Kardiologia Polska 2013; 71, 8: 839–844; DOI: 10.5603/KP.2013.0196 ISSN 0022–9032

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Ischaemic heart preconditioning in rats with adjuvant-induced arthritis

Małgorzata Wojciechowska[1, 2], Mateusz Wątroba[1], Grażyna Ciużyńska[1], Mariusz Bral[1], Dariusz Szukiewicz[1], Sławomir Maśliński[1]

[1]Department of General and Experimental Pathology, Medical University of Warsaw, Warsaw, Poland
[2]Invasive Cardiology Unit, Western Hospital, Grodzisk Mazowiecki, Poland

Abstract

Background: Adjuvant-induced arthritis (AIA) in rats is a model of chronic systemic inflammation and a model of rheumatoid arthritis in humans.

Aim: To investigate effectiveness of ischaemic preconditioning (IPC) in reducing the area of myocardial infarction in rats with AIA.

Methods: The study was performed in vivo in male SPRD/Mol/Lod rats. Animals were assigned to the experimental group (n = 15) or the control group (n = 14). In the experimental group, AIA was induced by subcutaneous administration of 1 mL of Freund's complete adjuvant, and the experiment was performed after 14 days. In control (healthy) animals, no procedures were performed prior to the proper experiment. Animals were anaesthesized (by intraperitoneal administration of ketamine and xylazine) and put on a ventilator. Then, myocardial infarction was induced, preceded by IPC in some animals. To induce infarction, left main coronary artery (LMCA) was occluded for 30 min, followed by 60 min of reperfusion. IPC protocol consisted of LMCA occlusion for 3 min, followed by 5 min of reperfusion and a second LMCA occlusion for 7 min. We evaluated a percentage ratio of the infarct size to the risk area (IS/RA). Necrosis area was stained with tetrazolium, and the area supplied by LMCA was determined using Evans blue. All areas were determined by planimetry. We used nonparametric Kruskal-Wallis rank ANOVA with multiple comparisons, and the results were shown as median values and 25th and 75th percentiles. $P < 0.05$ was considered statistically significant.

Results: In the control group with IPC (n = 7), the IS/RA ratio of 25% (23–38) was significantly reduced compared to the control group without IPC (n = 7) (58% [57–63], $p < 0.05$). In the AIA group with IPC (n = 7), the IS/RA ratio of 58% (51–65) did not differ significantly compared to the AIA group without IPC (n = 8) (65% [62–71]).

Conclusions: Our findings indicate that IPC in rats with AIA does not result in a significant reduction of myocardial necrosis area induced by 30 min of ischaemia and 60 min of reperfusion. This effect might have been related to the presence of chronic systemic inflammation. Absent or reduced benefits of IPC may be one reason for an increased cardiovascular risk in patients with rheumatoid arthritis.

Key words: ischaemic heart preconditioning, adjuvant-induced arthritis

Kardiol Pol 2013; 71, 8: 839–844

INTRODUCTION

Ischaemic preconditioning (IPC) is a major mechanism of cardioprotection that increases resistance of myocardium to damage during ischaemia and reperfusion. This was first described in 1986 by Murry et al. [1] who showed that infarct size in dogs can be reduced by nearly 75% if ischaemia resulting in an infarction is preceded by alternating periods of ischaemia and reperfusion lasting several minutes. In later years, IPC was shown both in other animals and in humans. Clinical evidence of IPC was also observed [2].

Remote IPC of the heart is also possible by inducing short episodes of ischaemia and reperfusion in peripheral tissues [3]. IPC-like properties were shown for many substances including proinflammatory cytokines [4–7] and histamine [8].

