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Low-intensity exercise training decreases cardiac output and hypertension in spontaneously hypertensive rats

ACÁCIO SALVADOR VÉRAS-SILVA, KATT COELHO MATTOS, NILO SÉRGIO GAVA, PATRICIA CHAKUR BRUM, CARLOS EDUARDO NEGRÃO, AND EDUARDO MOACYR KRIEGER
Hypertension Unit, Heart Institute, Faculty of Medicine, and Exercise Physiology Laboratory, Physical Education and Sports School, University of São Paulo, São Paulo, Brazil 05403-000

Véras-Silva, Acácio Salvador, Katt Coelho Mattos, Nilo Sérgio Gava, Patricia Chakur Brum, Carlos Eduardo Negrão, and Eduardo Moacyr Krieger. Low-intensity exercise training decreases cardiac output and hypertension in spontaneously hypertensive rats. *Am. J. Physiol.* 273 (*Heart Circ. Physiol.* 42): H2627–H2631, 1997.—The decrease in cardiac sympathetic tone and heart rate after low-intensity exercise training may have hemodynamic consequences in spontaneously hypertensive rats (SHR). The effects of exercise training of low and high intensity on resting blood pressure, cardiac output, and total peripheral resistance were studied in sedentary ($n = 17$), low- ($n = 17$), and high-intensity exercise-trained ($n = 17$) SHR. Exercise training was performed on a treadmill for 60 min, 5 times per week for 18 weeks, at 55% or 85% maximum oxygen uptake. Blood pressure was evaluated by a cannula inserted into the carotid artery, and cardiac output was evaluated by a microprobe placed around the ascending aorta. Low-intensity exercise-trained rats had a significantly lower mean blood pressure than sedentary and high-intensity exercise-trained rats (160 ± 4 vs. 175 ± 3 and 173 ± 2 mmHg, respectively). Cardiac index (20 ± 1 vs. 24 ± 1 and 24 ± 1 ml·min⁻¹·100 g⁻¹, respectively) and heart rate (332 ± 6 vs. 372 ± 14 and 345 ± 9 beats/min, respectively) were significantly lower in low-intensity exercise-trained rats than in sedentary and high-intensity exercise-trained rats. No significant difference was observed in stroke volume index and total peripheral resistance index in all groups studied. In conclusion, low-intensity, but not high-intensity, exercise training decreases heart rate and cardiac output and, consequently, attenuates hypertension in SHR.

blood pressure; exercise training intensity; hemodynamics

OUR GROUP HAS RECENTLY stated that low-intensity exercise training in spontaneously hypertensive rats (SHR) decreased sympathetic tone to the heart, which was associated with a reduction in heart rate (3). In addition, high-intensity exercise training, in contrast to low-intensity exercise training, had no effect on sympathetic tone or heart rate in SHR. The decrease in cardiac sympathetic tone in low-intensity exercise-trained SHR may cause hemodynamic changes and, consequently, an attenuation in hypertension. Therefore, we studied the hemodynamic changes provoked by different exercise training intensities in SHR.

Previous studies (5, 20, 24) have reported that exercise training can provoke important changes in the cardiovascular system in animals and humans with hypertension. Hagberg et al. (5) reported that low-intensity exercise training in older hypertensive individuals provoked a reduction in arterial blood pressure determined by a significant decrease in cardiac output. Similar results were observed in SHR (25). In contrast,

others (7, 8, 17) suggested that the reduction in arterial blood pressure in humans was due to a decrease in total peripheral resistance concomitant with a significant increase in cardiac output. It was interesting, however, that cardiac output was evaluated by an indirect technique in most of the previous studies (5, 7, 8, 17).

From these previous studies we learned that, in fact, exercise training reduces hypertension, but the mechanisms underlying this decrease in hypertension are controversial and not very conclusive.

In the present study, we found that low-intensity exercise training, in contrast to high-intensity exercise training, reduced heart rate, which in turn decreased cardiac output and, consequently, attenuated hypertension in SHR.

