serca, jednak mechanizm tego zjawiska nie jest dobrze poznany.

Cel. Celem pracy była ocena wpływu DHA+EPA na aktywność czynnika transkrypcyjnego NF-κB oraz odpowiedzi lewej komory (LV) serca na przeciążenie ciśnieniowe.

Materiał i metody. Badania były przeprowadzone na szczurach rasy Wistar, u których po tygodniu stosowania diety standardowej lub diety z dodatkiem DHA+EPA, wykonano

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zwężenie aorty brzusznej lub operację pozorną (n = 6-7/grupa). Po 12 tygodniach oceniono echokardiograficznie funkcję LV, oraz sercową aktywność NF-κB i ekspresji genów kontrolowanych przez NF-κB

Wyniki. U szczurów karmionych dietą standardową, przeciążenie ciśnieniowe prowadziło do przerostu, przebudowy i upośledzenia funkcji skurczowej LV, którym towarzyszył wzrost sercowej aktywności NF-κB. Dieta zawierająca DHA+EPA zapobiegała patologiom LV indukowanym przeciążeniem ciśnieniowym i zmniejszała aktywność NF-κB. Stosowanie tej diety było również związane z obniżeniem ekspresji mRNA dla genów kodujących białka regulujące odczyn zapalny (TNFα i IL-1β), apoptozę (Bcl2) i włóknienie (TGF-β1), których ekspresja jest regulowana aktywnością NF-κB.

Wnioski. Suplementacja diety kwasami DHA+EPA zapobiega przerostowi, przebudowie i upośledzeniu czynności LV w odpowiedzi na przeciążenie ciśnieniowe. Efektom tym towarzyszył spadek aktywności NF-κB i zmiany w ekspresji genów kontrolowanych przez NF-κB.

INTRODUCTION

Heart failure is the most common cause for hospitalization and death within Medicare population despite optimal treatment, therefore new therapeutic approaches are needed. Nutritional therapies aimed at stopping or slowing the development of heart failure are particularly attractive because they could work additively with current drugs. Some epidemiological and animal researches suggest that dietary supplementation with the ω-3 polyunsaturated fatty acids (ω-3 PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are highly concentrated in fish oil, may be effective in preventing the development and progression of heart failure (1, 2). Result from clinical studies show that treatment with DHA+EPA can improve left ventricular function and modestly reduce clinical events in heart failure patients (3, 4). However, there is modest evidence supporting the effectiveness of ω-3 PUFA in heart failure (5).

The mechanisms for a potential favorable effect of ω-3 PUFA in prevention the development and progression of heart failure are likely multifactorial and not well established. We previously reported that ω-3 PUFA supplementation increased adiponectin concentration in the plasma in a dose-dependent manner in rats, indicating a potential role for adiponectin in mediating the beneficial cardioprotective effect of ω-3 PUFA (6). Adiponectin is adipocyte-derived hormone that can limit the LV hypertrophy, remodeling and contractile dysfunction in response to pressure overload (7) or after myocardial infarction (8). The cardioprotective action of adiponectin has been linked to inhibition of the nuclear transcription factor kappa B (NF)-κB (9), which activity increased in the failing myocardium (10, 11). NF-κB exists in the cytoplasm in an inactive form, bound to the inhibitory protein, IκB. On stimulation, IκB is phosphorylated leading to the release of IκB, which then translocates to the nucleus and regulates expression an array of genes involved in inflammation, apoptosis and collagen metabolism (12). Activation of these mechanisms in myocardium, under increased hemodynamic load condition, initiates hypertrophy, inflammation, apoptosis, and fibrosis, culminating in contractile dysfunction and overt HF.

