Aerobic exercise attenuates pulmonary inflammation induced by
Streptococcus pneumoniae

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Aerobic exercise attenuates pulmonary inflammation induced by Streptococcus pneumoniae. J Appl Physiol 117: 998–1007, 2014. First published September 4, 2014; doi:10.1152/japplphysiol.00290.2014.—Aerobic exercise has been recognized as a stimulator of the immune system, but its effect on bacterial infection has not been extensively evaluated. We studied whether moderate aerobic exercise training prior to Streptococcus pneumoniae infection influences pulmonary responses. BALB/c mice were divided into four groups: Sedentary Untreated (sedentary without infection); Sedentary Infected (sedentary with infection); Trained Untreated (aerobic training without infection); and Trained Infected (aerobic training with infection). Animals underwent aerobic training for 4 wk, and 72 h after last exercise training, animals received a challenge with S. pneumoniae and were evaluated either 12 h or 10 days after instillation. In acute phase, Sedentary Infected group had an increase in respiratory system resistance and elastance; number of neutrophils, lymphocytes, and macrophages in bronchoalveolar lavage fluid (BAL); polymorphonuclear cells in lung parenchyma; and levels of keratinocyte-derived chemokine (KC), tumor necrosis factor-α (TNF-α), and interleukin (IL)–1β (IL-1β) in lung homogenates. Exercise training significantly attenuated the increase in all of these parameters and induced an increase in expression of antioxidant enzymes (CuZnSOD and MnSOD) in lungs. Trained Infected mice had a significant decrease in the number of colony-forming units of pneumococci in the lungs compared with Sedentary Infected animals. Ten days after infection, Trained Infected group exhibited lower numbers of macrophages in BAL, polymorphonuclear cells in lung parenchyma and IL-6 in lung homogenates compared with Sedentary Infected group. Our results suggest a protective effect of moderate exercise training against respiratory infection with S. pneumoniae. This effect is most likely secondary to an effect of exercise on oxidant-antioxidant balance.

METHODS

This study was approved by the review board for human and animal studies of the School of Medicine of the University of São Paulo (São Paulo, Brazil). All of the animals (male BALB/c mice) in the study received humane care in compliance with the Guide for the Care and Use of Laboratory Animals (26).

Bacterial Strain and Growth Conditions

Streptococcus pneumoniae M10 strain (serotype 11A) was plated on blood agar overnight at 37°C and then grown in Todd-Hewitt broth (Difco) supplemented with 0.5% yeast extract (THY) to an OD600nm = 0.4. The bacterial stocks were then frozen at −80°C in THY containing 20% glycerol for later use (9).
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Intranasal Challenge

For infection with S. pneumoniae, the mice were anesthetized through the intraperitoneal route with 200 μl of a 0.2% xylazine and 1.0% ketamine mixture and were then challenged with the M10 strain (10⁶ CFU/animal) through the inoculation of 50 μl of the suspension of bacteria in 0.9% saline into one nostril. Animals from the control groups did not receive any challenge (9).

Aerobic Exercise Training Protocol

Initially, the animals were adapted to the treadmill designed for the training of rodents (Super ATL, Imbramed, RS, Brazil) by training for 3 days (5 min, 25% inclination, 0.2 km/h). After that, an individual maximal exercise capacity test was performed with an increase in the treadmill speed (0.1 km/h every 2.5 min, 25% inclination) until animal exhaustion (until they were not able to run even after gentle mechanical stimulus), which was defined as the maximum speed reached by the animal. The speed of the exercise training was calculated as 50% of the average of the maximal speed achieved for each animal in the exercise test. The mice were then trained for 60 min/day, 5 days/wk for 4 wk. At the end of the protocol, the exercise capacity test was repeated to evaluate their aerobic conditioning (46).

Study Design

BALB/c mice (20–25 g) were randomly divided into four groups: Sedentary Untreated group animals that remained sedentary and did not receive any instillation of bacteria, Sedentary Infected group animals that remained sedentary and received an intranasal instillation of S. pneumoniae, Trained Untreated group animals that underwent aerobic exercise training and did not receive any instillation of bacteria, and Trained Infected group animals that underwent aerobic exercise training and received an intranasal instillation of S. pneumoniae.