In the recent years, reports of absent or reduced IPC in some diseases and during aging were published [9–11]. Tolerance to

Address for correspondence:
Małgorzata Wojciechowska, MD, PhD, Department of General and Experimental Pathology, Medical University of Warsaw, Krakowskie Przedmieście 26/28, 00–927 Warszawa, Poland, e-mail: gosiawojciech@yahoo.com
Received: 01.06.2012 **Accepted:** 27.02.2013

preconditioning, manifested by lack of beneficial effects of preconditioning with too many repetitions or prolonged exposure to the preconditioning stimulus, was also discovered [12, 13].

Chronic inflammation plays a major role in the pathogenesis of many diseases. These include systemic connective tissue diseases, e.g. rheumatoid arthritis (RA) and systemic lupus erythematosus, and also other conditions such as heart failure, diabetes, obesity, hypertension, atherosclerosis, and depression. As far as we know, it has not been established whether IPC results in beneficial effects in the presence of chronic inflammation.

In rats, subcutaneous administration of Freund's complete adjuvant, i.e. inactivated mycobacteria emulsified in mineral oil, results in the development of adjuvant-induced arthritis (AIA). This phenomenon was discovered and described in 1956 by Pearson [14]. AIA in rats is an established model of chronic inflammation [15]. Due to many similarities, it is also considered a model of human RA [16].

The aim of this study was to investigate the effect of AIA/chronic inflammation on IPC in rats.

METHODS

Experimental animals

We studies 29 male Sprague-Dawley (SPRD/Mol/Lod) rats weighing 270–370 g. Animals were kept in controlled conditions under mechanical ventilation, time-controlled lighting (12 h/12 h) and temperature of 22–24ºC, with free access to water and processed granulated forage.

The study was approved by a local ethics committee for animal experimentation at the Medical University of Warsaw.

Anaesthesia

All invasive procedures (including induction of AIA) were performed under general anaesthesia using ketamine (100 mg/kg of body mass) and xylazine (10 mg/kg) administered intraperitoneally.

During the actual experiment, i.e. induction of ischaemia and reperfusion, one third of these doses of anaesthetic agents were repeated every about 40 min to keep anaesthesia at a constant level.

Adjuvant-induced arthritis

AIA was induced by administering 1 mL of Freund's complete adjuvant into the left hind limb. The actual experiment was performed after 14 days. This timing was chosen because literature data indicate that by that time inflammation becomes systemic and chronic [16] but body organs and blood vessels are not involved yet, which might affect the results of the experiment.

Inflammatory joint changes. Macroscopic (visual) evaluation of inflammatory joint changes in AIA is thought to correlate well with the severity of systemic inflammation, including levels of proinflammatory cytokines and C-reactive protein (CRP), leukocyte count in the peripheral blood, and the severity of histological changes in the affected joints [17].

At 14 days after administration of Freund's complete adjuvant, rats were evaluated using the commonly used arthritic index (AI) score ranging from 0 to 4, where score of 0 corresponds to no reddening and oedema of the periarticular tissues, mild reddening or oedema of 1 or more toes is scored 1, moderate reddening or oedema of the whole foot is scored 2, reddening or oedema in the ankle joint area is scored 3, and ankle joint stiffening with inability to bend is scored 4.

Leukocyte count. In animals susceptible to Freund's adjuvant, a marked increase in leukocyte count can be observed in the peripheral blood already during the first days of the disease [17, 18], and this condition persists for many weeks during further follow-up.

In our experiment, 0.5 mL of blood was collected from a jugular vein to determine leukocyte count using Bürker's counting chamber.

Induction of myocardial infarction with subsequent reperfusion

The chest was open through the fifth intercostal space. After exposing the heart and removing the pericardial sac, a Dacron 5–0 suture was tied on the left main coronary artery (LMCA) 2–3 mm below the left atrial appendage using. Both endings of the suture were drawn through a 1 cm long, 2 cm wide polyurethane catheter. After a 5-min period of stabilisation of the general condition of the animal, the catheter was pushed to the myocardium using a Kocher forceps, thus occluding the artery. Artery occlusion was evidenced by the pale colour of the myocardium supplied by the occluded artery, and ST segment elevation in the electrocardiogram. The wound was then closed by tightening a previously prepared cutaneous suture, with air evacuation using a syringe connected to a soft catheter. The wound was packed with moist gauze. After 30 min of ischaemia, occlusion was released for 60 min of reperfusion [19, 20].