AIM

The goal of the present investigation was to assess the ability of clinical relevant dose of ω-3 PUFA (DHA+EPA) to prevent LV pathology and NF-κB activation in response to pressure overload. We hypothesize that DHA+EPA supplementation decreases cardiac activity of NF-κB and modulates the expression of NF-κB target genes, which attenuates LV hypertrophy, remodeling and contractile dysfunction. This effect corresponds to the increased in plasma adiponectin concentration. Studies were performed in an established rat model of chronic pressure overload induced by abdominal aortic banding. This model results in the LV hypertrophy and the development of heart failure as evidenced by an increase in LV end-diastolic and end-systolic, and expansion of fetal genes.

MATERIAL AND METHODS

Experimental design

The animal protocol was conducted according to the local and institutional regulation. The study conformed to the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23). Animals were maintained on a reverse 12-hour light-dark cycle.

Five-week old male Wistar rats were fed either a standard chow or a modified standard chow containing ω-3 PUFA from fish oil. After one week on the assigned diet, rats were randomly assigned to either sham surgery or abdominal aortic banding (AAB) (n = 6-7/group), and dietary treatment was continued for 12 wks. Echocardiographic assessment of LV function was performed 1-2 days before and 12 weeks post-surgery. Twelve weeks after surgery, rats were weighed and anesthetized with 1.5-2.0% isoflurane, and 3 mL blood was drawn from the inferior vena cava for biochemical measurements. The LV tissue was quickly removed, weighed, freeze clamped and stored at -80°C for biochemical analysis.

Diets

All chows were custom manufactured (Research Diets Inc., USA). The standard chow was similar to typical commercial rodent chows, with 70% of total energy from carbohydrate (75% from cornstarch, 15% malto-

dextrin and 10% from sucrose by energy), 10% of energy from fat (78% from cocoa butter and 22% from soybean oil) and 20% protein (casein supplemented with L-cystine). ω-3 PUFA diet also derived 10% of the total energy from fat, with 3% the total energy as DHA+EPA (1:1) from fish oil (gift from KD Pharma, Germany), 4.8% from cocoa butter, and 2.2% from soybean oil. The protein and carbohydrate composition of the ω-3 PUFA diet matched the standard chow.

Abdominal aortic banding

The rats (170-220 g) were anesthetized with 2.0-2.5% isoflurane by mask. A midline abdominal incision was used to expose the suprarenal abdominal aorta. The aorta was tied with a 3-0 silk suture against a blunt needle (21G). The needle was immediately removed, leaving the aortic lumen constricted to the diameter of the needle. Sham surgery animals were subjected to the same procedure without the aortic banding.

Echocardiography

Echocardiography was performed using MYLab25 (Esaote, Italy) with a 13-MHz linear array transducer. Briefly, rats were anesthetized with 1.5-2.0% isoflurane by mask, the chest was shaved and the animal was situated in the supine position. Two-dimensional cine loops and guided M-mode frames were recorded from parasternal short and long axis. All data were analyzed offline with software resident on the ultrasound system at the end of the study.

Biochemical measurements

LV tissue was analyzed for phospholipid fatty acid composition by gas-liquid chromatography as described previously (13). Myocardial DNA binding activity of NF-κB in nuclear extracts was also measured by ELISA (Cayman Chemical, USA) and nuclear extract was isolated using the NE-PER Kit following the manufacturer's instructions (Thermo Scientific, USA). Plasma concentration of adiponectin was measured by enzyme-linked immunosorbent assay (ELISA) (ALPCO Diagnostics, USA).

mRNA measurement

For assessment of mRNA expression, frozen LV tissue was homogenized using a Tissue Lyser (Qiagen, USA), RNA was isolated using the RNeasy Mini Kit following the manufacturer's instructions (Qiagen), and Real time RT-PCR was performed as previously described (2). The following genes were analyzed, using TaqMan gene expression assays (Applied Biosystems, USA): atrial natriuretic peptide (Rn00561661_m1); myosin heavy chain α (Rn00568304_m1); myosin heavy chain β (Rn00568328_m1), TNFα (Rn_01473656_g1), IL-1β (Rn_99999009_m1), Bcl2 (Rn_99999125_m1), caspase 3 (Rn_00563902_m1), TGF-β1 (Rn_01475963_m1), and cyclophilin A (Rn00690933_m1). mRNA was normalized to fold increase to the standard diet sham group.