METHODS

Study Population

Fifty-one male SHR (Paulista Medical School, Brazil; 60–70 g body wt, 3–4 rats/cage) were fed standard laboratory chow and water ad libitum in a temperature-controlled room (22°C) with a 12:12-h dark-light cycle. The rats were assigned randomly into three groups: sedentary ($n = 17$), low-intensity exercise-trained ($n = 17$) and high-intensity exercise-trained ($n = 17$) rats. From these groups, 7 sedentary, 7 low-intensity exercise-trained, and 8 high-intensity exercise-trained rats were assigned to *protocol 1*, and 10 sedentary, 10 low-intensity exercise-trained, and 9 high-intensity exercise-trained rats were assigned to *protocol 2*, as described in *Experimental Protocols*.

Maximal Oxygen Uptake

Maximal oxygen uptake ($\dot{V}O_{2\max}$) was measured by means of expired gas analysis during a progressive exercise test on a treadmill with 5 m/min increments (5–35 m/min) every 4 min and no grade, according to the procedure described previously (3). Oxygen and carbon dioxide concentrations were analyzed by the Scholander microtechnique (Godart-Statham, Bilthoven, Holland).

Exercise Training

Exercise training was performed on a motor treadmill for 18 weeks, 5 times per week for 60 min, gradually progressing toward 55% $\dot{V}O_{2\max}$ (16–20 m/min) for the low-intensity exercise-trained rats and 85% $\dot{V}O_{2\max}$ (25–30 m/min) for the high-intensity exercise-trained rats, as previously described elsewhere (3). The sedentary rats were handled at least 3 days/wk to become accustomed to the experimental protocols.

Measurement of Arterial Blood Pressure

One cannula (PE-50) was inserted, under ether anesthesia, into the carotid artery and emerged through the back of the rat. During the experimental session, this cannula was

connected to a strain-gauge transducer (P23 Db; Gould-Statham). The signal from this transducer was fed into an amplifier (GPA 4-channel, model 2; Stemtech) and a 16-channel analog-to-digital converter (Stemtech) and then to a microcomputer (4DX2-66V Gateway 2000) for direct arterial pressure measurements. Arterial blood pressure was recorded on a beat-to-beat basis (AT/CODAS) at a frequency of 100 Hz for 30 min in quiet, conscious, unrestrained rats. The data reported indicate the average of all values of systolic, diastolic, and mean arterial pressure over the entire 30-min period.

Measurement of Cardiac Output

The rats were lightly anesthetized with ether to allow placement of a tracheal cannula (PE-260) for artificial respiration. A cannula (PE-50) was also inserted into the jugular vein to infuse pentobarbital sodium (30 mg/kg) in small doses (0.2–0.5 ml) during the surgery when needed. To compensate for the normal loss of body fluid due to the open chest, 2 ml/h of sterile saline (0.9% NaCl) were continuously infused into the jugular vein. A transversal incision was performed on the right side of the chest wall in the second intercostal space just below the axillary area. The pectoral musculature was carefully opened by following the fiber orientation to avoid damage. During this procedure, the bleeding was contained with homeostatic collagen (Lyostypt, B. Braun Melsungen). Artificial respiration was performed with the use of a rodent ventilator (model 683; Harvard) at a frequency of 60 breaths/min at 2.5 ml/breath during all surgical procedures. An ultrasonic perivascular flow probe (2SB; Transonic Systems) was placed around the ascending aorta just above the coronary arteries and emerged through the back of the rat. Body temperature was maintained stable (37°C) by heating. After surgery, the rat received veterinary pentabiotic (Wyeth-Ayerst Labs) and was returned to its cage. During the experimental session, the microprobe was connected to an ultrasonic flowmeter (model T206; Transonic Systems). The signal from the flowmeter was fed into an amplifier and a 16-channel analog-to-digital converter and then to a microcomputer for a direct cardiac output measurement. Cardiac output was recorded on a beat-to-beat basis at a frequency of 100 Hz for 30 min in quiet, conscious, unrestrained rats. Cardiac output was measured simultaneously with arterial blood pressure.

Experimental Protocols

Protocol 1: Blood pressure and heart rate responses after exercise training. To evaluate the effect of exercise training intensity on arterial blood pressure in spontaneous hypertension, we studied seven sedentary, seven low-intensity exercise-trained, and eight high-intensity exercise-trained male SHR. After the last training session, one cannula was inserted into the carotid artery. Twenty-four hours after the cannula was implanted, arterial pressure was analyzed for 30 min in quiet, conscious, unrestrained rats, and heart rate was counted from arterial blood pressure pulses.