Ischaemic preconditioning

In animals undergoing IPC, after chest opening through the fifth intercostal space, preparation of the heart as described above, and a 5-min period of stabilisation, the coronary artery was occluded for 3 min, followed by 5 min of reperfusion and a second occlusion for 7 min. After another 5 min of reperfusion, myocardial infarction was induced as described above.

Evaluation of the infarct size

Due to different heart sizes and anatomical variability of coronary perfusion, a percentage ratio of the infarct size to the risk area (IS/RA) was calculated to compare the size of myocardial infarction between animals. Necrosis area was stained with tetrazolium [21], and the area supplied by LMCA was determined using Evans blue.

Details of staining. After 60 min of reperfusion, LMCA was occluded again, and 2 mL of 5% Evans blue were administered intravenously. The stain reached all tissues and

organs via capillaries, resulting in their dark blue colour. The only unstained, i.e. light pink tissue was the myocardium supplied by the occluded artery. About 1 min after administration of Evans blue, the heart was extracted, wrapped around with cling film, and placed into a freezer for about 10 min at –20°C. Then, after atria were removed, 2–3 mm thick ventricular cross-sections were made using a scalpel, which allowed obtaining 4–5 sections depending on the heart size. These sections were placed in a previously prepared buffered tetrazolium solution at pH 7.4 and incubated in water bath for 20 min at 37°C. As tetrazolium stains viable tissue red, myocardial cross-sections were ultimately stained with 3 colours: blue (out-of-interest), red (ischaemic but viable areas) and light pink (necrosis, i.e. IS).

After staining, colours were contrasted and fixed by placing myocardial cross-sections in formalin for 10–20 min, followed by bilateral scanning of cross-sections. To obtain the same thickness of all cross-sections, they were placed under a specially prepared plexiglas plate with 2 mm long legs.

All areas were determined by planimetry using freely available Image Tool software.

Conduct of the experiment

Male SPRD/Mol/Lod rats were assigned to the experimental group (n = 15) or the control group (n = 14). AIA was induced in the experimental group, and the effects of IPC were evaluated after 14 days. In control, no procedures were performed prior to the proper experiment.

The actual experiment began with anaestesizing animals with ketamine and xylazine. Blood was then collected from a jugular vein to evaluate leukocyte count and tracheostomy was performed. Animals were put on a Harvard Rodent Ventilator and ventilated with room air at the breathing rate of 100/min and the tidal volume of 1 mL/100 g body mass. Electrocardiographic monitoring was performed, and the temperature of the animals was kept at 37–38°C using a heated operating table.

Myocardial infarction was induced in all animals, and in some of them it was preceded by IPC. Ultimately, 4 groups of animals were obtained, including the control group with myocardial infarction without IPC (KZ; n = 7), the control group with myocardial infarction preceded by IPC (KH; n = 7), the experimental group with myocardial infarction without IPC at 14 days of AIA (DZ; n = 8), and the experimental group with myocardial infarction preceded by IPC at 14 days of AIA (DH; n = 7).

The experiment concluded with a 60 min reperfusion period followed by LMCA reocclusion, intravenous administration of Evans blue, heart extraction and further staining as described above.

Animal sacrifice

Animals anaesthesized at the beginning of the actual experiment were not recovered from anaesthesia until the end of the experiment. They were sacrificed by exsanguination induced by severing large blood vessels at the base of the heart.