Statistical analysis

Mean values are presented ± S.E.M and a $P < 0.05$ level of significance was used. Comparisons were made using a two way ANOVA with the Bonferroni test for multiple comparisons.

RESULTS

LV phospholipids composition

Dietary supplementation with ω-3 PUFA causes considerably change in phospholipid fatty acid composition in both AAB and sham rats, as seen in the elevated DHA and EPA and in the decreased arachidonic acid (AA) contents (tab. 1).

LV mass, remodeling and contractile function

Initial body mass was matched among groups, and was similar at the termination of treatment among standard diet and DHA+EPA diet groups (tab. 2). Average daily food consumption also was not different among groups (data not shown). There was no difference in tibia length among dietary treatment groups (tab. 2). At 12 weeks AAB caused increase in LV mass normalized to tibia length in both groups; however the increase was greater with the standard diet (44%) than with DHA+EPA diet (18%) (fig. 1a). Neither DHA+EPA supplementation nor AAB affected RV mass/tibia length (tab. 2). With standard chow diet there was significant LV remodeling and systolic dysfunction with AAB compared to sham, as seen in the increase in end diastolic and systolic volumes and a reduction in ejection fraction, which was attenuated by the DHA+EPA diet (fig. 1b and c, tab. 2).

Table 1. Fatty acid composition of phospholipids in left ventricle and mRNA expression of markers of the heart failure.

	Standard Chow Sham (n = 6)	Standard Chow AAB (n = 6)	DHA+EPA Sham (n = 6)	DHA+EPA AAB (n = 6)
DHA	5.32 ± 0.12	5.06 ± 0.17	12.52 ± 0.32$^{\#}$	12.74 ± 0.52$^{\#}$
EPA	0.69 ± 0.08	0.66 ± 0.01	4.01 ± 0.18$^{\#}$	3.64 ± 0.29$^{\#}$
AA	24.67 ± 0.77	23.30 ± 0.74	13.19 ± 0.44$^{\#}$	11.95 ± 0.73$^{\#}$
ANP	1.00 ± 0.20	5.04 ± 0.82*	1.08 ± 0.25	2.32 ± 0.48*$^{\#}$
MHCβ/MHCα	1.00 ± 0.23	3.47 ± 0.64*	1.05 ± 0.24	1.96 ± 0.18*$^{\#}$

Cardiac content eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA) expressed as % of total fatty acids. The mRNA expression for the atrial natriuretic peptide (ANP), myosin heavy chain (MHC) α and β expressed as a fraction of the sham standard chow diet. Data are the mean ± SEM.