Protocol 2: Hemodynamic responses after exercise training. To evaluate the effect of exercise training intensity on hemodynamic responses in spontaneous hypertension, we studied 10 sedentary, 10 low-intensity exercise-trained, and 9 high-intensity exercise-trained male SHR. After the last training session, an ultrasonic perivascular flow probe was placed around the ascending aorta according to the procedure described previously. Three days after surgery, exercise training on treadmill restarted, and it lasted until the rats could run at the same speed and duration performed before the surgical

procedure. At least 10 days were necessary for the rats to achieve a complete recovery.

Heart rate was counted from arterial blood pressure pulses. Stroke volume was calculated from the division of cardiac output by heart rate, and total peripheral vascular resistance was calculated from the division of mean arterial blood pressure by cardiac output.

Statistical Analysis

Data for $\dot{V}O_{2max}$, arterial blood pressure and heart rate responses, and hemodynamic responses are presented as means \pm SE. Data for all three groups studied were subjected to a one-way analysis of variance. When a significance was found, Tukey's post hoc comparison was performed. $P < 0.05$ was considered statistically significant.

RESULTS

Body Weight and $\dot{V}O_{2max}$

The results of body weight and $\dot{V}O_{2max}$ before and after exercise training are presented in Table 1. Before exercise training, there was no significant difference in body weight in all groups studied. Similar results were observed after exercise training. Before exercise training, $\dot{V}O_{2max}$ corrected to body weight was similar in all groups studied. After exercise training of low and high intensity, however, $\dot{V}O_{2max}$ was significantly ($P < 0.05$) higher in exercise-trained rats when compared with sedentary rats.

Blood Pressure and Heart Rate Responses After Exercise Training

The results for systolic, diastolic, and mean arterial blood pressure obtained in *protocol 1* are shown in Table 2. Low-intensity exercise-trained rats had significantly ($P < 0.05$) lower systolic, diastolic, and mean arterial blood pressure than both sedentary and high-intensity exercise-trained rats, whereas no significant difference was observed between high-intensity exercise-trained rats and sedentary rats.

The results for heart rate obtained in *protocol 1* are also shown in Table 2. Low-intensity exercise-trained rats had a significantly ($P < 0.05$) lower heart rate than both sedentary and high-intensity exercise-trained rats. However, no significant difference was observed between high-intensity exercise-trained rats and sedentary rats.

Table 1. Body weight and maximal oxygen uptake before and after low- and high-intensity exercise training in spontaneously hypertensive rats

| | n | Body Weight, g | | $\dot{V}O_{2max}$, ml O ₂ · kg ⁻¹ · min ⁻¹ | |
|-----|----|----------------|---------|--|----------|
| | | Before | After | Before | After |
| SED | 17 | 63 ± 3 | 256 ± 7 | 107 ± 2 | 90 ± 1 |
| LT | 17 | 63 ± 4 | 254 ± 6 | 103 ± 2 | 100 ± 1* |
| HT | 17 | 63 ± 3 | 247 ± 4 | 104 ± 2 | 99 ± 2* |

Data are means \pm SE. $\dot{V}O_{2max}$, maximal oxygen uptake; SED, sedentary rats; LT, low-intensity exercise-trained rats; HT, high-intensity exercise-trained rats. *Significant difference compared with sedentary rats ($P < 0.05$).



Table 2. Systolic, diastolic, and mean arterial pressure and heart rate in sedentary, low-, and high-intensity exercise-trained spontaneously hypertensive rats

| | n | SAP, mmHg | DAP, mmHg | MAP, mmHg | HR, beats/min |
|-----|---|-----------|-----------|-----------|---------------|
| SED | 7 | 204 ± 4 | 147 ± 3 | 175 ± 3 | 359 ± 9 |
| LT | 7 | 187 ± 5*† | 133 ± 4*† | 160 ± 4*† | 318 ± 8*† |
| HT | 8 | 204 ± 2 | 144 ± 3 | 173 ± 2 | 349 ± 7 |

Data are means ± SE. SAP, systolic arterial blood pressure; DAP, diastolic arterial blood pressure; MAP, mean arterial blood pressure; HR, heart rate. * Significant difference compared with sedentary rats ($P < 0.05$); † significant difference compared with high-intensity exercise-trained rats ($P < 0.05$).