Statistical analysis

Variable distribution was evaluated using the Shapiro-Wilk test. Depending on the variable distribution, we used parametric or nonparametric tests (univariate analysis of variance [ANOVA] with the use of the Tukey test and Kruskal-Wallis rank ANOVA with multiple comparisons, respectively) for statistical analysis. $P < 0.05$ was considered statistically significant. Normally distributed variables (leukocyte count) were shown as mean values and standard errors, and non-normally distributed variables (IS/RA ratio) were shown as median values and 25th and 75th percentiles.

RESULTS

Arthritic index score

At 14 days after administration of Freund's adjuvant, massive oedema and reddening of the left hind limb (i.e. the one into which Freund's adjuvant was administered) was seen. Interdigital, metatarsal, and ankle joints were stiffened and distorted. No changes in more proximal joints and joints of the remaining limbs were seen. At 14 days of AIA, all rats scored 3 or 4 in the above described arthritic index scale.

Leukocyte count

Mean leukocyte count was 3653.6 ± 625.9/mL in control animals (n = 14) and 6116.7 ± 787.0/mL in animals with chronic inflammation at 14 days (n = 15), a statistically significant difference ($p < 0.05$). Results obtained in the study groups are shown in Figure 1. Elevated leukocyte count in the experimental group is consistent with the systemic nature of the inflammatory response to the administered adjuvant.

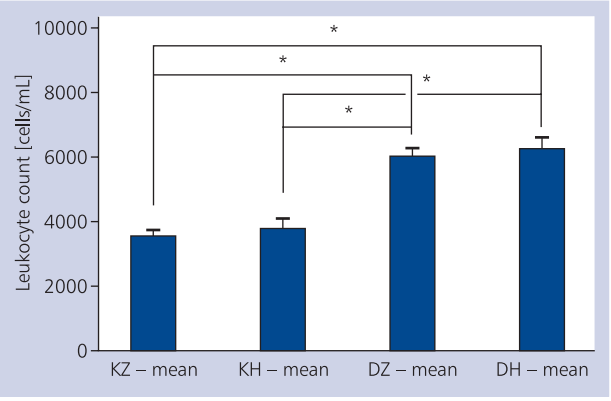

Figure 1. Leukocyte count. Mean values and standard errors are shown. Between-group (KZ, KH, DZ, DH) comparison using univariate analysis of variance yielded $F(3.25) = 27.969$ ($p < 0.001$); *$p < 0.05$ by post-hoc analysis using the Tukey test

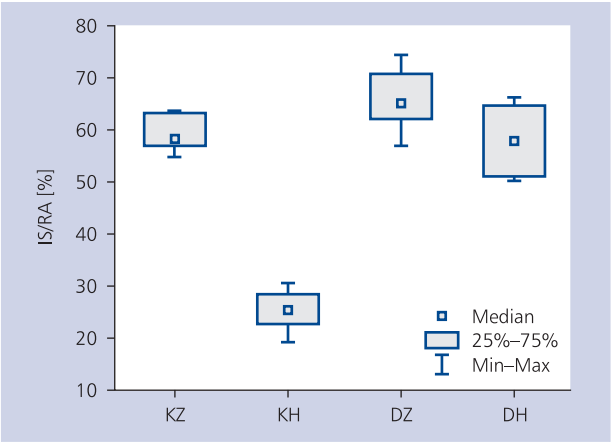

Figure 2. Median values and 25th and 75th percentiles of the infarct size (IS) to the risk area (RA) ratio. Between-group (KZ, KH, DZ, DH) comparison using the Kruskal-Wallis rang ANOVA yielded H (3, n = 29) = 18.723 ($p < 0.01$); *$p < 0.05$ by post-hoc analysis using the multiple comparison test

IS/RA ratio

The following values of the IS/RA ratio were obtained in the study groups: 58% (57–63) in the control group without IPC, 25% (23–28) in the control group with IPC, 65% (62–71) in the experimental group without IPC, and 58% (51–65) in the experimental group with IPC. The IS/RA ratio in the control group with IPC was significantly lower than in the control group without IPC ($p < 0.05$). In contrast, no significant difference in the IS/RA ratio was found between the experimental group with IPC and the experimental group without IPC (Fig. 2).