*$p < 0.05$ vs. respective sham

$^{\#}p < 0.05$ vs. standard diet

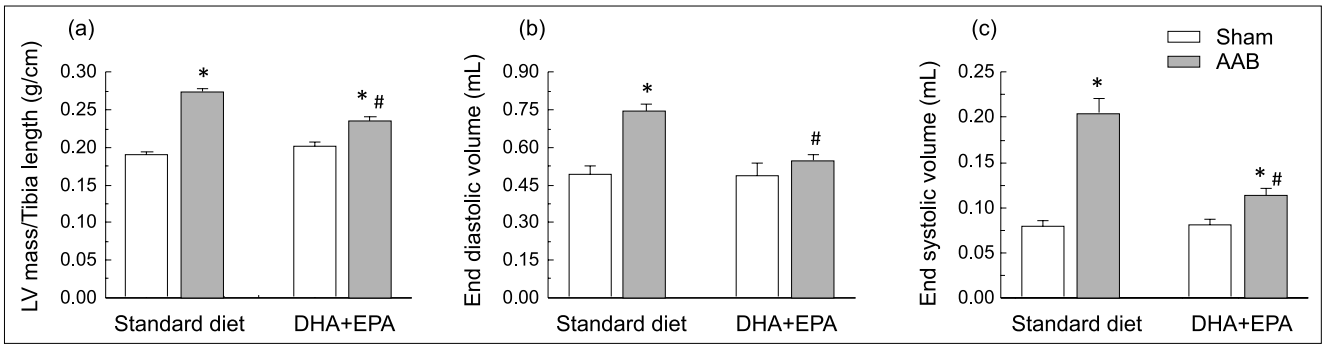

Fig. 1. LV mass/tibia length ratio (a) and echocardiograpgic assessment of LV end diastolic volume (b), and end systolic volume (c). Data are the mean ± SEM.
*p < 0.05 vs. respective sham
#p < 0.05 vs. standard diet (n = 6-7/group)

Table 2. Heart and body masses, and echocardiography results.

	Standard Chow Sham (n = 6)	Standard Chow AAB (n = 7)	DHA+EPA Sham (n = 7)	DHA+EPA AAB (n = 7)
Pre-surgery body mass (g)	200 ± 6	207 ± 4	194 ± 3	198 ± 6
Terminal body mass (g)	507 ± 14	530 ± 25	486 ± 10	507 ± 17
Tibia length (cm)	4.50 ± 0.06	4.53 ± 0.05	4.30 ± 0.05	4.57 ± 0.09
RV mass/tibia length (g/cm)	0.051 ± 0.002	0.053 ± 0.003	0.050 ± 0.002	0.047 ± 0.002
Biventricular mass/ tibia length (g/cm)	0.24 ± 0.01	0.33 ± 0.08*	0.25 ± 0.01	0.28 ± 0.07*#
Ejection fraction (%)	83.8 ± 0.2	71.8 ± 2.8*	83.5 ± 0.5	79.0 ± 1.5#
Heart rate (bpm)	372 ± 10	350 ± 9	374 ± 9	360 ± 11
Anterior wall thickness (mm)	1.72 ± 0.03	2.21 ± 0.06*	1.86 ± 0.07	2.06 ± 0.07*
Posterior wall thickness (mm)	1.90 ± 0.06	2.71 ± 0.07	2.03 ± 0.08	2.29 ± 0.08
Relative wall thickness (mm)	0.49 ± 0.02	0.61 ± 0.02	0.53 ± 0.02	0.57 ± 0.02

Data are the mean ± SEM
*p < 0.05 vs. respective sham
#p < 0.05 vs. standard diet

The increase in the mRNA expression for fetal genes ANP and MHCβ and a decrease in MHCα (adult isoform) are established molecular markers of the heart failure (14). AAB produced an increase in mRNA expression of ANP and MHCβ/MHCα ratio; however the increase was significant higher with the standard diet than with DHA+EPA diet (tab. 1).

Adiponectin and NF-κB DNA binding activity

In myocardium, nucleus NF-κB DNA binding activity was significantly higher in the standard diet in AAB rats compared with sham rats, which was blunted by DHA+EPA supplementation (fig. 2a). The constitutive NF-κB activity was no affected by DHA+EPA diet. Plasma concentration of adiponectin was not affected by AAB in rats fed the standard diet, but was raised by DHA+EPA diet both sham and AAB groups (fig. 2b). End diastolic volume was positively correlated with cardiac NF-κB DNA binding (fig. 3a), and cardiac NF-κB DNA binding was negative correlated with plasma adiponectin concentration (fig. 3b).