We performed two experimental protocols: acute (early) Phase and Late Phase S. pneumoniae infection. In the acute phase protocol, the animals were studied 12 h after the intranasal instillation of S. pneumoniae. In the late phase protocol, the mice were studied 10 days after the intranasal instillation of S. pneumoniae. In both experimental protocols the aerobic training in all of the groups was stopped 72 h before the intranasal instillation of bacteria (Fig. 1).

Acute (Early) Phase Protocol

First session of exercise

Instillation of S pneumonieae

Aerobic Training

4 weeks

72hs

Day 1

Day 29

Day 26

Euthanized

Late Phase Protocol

First session of exercise

Instillation of S pneumonieae

Aerobic Training

4 weeks

72hs

Day 1

Day 29

Day 26

Euthanized

Day 30

Fig. 1. Timeline of the experimental protocol. Acute (early) phase of the protocol (A) and late phase of the protocol (B).

Palmonary Mechanics Evaluation

The mice were deeply anesthetized by an intraperitoneal injection of thiopental (70 mg/kg), tracheotomized, and a polyethylene tube (internal diameter = 1.7 mm) was inserted into the trachea and connected to a ventilator for small animals (Harvard 683; Harvard Apparatus, South Natick, MA) with a tidal volume of 10 ml/kg and 150 breaths/min in order of perform measurements of respiratory system resistance (Rrs) and elastance (Ers). Briefly, the tracheal pressure (Ptr) was measured with a differential pressure transducer (DP 45-28-2114; Validyne, Northridge, CA) connected to a side tap in the tracheal cannula. Airflow (V) was measured with a pneumotachograph (Fleisch no. 4-0) attached to the tracheal cannula and to a differential pressure transducer (Validyne DP-45-16-2114). V changes were obtained by electronic integration of the volume (V). Ptr and V signals were registered and stored in a microcomputer. Nine to 10 respiratory cycles were averaged to provide one data point (26). Rrs and Ers were obtained using the equation of motion of the respiratory system, as follows: Pr(t) = Ers . V(t) + Rrs . V(t), where t is time (12).

Bronchoalveolar Lavage Fluid Evaluation

At the end of the mechanical evaluation, a 2-cm incision was made in the abdomen, and the animals were exsanguinated by an incision in the abdominal aorta. Bronchoalveolar lavage fluid (BAL) was obtained through the tracheal cannula by washing the airway lumen with 3 × 0.5 ml of sterile saline. For the total and differential cell counting, the BAL was centrifuged at 800 rpm at 4°C for 10 min, and the cell pellet was resuspended in 0.2 ml of sterile saline. The total number of viable cells was determined in a Neubauer hemocytometer counting chamber. Differential cell counts were performed in cytocentrifuged preparations of the BAL (450 rpm for min) (Cytospin, Cheshire, UK) and stained with Diff-Quick (Biochemical Sciences, Swedesboro, NJ). At least 300 cells were counted according to standard morphologic criteria (34, 42, 46).

Lung Histology and Morphometry

After the BAL collection, the anterior chest wall was opened; the lungs were then removed en bloc, fixed with 4% formaldehyde for 24 h and submitted for conventional histological techniques. Briefly, sections of the lungs were embedded in paraffin and 5-μm sections were obtained and stained with hematoxylin and eosin to evaluate the density of the polymorphonuclear (PMN) and mononuclear cells in the lung parenchyma.

We evaluated the density of the PMNs and mononuclear cells in the lung parenchyma by conventional morphometry using an ocular microscope with an integrating eyepiece with 100 points and 50 lines (point-counting technique) (47) with a known area (at ×400 magnification, 62,500 μm² area). We chose 15 random parenchymal fields in each lung; we then counted the number of cells in the area and divided by the number of points hitting the lung parenchyma. The results were expressed in cells per square micrometers (1, 12, 34, 46).

Cytokine Analysis

Five animals from each group were randomly separated to assess cytokine levels exclusively. The lungs of these animals were collected and disrupted in half saline with the use of a cell strainer. The samples were centrifuged for the storage of the supernatants at −80°C for subsequent cytokine analysis. The levels of KC, interleukin (IL)−1β, IL-6, and tumor necrosis factor-α (TNF-α) were measured using commercial ELISA kits, according to the manufacturer’s instructions (R&D Systems, Minneapolis, MN).