DISCUSSION

Our findings in the control group confirmed than IPC in healthy animals reduces the area of necrosis induced by prolonged ischaemia and reperfusion [1, 20]. The results in the experimental group suggest that IPC may have a limited importance in the presence of systemic inflammation.

Ischaemic preconditioning in the presence of chronic inflammation?

Numerous experiments showed that in addition to elevated leukocyte count, increased blood levels of proinflammatory cytokines: interleukin (IL)-1β, IL-6 and tumour necrosis factor-α [17], monocyte chemotactic protein-1 (MCP-1) chemokine [17], and histamine [22] can be shown in animals with AIA. On the other hand, it was also shown that some inflammatory mediators, e.g. the above mentioned proinflammatory cytokines [4–7], MCP-1 [23], histamine [8], and even reactive oxygen species [24], used in an appropriate single dose, imitate IPC. As tolerance to preconditioning (tachyphylaxis) develops with multiple repetitions or prolonged exposure to the preconditioning mimetic agents [12, 13], it is possible that such tolerance may also develop during chronic inflammation which is characterised by prolonged elevation of blood levels of substances that might mimic IPC.

Tolerance to preconditioning might be caused by down-regulation of receptors, secondary messengers (e.g. protein G or protein kinase C), or preconditioning effectors during their chronic stimulation [25]. It seems that inducing preconditioning in these circumstances might be possible but would require the use of stronger stimuli, which in practice might translate to an increased number and/or duration of ischaemia and reperfusion cycles.

Taking the above into account, it seems likely that the effects of IPC were not observed in animals with AIA due to tachyphylaxis caused by prolonged exposure to preconditioning mimetics. It remains possible, however, that the use of some stronger preconditioning stimulus in animals with AIA would allow reduction of the infarct size.

These hypotheses are very preliminary and would require testing in appropriately designed experiments.

Limitations of the study

We did not measure blood CRP level in our animals as joint oedema and reddening in combination with elevated leukocyte count were considered adequate evidence of the development of arthritis. A hypothesis that proinflammatory cytokines, chemokines or histamine as preconditioning mimetics might induce tolerance to preconditioning in animals with AIA was generated after the experiment was conducted, when measuring these substances was no longer possible.

Clinical implications

AIA is a model of RA in humans [16]. Both conditions are characterised by systemic inflammatory response and increased blood levels of inflammatory mediators including proinflammatory cytokines. Our findings suggest that IPC may have limited importance in patients with RA.

Numerous clinical studies showed increased cardiovascular risk in patients with RA, resulting, among others, from an earlier development and increased severity of atherosclerosis. We believe that an additional factor may be absent or reduced effects of naturally occurring IPC in these subjects.

As AIA is a model of chronic inflammation [15], a question arises whether IPC might be less beneficial or more difficult to induce also in other conditions characterised by systemic inflammation. One may also ask whether the reported lack of benefits of IPC related to aging, diabetes, obesity, advanced atherosclerosis, hypertension, or heart failure might be caused by chronic inflammation.

CONCLUSIONS

Our findings indicate that IPC may have a limited importance in rats with AIA.

Conflict of interest: *none declared*

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Hartowanie przez niedokrwienie u szczurów z adiuwantowym zapaleniem stawów

Małgorzata Wojciechowska[1, 2], Mateusz Wątroba[1], Grażyna Ciużyńska[1], Mariusz Bral[1], Dariusz Szukiewicz[1] Sławomir Maśliński[1]

[1]Katedra i Zakład Patologii Ogólnej i Doświadczalnej, Warszawski Uniwersytet Medyczny, Warszawa
[2]Oddział Kardiologii Inwazyjnej, Szpital Zachodni, Grodzisk Mazowiecki

Streszczenie

Wstęp: Adiuwantowe zapalenie stawów (AIA) u szczurów jest modelem przewlekłego ogólnoustrojowego zapalenia i jednocześnie modelem ludzkiego reumatoidalnego zapalenia stawów.