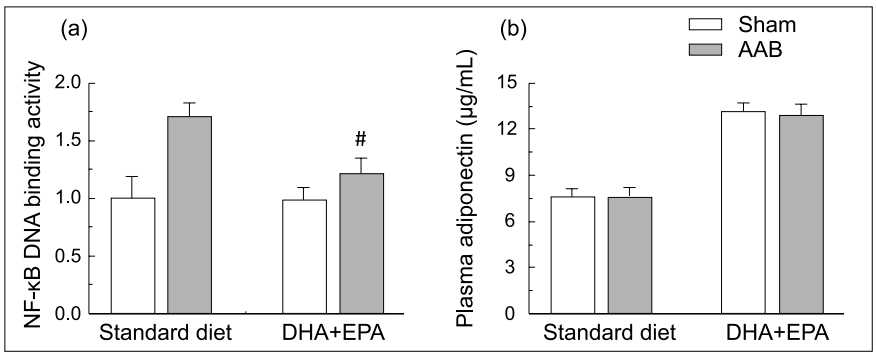

Fig. 2. Cardiac NF-κB DNA binding activity expressed as a fraction of the sham standard diet (a), and plasma levels of adiponectin (b). Data are the mean ± SEM.
*p < 0.05 vs. respective sham
#p < 0.05 vs. standard diet (n = 6/group)

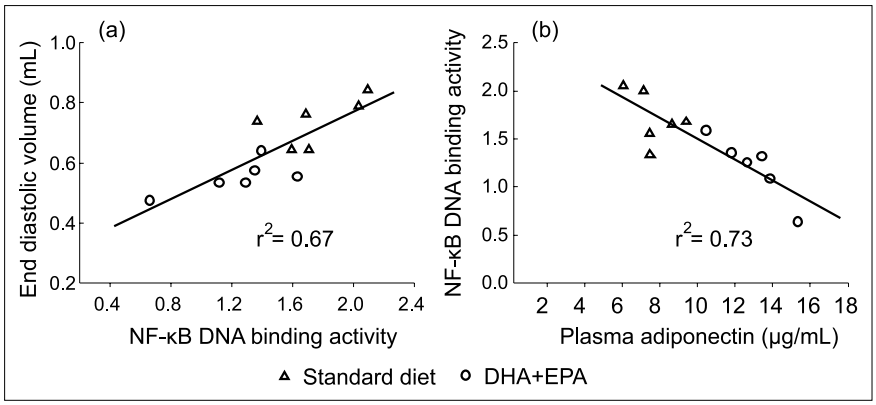

Fig. 3. Left ventricular end diastolic volume plotted as a function of cardiac NF-κB DNA binding activity (a). Cardiac NF-κB DNA binding activity plotted as a function plasma adiponectin concentration (b).

mRNA expression of NF-κB target genes

Next we investigated the mRNA expression of NF-κB target genes encoding proteins involved in regulation of inflammation – TNFα and IL-1β, apoptosis – Bcl2, and fibrosis – TGFβ.

The mRNA for TNFα and IL-1β was significantly increased in the standard diet in AAB group compared with sham group, which was abolished with DHA+EPA diet (fig. 4a and b). Similarly, in sham group, DHA+EPA diet decrease mRNA expression of TNFα and IL-1β.

The DHA+EPA supplementation increased mRNA expression of Bcl2 in both sham and AAB rats (fig. 4c). In contrast, DHA+EPA diet and had no effect on mRNA for caspase-3, which is inhibiting by Bcl2 (fig. 4d). There was an insignificant trend for down-regulation of Bcl2 expression and up-regulation of caspase-3 expression with AAB on the standard diet.

With standard diet there was significant elevate mRNA for TGFβ in AAB rats compared with sham rats, which was attenuate by the DHA+EPA diet (fig. 4e).

DISCUSSION

The main novel finding of the present study is that DHA+EPA supplementation can prevent the increase in the level of cardiac NF-κB activity and changes in the expression of NF-κB dependent genes. Theses maintenance corresponded with attenuated LV hypertrophy, remodeling and contractile dysfunction. In addition, DHA+EPA treatment elevates plasma adiponectin concentration.