Oxidants/Antioxidants

In the group of animals undergoing the, we also studied the oxidant/antioxidant levels in the lung parenchyma. The lung tissue...
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**RESULTS**

**Exercise Capacity Test**

After 4 wk of aerobic training, the mice reached a higher speed in the exercise test compared with their pret raining values (*P < 0.001*) (Fig. 2). In contrast, sedentary mice (not undergoing aerobic training) had a significant decrease in the maximal speed reached in the exercise test (*P < 0.001*).

**Recovery of Pneumococci from Lungs**

Animals that were trained before infection with *S. pneumoniae* (Trained Infected group) presented significantly lower number of CFUs in lungs compared with animals which remained sedentary and were challenged with the same bacteria (Sedentary Infected group), 12 h (*P = 0.011*) (Fig. 3A) as well as 24 h (*P = 0.043*) (Fig. 3B) after challenge.

**Pulmonary Mechanics Evaluation**

**Acute phase.** Animals from the Sedentary Infected group had an increase in their respiratory system resistance (Rrs) (*P < 0.05*) and elastance (Ers) (*P < 0.005*) compared with the other three groups. Exercise training resulted in an attenuation of the respiratory system mechanical changes induced by *S. pneumoniae*. In fact, we did not observe significant differences among the Sedentary Untreated, Trained Untreated, and Trained Infected (Fig. 4, A and B).

**Late phase.** There were no significant differences among the four experimental groups in either the Rrs or the Ers values (Fig. 4, C and D).

**Lung Inflammation**

**Acute phase.** Bacteria instillation induced a significant increase in the number of total cells in the BAL (*P < 0.001*) as well as neutrophils (*P < 0.001*), macrophages (*P < 0.001*), and lymphocytes (*P < 0.002*) in the Sedentary Infected group compared with the other three groups (Fig. 5A). The animals that underwent physical exercise and received an instillation of bacteria (Trained Infected group) had fewer total cells (*P < 0.001*), neutrophils (*P < 0.001*), macrophages (*P < 0.001*), and lymphocytes (*P = 0.002*) in the BAL when compared with...
the Sedentary Infected group, although the number of total cells and neutrophils remained higher than in the control groups (Sedentary Untreated and Trained Untreated group, \( P < 0.001 \)). In the lung parenchyma of the animals that received an instillation of bacteria (Sedentary Infected and Trained Infected groups) there was an increase in the number of PMN cells compared with the animals that did not receive a bacterial instillation (Sedentary Untreated and Trained Untreated groups) \( (P < 0.001) \) (Fig. 5B). However, the Trained Infected group had fewer PMN cells in the lung parenchyma than the Sedentary Infected group \( (P = 0.017) \).

**Late phase.** Ten days after the instillation of *S. pneumoniae* (Sedentary Infected and Trained Infected groups) an increase in the number of total cells \( (P < 0.001) \), macrophages \( (P < 0.001) \), neutrophils \( (P < 0.001) \), and lymphocytes \( (P = 0.006) \) remained in the BAL compared with the control groups (Sedentary Untreated and Trained Untreated groups) (Fig. 5C). In addition, there was an attenuation of the increase in the infected group compared with the other 3 groups. Polymorphonuclear (PMN) cells in the pulmonary parenchyma \( (*P < 0.001) \) with the Sedentary Untreated and Trained Untreated groups and \( P = 0.017 \) compared with the Trained Infected group; \( **P < 0.002 \) compared with the Sedentary Untreated and Trained Untreated groups) (B). Late phase (10 days after *S. pneumoniae* administration): total cells and macrophages in the BAL \( (*P < 0.001) \) compared with the other 3 groups and **\( P < 0.001 \) compared with the Sedentary Untreated and Trained Untreated groups; neutrophils \( (\Delta P < 0.001) \) compared with the Sedentary Untreated and Trained Untreated groups) and lymphocytes \( (\Delta P = 0.006) \) compared with the Sedentary Untreated and Trained Untreated groups) (C). Polymorphonuclear cells in the lung parenchyma \( (*P < 0.025 \) compared with the other three groups) (D). The values are the means and SD.
number of total cells and macrophages in the mice that underwent aerobic conditioning ($P < 0.001$ comparing Sedentary Infected with the Trained Infected groups). The lung parenchyma of the mice from the Sedentary Infected group had more PMN cells compared with the other three groups ($P < 0.025$) (Fig. 5D). We did not observe any significant differences in the numbers of mononuclear cells in the lung parenchyma among the four experimental groups in either the acute phase or the late phase protocols (data not shown). Figure 6 shows representative photomicrographs of lung histological sections stained with hematoxylin and eosin, obtained from the Sedentary Untreated, Trained Untreated, Sedentary Infected (acute and late phases), and Trained Infected (acute and late phases) groups.