Hemodynamic Responses After Exercise Training

In confirmation of the results obtained in *protocol 1*, low-intensity exercise-trained rats had a significantly ($P < 0.05$) lower systolic, diastolic, and mean arterial blood pressure than sedentary and high-intensity exercise-trained rats, but no significant difference was found between sedentary rats and high-intensity exercise-trained rats (Fig. 1A).

Cardiac output was reduced significantly ($P < 0.05$) in low-intensity exercise-trained rats compared with that in sedentary and high-intensity exercise-trained rats (50 ± 3 vs. 60 ± 2 and 58 ± 3 ml/min, respectively), but no significant difference was observed between high-intensity exercise-trained rats and sedentary rats. Similar results were found for cardiac output corrected to body weight. Low-intensity exercise-trained rats had a significantly ($P < 0.05$) lower cardiac index than sedentary and high-intensity exercise-trained rats ($20 \pm$

1 vs. 24 ± 1 and 24 ± 1 ml · min⁻¹ · 100 g⁻¹, respectively; Fig. 1B), whereas no significant difference was observed between high-intensity exercise-trained rats and sedentary rats.

In confirmation of the results obtained in *protocol 1*, low-intensity exercise-trained rats had a significantly ($P < 0.05$) lower heart rate than sedentary and high-intensity exercise-trained rats, and no significant difference was observed between high-intensity exercise-trained rats and sedentary rats (Fig. 1C). Stroke volume index (Fig. 1D) and total peripheral resistance index (Fig. 1E) were similar in all groups studied.

DISCUSSION

The major findings of the present investigation are: 1) exercise training at 55% $\dot{V}O_{2\max}$ significantly decreases resting heart rate and cardiac output in SHR but causes no change in total peripheral resistance; 2) exercise training at 85% $\dot{V}O_{2\max}$ does not change resting cardiac output and heart rate in SHR; 3) exercise training at 55% $\dot{V}O_{2\max}$ provokes a significant reduction in resting systolic, diastolic, and mean arterial blood pressure in SHR; and 4) exercise training at 85% $\dot{V}O_{2\max}$ has no effect on resting systolic, diastolic, and mean arterial blood pressure in SHR.

The increased $\dot{V}O_{2\max}$ in the low- and high-intensity exercise-trained rats shows the effectiveness of the present exercise-training protocol. Moreover, these data demonstrate that exercise training attenuates the decrease in $\dot{V}O_{2\max}$ corrected to body weight that has been described during the rat's life span (24).