Cel: Celem niniejszej pracy było zbadanie skuteczności hartowania przez niedokrwienie (IPC) w redukcji obszaru zawału u szczurów z AIA.

Metody: Badania przeprowadzono *in vivo* na szczurach SPRD/Mol/Lod (samce). Zwierzęta przydzielono do jednej z grup: doświadczalnej (n = 15) lub kontrolnej (n = 14). U zwierząt z grupy D wywoływano AIA, podając podskórnie 1 ml kompletnego adiuwantu Freunda. Doświadczenia przeprowadzano w 14. dniu trwania choroby. U zwierząt kontrolnych (zdrowych) nie stosowano przed właściwym doświadczeniem żadnych procedur. Zwierzęta znieczulano (ketamina i ksylazyna podawane dootrzewnowo) i podłączano do respiratora. Następnie wywoływano zawał serca, u części przed zawałem stosowano IPC. W celu wywołania zawału na 30 min zamykano lewą tętnicę wieńcową (LMCA), po tym czasie następowała 60-minutowa reperfuzja. W celu zahartowania miokardium zamykano LMCA 2-krotnie: pierwszy raz na 3 min, drugi na 7 min, epizody te oddzielała 5-minutowa reperfuzja. Oceniano stosunek powierzchni objętej zawałem (IS) do całego obszaru unaczynionego przez LMCA (RA); wynik wyrażano w procentach. Do wyróżnienia zakresu martwicy posługiwano się metodą barwienia tetrazolium. Obszar unaczynienia LMCA oznaczano błękitem Evansa. Poszczególne obszary obliczano metodą planimetryczną. Użyto nieparametrycznego testu ANOVA rang Kruskala-Wallisa z wielokrotnymi porównaniami. Wyniki podano jako mediany oraz 25. i 75. centyle. Za poziom istotności statystycznej przyjęto $p < 0,05$.

Wyniki: W grupie kontrolnej, gdy przed zawałem stosowano IPC (n = 7) IS/RA wyniósł 25% (23–28) i był istotnie mniejszy ($p < 0,05$) niż u zwierząt bez poprzedzającego hartowania (n = 7) — 58% (57–63). U zwierząt z AIA, gdy stosowano IPC (n = 7) IS/RA wyniósł 58% (51–65) i nie różnił się istotnie od wyniku uzyskanego w przypadku szczurów bez IPC (n = 8) — 65% (62–71).

Wnioski: Na podstawie uzyskanych wyników stwierdzono, że hartowanie przez niedokrwienie u szczurów z AIA nie prowadzi do istotnej redukcji obszaru martwicy wywołanej 30-minutowym niedokrwieniem i 60-minutową reperfuzją. Możliwe jest, że za zaobserwowany efekt odpowiada obecność ogólnoustrojowego przewlekłego zapalenia. Zanik/ograniczenie korzystnych efektów wynikających z IPC może być jedną z przyczyn zwiększonego ryzyka sercowo-naczyniowego u pacjentów z reumatoidalnym zapaleniem stawów.

Słowa kluczowe: hartowanie przez niedokrwienie, adiuwantowe zapalenie stawów

Kardiol Pol 2013; 71, 8: 839–844

Adres do korespondencji:
dr hab. n. med. Małgorzata Wojciechowska, Katedra i Zakład Patologii Ogólnej i Doświadczalnej, Warszawski Uniwersytet Medyczny, Krakowskie Przedmieście 26/28, 00–927 Warszawa, e-mail: gosiawojciech@yahoo.com
Praca wpłynęła: 01.06.2012 r. **Zaakceptowana do druku:** 27.02.2013 r.