Measurement of Cytokines in the Lung

**Acute phase.** The Sedentary Infected group showed an increase in the chemokine KC ($P < 0.001$) (Fig. 7A) and in proinflammatory cytokines TNF-$\alpha$ ($P < 0.001$) and IL-1$\beta$ ($P = 0.03$) in lung homogenates compared with the other three groups (Fig. 8A and B). Exercise training resulted in an attenuation of these increases induced by *S. pneumoniae*. In fact, we did not observe significant differences among the Sedentary Untreated, Trained Untreated, and Trained Infected groups. We did not observe significant differences among the four experimental groups in IL-6 levels (Fig. 8C).

**Late phase.** Animals from the Sedentary Infected group still presented an increase in KC compared with the other three groups ($P < 0.001$) (Fig. 7B). There were no significant differences in the levels of TNF-$\alpha$ comparing the four groups (Fig. 8D). The mice that received an instillation of bacteria (Sedentary Untreated and Trained Infected groups) had more IL-1$\beta$ when compared with the animals that did not receive a bacterial instillation (Sedentary Untreated and Trained Untreated groups, $P = 0.002$) (Fig. 8E). The mice from the Sedentary Infected group had more IL-6 ($P = 0.005$) compared with the other three groups. Physical activity was effective in reducing this cytokine in the animals that received an instillation of bacteria ($P < 0.001$) (Fig. 8F).

Measurement of Oxidative Stress in the Lungs

Mice from the groups that underwent training (Trained Untreated and Trained Infected groups) had greater expression of CuZnSOD ($P < 0.001$) (Fig. 9A) and MnSOD ($P = 0.005$) (Fig. 9C) compared with those groups that remained sedentary (Sedentary Untreated and Sedentary Infected groups) 12 h after the bacterial challenge (acute phase). We also found an increase in the expression of CuZnSOD in the Sedentary Infected
group compared with the Sedentary Untreated group ($P < 0.001$). In the groups that received a challenge with *S. pneumoniae* (Sedentary Infected and Trained Infected groups) we also observed an increase in the expression of Gpx ($P = 0.05$) (Fig. 9B) and gp91 phox ($P = 0.01$) (Fig. 9D) compared with the groups that did not receive the instillation (Sedentary Untreated and Trained Untreated groups). When we evaluated for the expression of iNOS (Fig. 10), the groups that received a bacterial challenge showed greater expression of this enzyme compared with the other two groups ($P = 0.001$). In addition, the Trained Infected group had higher values than the Sedentary Infected group ($P < 0.007$).

**DISCUSSION**

The main findings of this study are that physical activity decreased the amount of bacteria in the lungs and attenuated lung inflammation in the mice infected with *S. pneumoniae*. This effect of physical conditioning on pulmonary inflammation was observed in both the acute and late phases of infection.

We observed significant increases in both the respiratory elastance and resistance in the mice that received *S. pneumoniae*. These changes were observed only in the groups that were studied 12 h after the infection, suggesting that these changes could be detected only when the inflammatory processes were more intense. These changes in respiratory mechanics were also attenuated in the groups of mice that underwent aerobic conditioning.