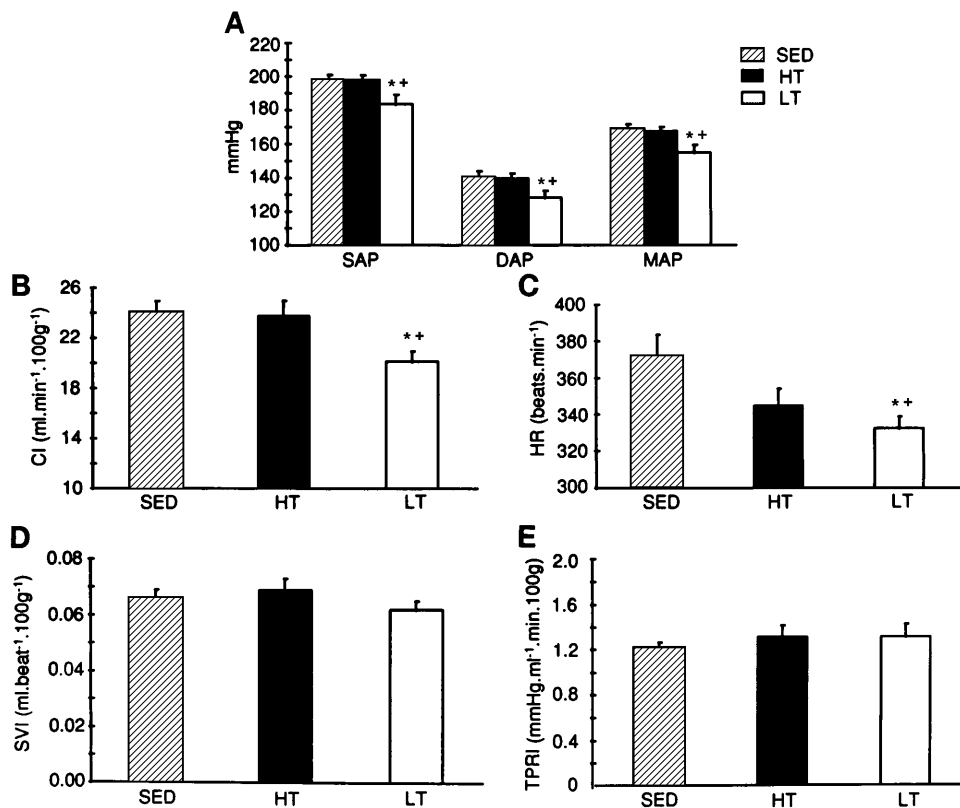


Fig. 1. Systolic (SAP), diastolic (DAP), and mean (MAP) arterial blood pressure (A), cardiac index (CI; B), heart rate (HR; C), stroke volume index (SVI; D), and total peripheral resistance index (TPRI; E) in spontaneously hypertensive rats after low- and high-intensity exercise training. Data are presented as means ± SE. SED, sedentary rats ($n = 10$); LT, low-intensity exercise-trained rats ($n = 10$); HT, high-intensity exercise-trained rats ($n = 9$). * Significant difference compared with sedentary rats ($P < 0.05$); † significant difference compared with high-intensity exercise-trained rats ($P < 0.05$).

Bradycardia has been considered a good marker of exercise training adaptation in different species (9, 12, 16, 19). The present data confirm these findings in SHR, except that high-intensity exercise training showed no effect on resting heart rate. In SHR and in humans with essential hypertension, resting bradycardia after exercise training has been observed by some (6, 17) but not by others (25, 26). This discrepancy may be explained by differences in exercise-training protocol or in exercise-training intensity. Hoffmann et al. (6) observed that spontaneous running exercise caused resting bradycardia in SHR, whereas Tipton et al. (25) found no effect of low to moderate exercise training on resting heart rate in unanesthetized SHR. Nelson et al. (17) reported that bicycling at 60–70% maximal working capacity 3 and 7 times per week for 4 weeks provoked resting bradycardia in hypertensive men, whereas Urata et al. (26) did not observe any significant change in resting heart rate after exercise training at 40–60% $\dot{V}O_{2\max}$ 3 times per week for 10 weeks in hypertensive men. Our data agree with those (6, 17) that showed a significant reduction in resting heart rate after exercise training.

It was observed (25) that exercise training within 40–70% $\dot{V}O_{2\max}$ decreased arterial blood pressure and cardiac output in unanesthetized SHR. Surprisingly, however, no reduction in resting heart rate was demonstrated. The heart rate of the exercise-trained rats was similar to that of untrained rats. One possible explanation for those results is the period between the surgical procedure for probe implantation and the performance of the experimental protocol, which averaged 6 ± 0.6 days in that study. This period might not be sufficient for a complete recovery of the animal or for returning to the same exercise-training status. In the present study, the rats were studied when they could run at the same exercise-training intensity and duration performed before the surgical procedure, which took at least 10 days.

Although little doubt exists about the effect of exercise training on the essential hypertension, the mechanisms underlying this response still remain controversial and not very conclusive (1, 4, 23). There are indications that exercise training provokes a reduction in cardiac output (5, 25) or a decrease in total peripheral resistance (7, 8, 14, 17). More recently, it has also been argued that exercise training causes a decrease in blood volume which, in turn, reduces arterial blood pressure (1, 26). According to our present data, exercise training performed at 55% $\dot{V}O_{2\max}$ significantly decreases resting cardiac output in SHR mainly due to a significant decrease in resting heart rate.

The attenuation of hypertension in SHR presently observed cannot be explained by a decrease in total peripheral vascular resistance. Although some investigators have suggested that exercise training significantly decreases plasma norepinephrine levels in hypertensive rats (27) and humans (2, 7, 8, 14, 17), this response may not cause reduction in total peripheral vascular resistance. Tashiro et al. (22) found a significant decrease in norepinephrine and arterial blood pressure in hypertensive humans but no change in total peripheral resistance. Negrão et al. (15) observed

that moderate exercise training provoked a significant decrease in renal sympathetic nerve activity in normotensive rats but no change in arterial blood pressure. More recently, Gava et al. (3) found that low-intensity exercise training caused resting bradycardia and a significant decrease in sympathetic tone to the heart in SHR. Therefore, the decrease in peripheral sympathetic activity after low-intensity exercise training in SHR seems to play an important role in the heart, provoking a significant reduction in heart rate and a slight decrease in stroke volume, but not in blood vessels.