It is well know that the NF-κB activation contribute to development of heart failure (12, 15). In the present study, prolonged pressure overload condition was associated with elevated NF-κB activity, and there was a positive correlation between cardiac NF-κB activity and LV remodeling. The attenuation of this LV pathology by DHA+EPA supplementation was accompanied by a decline in myocardium NF-κB activity. What must be amphasized, ω-3 PUFA reduced NF-κB activity only in pressure overload and did not affect baseline NF-κB activity in control animals. This is important in view of

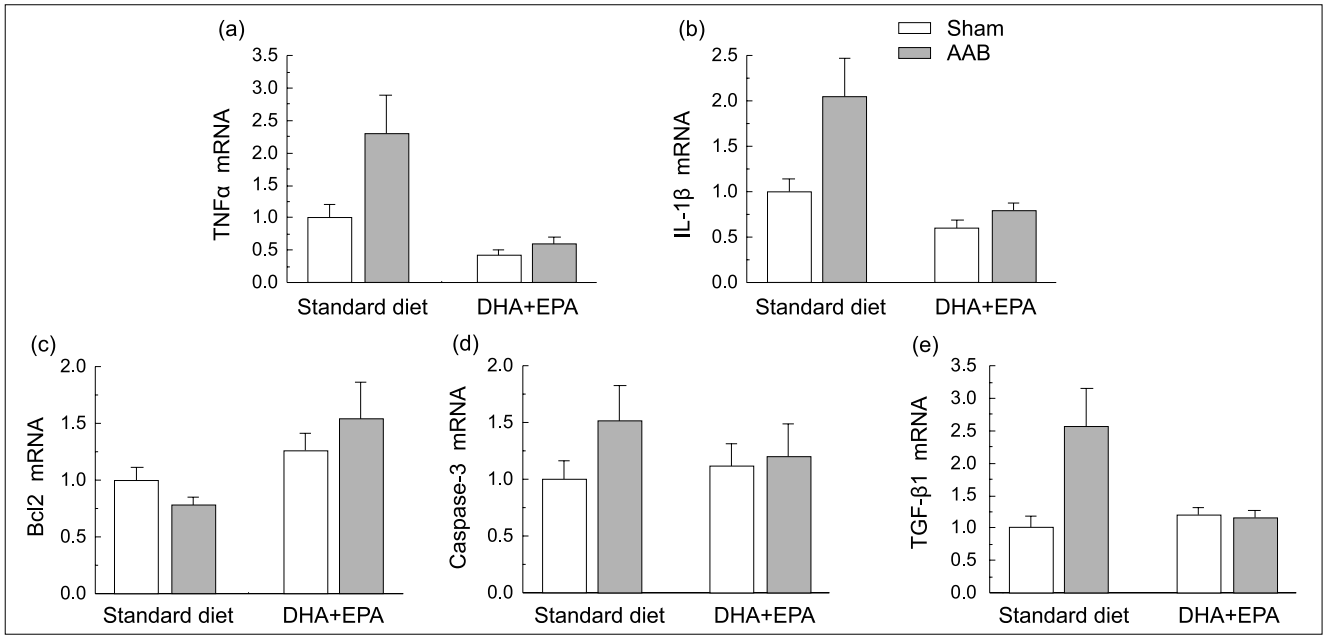

Fig. 4. Cardiac mRNA expression of NF-κB target genes: TNFα (a), IL-1β (b), Bcl2 (c), caspase-3 (d), and TGFβ (e) expressed as a fraction of the sham standard diet. Data are the mean ± SEM.
*p < 0.05 vs. respective sham
#p < 0.05 vs. standard diet (n = 6/group)

the fact that NF-κB controls multiple pro-life signaling pathways (16). Mice with cardiomyocyte-specific deletion of the p65 subunit of NF-κB were shown to manifest complete NF-κB shutdown in the model of pressure overload, which was also detrimental and led to maladaptive left ventricular hypertrophy and accelerated progression toward heart failure (17).