Many research groups have previously developed experimental models of pneumococcal pneumonia to understand the pathophysiology of the disease and consequently suggest better treatments (14, 17, 40). It was observed that the outcomes of infection in mouse models of pneumonia are dependent on the bacterial strain as well as the mouse strain (9, 24). Our study was performed with a serotype 11A *S. pneumoniae* strain (the M10 strain). Ferreira et al. (9) challenged BALB/c mice with two different pneumococcal strains (serotype 3 strain ATCC6303 or serotype 11A strain M10). Both strains induced signs of disease 12 h after the inoculation; however, while the first one caused death in all animals in 5 days, in the group of mice that was inoculated with the M10 strain, no bacteria could be recovered from the lung homogenates 36 h after the inoculation. In previous studies, mice challenged with the M10 strain presented a rapid increase in cells and cytokines 12 h after the pneumococcal inoculation. Our results are in agreement with these previous studies, once we could recover bacteria from lung homogenate 12 h after challenge, and at 24 h the number recovered decreased, suggesting a spontaneous recovery from infection. We also observed an increase in a neutrophil chemoattractant (KC) and...
consequently an increase in inflammatory cells, mainly neutrophils in the BAL and in the lung parenchyma within 12 h of the infection as well as an increase in proinflammatory cytokines, such as TNF-α and IL-1β.

Although alveolar macrophages constitute the first line of defense during a respiratory tract infection, at higher inocula or with more virulent pathogens, these cells are unable to overcome the invasion. Alveolar macrophages orchestrate a complex network of cytokines and the recruitment of PMNs and monocytes to combat pathogens (48). One of these substances derived from macrophages that is capable of eliciting PMN migration into airways is KC, a mouse chemokines that is a homolog of IL-8 and a potent neutrophil chemoattractant (38). Macrophages are also required in a resolution phase of infection in order to phagocytose neutrophils, preventing a tissue injury (13). Some animal studies have shown that an intrapulmonary challenge with either bacteria or LPS elicits a rapid recruitment of PMN into the lungs 3–4 h after the challenge, possibly representing 60–80% of the total cells recovered from BAL (27, 48). Fillon et al. (10), in an experimental model of infection with *S. pneumoniae*, observed a rapid and time-dependent accumulation of neutrophils and macrophages into the lungs. In our study, the influx of inflammatory cells in the BAL collected from the Sedentary Infected group was mainly due to neutrophils and was attenuated by the aerobic exercise training. At the late phase, we found a higher number of macrophages in the BAL in the Sedentary Infected group that was also attenuated by the aerobic exercise training.

In the presence of bacterial infections, alveolar macrophages and neutrophils produce many cytokines that play a pivotal role in the inflammatory response. TNF-α and IL-1β are important cytokines in the early response. The former has been recognized as an “alarm” cytokine because it is rapidly produced following either antigen-specific or nonspecific stimulation (27) and can activate both macrophages and PMN, leading to an increase in phagocytosis as well as in oxidative burst. IL-1β is another important proinflammatory cytokine that may be responsible for a sustained increase in macrophages, as this cytokine remains high in the late phase (5, 32). Both cytokines are also potent inducers for the production of certain C-X-C chemokines, such as IL-8, by alveolar macrophages and other cells of airway which are the major chemoattractant for PMN recruitment into the lung during pulmonary infection (39). Because these proinflammatory cytokines indirectly produce a stimulatory effect in the production of macrophages, it has been suggested that these cytokines could be responsible for the initial accumulation of these cells in the BAL (4, 36). In addition, the excessive production of both proinflammatory cytokines plays a prominent role in the pathogenesis of sepsis syndrome, and high levels of both are found in lethal experimental sepsis; the neutralization of either of these mediators confers protection against death in animal models of sepsis (4, 36). Although TNF-α and IL-1β may be important in the process of the killing of pathogens, an exacerbation in the inflammatory response can be deleterious. Our results showed an attenuation of both cytokines in the acute phase of the infection by aerobic exercise training, while in the late phase both groups that received bacterial challenge showed increased levels of IL-1β in the pulmonary tissue.

Under the influence of these cytokines, IL-6 is produced by many cells, including macrophages and parenchymal cells. IL-6 can be found in higher concentrations in the lungs during pneumonia but it is both a pro- and anti-inflammatory cytokine (4, 36). Antunes et al. (2) detected higher concentrations of IL-6 and TNF-α in the blood of most patients admitted to the hospital with community-acquired pneumonia. Kohut et al.
There are three different isozymes of superoxide dismutase (SOD): cytosolic copper-zinc SOD (CuZnSOD), mitochondrial manganese SOD (MnSOD), and extracellular CuZnSOD. These enzymes act on superoxide radicals to form oxygen and the lesser reactive nonradical species, hydrogen peroxide. Glutathione peroxidase is another antioxidant enzyme that removes hydrogen peroxide and organic hydroperoxides from the cell that serves as an important cellular protectant against free radical induced damage to membrane lipids, proteins, and nucleic acids (22). A part of the NADPH complex in cell membranes is gp91phox which produces superoxide anions that can result in the killing of bacteria. NO and reactive nitrogen species together are essential in several physiological processes, including the killing of invading microorganisms (35).