In agreement with other studies (5, 7, 8, 10, 11, 13, 17, 21, 22, 24, 26), the present data confirm that exercise training attenuates hypertension. Moreover, they demonstrate that an appropriate exercise-training intensity is crucial to obtain the decrease in high blood pressure, because only low-intensity exercise training produces beneficial effects on hypertension. The effect of exercise intensity on resting blood pressure was first documented by Shindo et al. (20). Almost 10 years later, Tipton et al. (24) demonstrated that exercise training performed at 55% $\dot{V}O_{2\max}$ had a better effect on resting caudal arterial systolic blood pressure in SHR than exercise training in excess of 75% $\dot{V}O_{2\max}$. In the present study, the intra-arterial pressure, measured on a beat-to-beat basis (computer frequency 100 Hz), confirmed the previous observation of Tipton et al. (24), who measured resting caudal systolic pressure in SHR.

The lack of attenuation in high blood pressure after high-intensity exercise training found in our study is in agreement with some studies (18, 24) that showed no effect of exercise training in excess of 75% $\dot{V}O_{2\max}$ or 70% the maximum heart rate on arterial blood pressure. The present study showed that high-intensity exercise training failed not only in reducing resting arterial blood pressure but also in decreasing cardiac output and heart rate. Moreover, these data provide important evidence for the suggestion that the decrease in cardiac output is the actual mechanism by which low-intensity exercise training attenuates hypertension in SHR.

Our data provide no explanation for why high-intensity exercise training failed to decrease high blood pressure in SHR. However, we can speculate that our SHR were exposed to such a high sympathetic drive during high-intensity exercise that they never had a complete recovery after each exercise bout. This chronic exposure to high sympathetic activity may have overridden the benefits of exercise training usually seen in hypertensive humans and animals.

Limitations

The exercise training protocols (55% and 85% $\dot{V}O_{2\max}$) presently used give important information in regard to their effects on high blood pressure as well as hemodynamic mechanisms, but they do not determine which is the best exercise training intensity or frequency to treat essential hypertension. Nelson et al. (17) reported that 45 min of bicycling 7 times per week reduced systolic and diastolic arterial blood pressure by 16 and 11 mmHg, respectively, in untreated hypertensive men,

whereas 45 min of bicycling 3 times per week reduced systolic and diastolic arterial blood pressure by 11 and 9 mmHg, respectively. The present study showed that running on a treadmill 5 times per week caused a decrease of 14 and 11 mmHg in systolic and diastolic arterial blood pressure, respectively, in SHR. Therefore, besides intensity, frequency of exercise must be taken into consideration to reduce high arterial blood pressure.

In the present study, exercise training began when SHR were 4 wk old, that is, before high blood pressure started developing, as observed by indirect caudal systolic pressure measurements (138 ± 4 in sedentary rats, 140 ± 4.5 in high-intensity exercise-trained rats, and 138 ± 3.2 mmHg in low-intensity exercise-trained rats). Hoffmann et al. (6) suggested that chronic voluntary exercise in SHR with established hypertension did not reduce blood pressure, whereas Hagberg et al. (5) reported an attenuation of high blood pressure in older hypertensive men. Tipton et al. (24) found that exercise training in older hypertensive rats restrains the enhancement of blood pressure. Our protocol gives no information on the effect of exercise training after the development of high arterial blood pressure. Therefore, future studies are needed to address the effect of different exercise training intensities on the development of hypertension as well as on their mechanisms.

In conclusion, low-intensity exercise training decreases heart rate and cardiac output and, in consequence, attenuates hypertension in SHR. In contrast, high-intensity exercise training neither decreases heart rate and cardiac output nor attenuates high arterial blood pressure in SHR.

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Address for reprint requests: C. E. Negrão, Hypertension Unit, Heart Institute, Faculty of Medicine, Univ. of São Paulo, Av. Dr. Enéas Carvalho de Aguiar, 44, São Paulo, Brazil 05403-000.

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