Left ventricular hypertrophy is an adaptive response to preserve LV function in response to stress, however sustained stress lead to pathological remodeling and development of heart failure. The NF-κB – dependent signaling pathways, such as inflammation, apoptosis and fibrosis play a critical role in this transformation (18-20). This study demonstrated that pressure overload rinsed mRNA expression of pro-inflammatory cytokines – TNFα and IL-1β, and DHA+EPA supplementation blunted this effect. Our observation is consistent with previous studies that showed reduced inflammation, apoptosis, fibrosis and improved cardiac function in TNFα – knockout mice in response to both pressure and volume overload (21). Additionally, we showed that treatment with DHA+EPA decreased mRNA for TNFα and IL-1β independent of overload condition, which suggests that ω-3 PUFA may additionally inhibit inflammation in the NF-κB-dependent mechanism. What is interesting, NF-αB controls expression of pro-inflammatory cytokines and these cytokines increase NF-αB activity. In order to determinate the pro-apoptosis pathway activity, we show that DPA+EPA supplementation was associated with rinse the mRNA expression of Bcl2 in rats with pressure overload. Bcl2 is negative regulator of caspase-3, and its regulatory effect depends on its expression (22). Caspase-3 is frequently activated apoptosis protease, catalyzing the specific cleavage of the protein involved in chromatin condensation, DNA fragmentation, and cytoskeleton destruction (23) and its activation has been documented in the myocardium of heart failure patients. Thus, the increased cardiac mRNA expression of Bcl-2 in our study can be linked to down-regulation of apoptosis with DHA+EPA treatment. Subsequent result demonstrated that pressure overload increased mRNA expression of know mediators of fibrosis TGF-β1 and this effect was attenuated by DHA+EPA supplementation. Fibrosis is characterized by expansion of the extracellular matrix by accumulation of collagen, which is synthesis by myofibroblast in response to TGF-β1 (24). Our data is consistent with previous observation, where ω-3 PUFA inhibited TGF-β1-stimulated cardiac fibroblast proliferation and transformation into myofibroblasts *ex vivo* (25). Taken together, in this study cardioprotective effect of ω-3 PUFA was associated with change in the mRNA expression levels of NF-κB-dependent mediators of inflammation, apoptosis and fibrosis.

In line with our previous work (5), the moderation of LV hypertrophy, remodeling and contractile dysfunction with ω-3 PUFA supplementation was associated with elevate plasma adiponectin concentration. Earlier studies showed that the elevation in plasma adiponectin with ω-3 PUFA supplementation is due to activation of PPARγ in adipose tissue and up-regulation of expression and secretion of adiponectin (26). Adiponectin knockout mice have enhanced LV hypertrophy and dysfunctions in response to pressure overload, and this can be rescued by adenovirus-mediated delivery of adiponectin (7). In this study, we observe a negative correlation between plasma adiponectin concentration and cardiac NF-κB activity, suggesting a casual role for DHA+EPA-induced elevation in adiponectin in the prevention of stress-induced NF-κB activation. Recently, Wang et al. showed that globular adiponectin can inhibit AT-II-induced NF-κB activation in neonatal rat ventricular myocytes (9).

Other mechanisms of NF-κB inhibition by ω-3 PUFA also suggested. Peroxisone proliferator-activated receptors (PPAR) – α and β, known to be activated by ω-3 PUFA (27), are endogenous inhibitors of NF-κB (28, 29). In this context, ω-3 PUFA were show to inhibit NF-κB activity in ischemic/reperfused liver mediated by PPAR-α/NF-κB complex (30).

CONCLUSIONS

In summary, the present study demonstrates that dietary supplementation with DHA+EPA attenuated pressure overload-induced LV hypertrophy, remodeling, and contractile dysfunction. The protective effect of DHA+EPA was associated with the decrease in the level of cardiac NF-κB activity and changes in the expression of NF-κB – dependent genes encoding proteins involved in regulation of inflammation, apoptosis and fibrosis.

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