We observed an increase in CuZnSOD and MnSOD in the lungs of the mice that underwent physical exercise, suggesting an antioxidant effect of exercise. However, the challenge with S. pneumoniae induced the expression of Gpx (glutathione peroxidase), gp91phox, and iNOS (inducible nitric oxide synthase) in the lungs. Furthermore, the animals that had increased physical activity and received challenge with bacteria had a greater increase in the expression of iNOS.

Gonçalves et al. (12) found an increase in the expression of MnSOD in mice undergoing a low-intensity physical exercise protocol and an increase in the expression of Gpx in animals that were challenged with LPS. Marriot et al. (21), in a study using gp91phox (gp91phox−/−) knockout mice infected with pneumococci, observed a decrease in inflammation but not in microbial killing, suggesting that NADPH oxidase activation regulates the inflammatory response more than microbial killing. In addition, the same group (20) demonstrated a decreased rate of macrophage apoptosis in the lungs of iNOS−/− mice infected with pneumococci associated with increased markers of inflammation in the lung. Considering these previous studies, we could suggest that one of the possible mechanisms of the attenuation of the inflammatory process caused by S. pneumoniae, in our study, was due to an increase in the expression of iNOS and in antioxidant enzymes, such as CuZnSOD and MnSOD, induced by physical exercise.

These anti-inflammatory effects of aerobic conditioning observed in this study have also been described in other experimental models. Vieira et al. (45), Silva et al. (37), and Olivo et al. (31) observed this effect in different animal models of asthma. Toledo et al. (42) also observed attenuation in the pulmonary inflammation induced by cigarette smoke in mice that underwent an aerobic conditioning protocol. Gonçalves et al. (12) observed that mice that underwent aerobic exercise training and received LPS showed a decrease in neutrophil numbers and TNF-α expression in their lung tissue as well as increased levels of IL-6, IL-10, MnSOD in the lung tissue, and IL-1β in the BAL, suggesting that aerobic exercise can modulate the inflammatory–anti-inflammatory and oxidative-anti-oxidative balances in the early phase of ARDS (acute respiratory distress syndrome).

There is much epidemiological evidence that moderate exercise may reduce the risks or the severity of infections, whereas exhaustive exercise may increase the risks, although the majority of these studies were related to the risks of viral infections (23, 29). These effects of different intensities of exercise have also been shown in animal models of respiratory viral infection, where moderate exercise tended to decrease morbidity and mortality, whereas strenuous exercise increased mortality (8, 18, 25).
To our knowledge, no previous experimental studies have elucidated the main mechanisms by which regular physical activity results in anti-inflammatory effects against pulmonary bacterial infections. There are some hypotheses, such as the reduction of visceral fat mass, thus decreasing the release of proinflammatory cytokines from adipose tissue; an increase in cardiovascular health, thus decreasing the concentration of plasma triglycerides and low-grade lipoprotein (LDL) particles and increasing the concentration of protective high-density lipoprotein (HDL) cholesterol; the increase of circulating hormones, such as cortisol and catecholamines, that may have potent anti-inflammatory effects; and the increased production and release of anti-inflammatory cytokines from contracting muscles and the reduced expression of toll-like receptors on monocytes and macrophages. Some of these changes can induce an anti-inflammatory environment that brings to a physically active person many health benefits, such as reduced susceptibility to infectious diseases and poor outcomes. However, the molecular mechanisms responsible for the interactions between physical exercise and the attenuation of pulmonary bacterial infection remain to be fully elucidated (11).

In summary, we observed that regular physical exercise decreases the number of CFUs in the lungs and attenuates the inflammatory process in an experimental model of S. pneumoniae infection and that these benefits seem to begin in the acute phase of infection and remain in the late phase. These anti-inflammatory effects may be due to an antioxidant effect of physical conditioning.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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