Chronic intermittent hypoxia increases infarction in the isolated rat heart

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Joyeux-Faure, M., F. Stanke-Labesque, B. Lefebvre, P. Béguin, D. Godin-Ribuot, C. Ribuot, S. H. Launois, G. Bessard, and P. Lévy. Chronic intermittent hypoxia increases infarction in the isolated rat heart. J Appl Physiol 98: 1691–1696, 2005. First published December 23, 2004; doi:10.1152/japplphysiol.01146.2004.—Chronic intermittent hypoxia increases infarction in the isolated rat heart. J Appl Physiol 98: 1691–1696, 2005. First published December 23, 2004; doi:10.1152/japplphysiol.01146.2004.—Coronary heart disease is frequently associated with obstructive sleep apnea syndrome and treating obstructive sleep apnea appears to significantly improve the outcome in coronary heart disease. Thus we have developed a rat model of chronic intermittent hypoxia (IH) to study the influence of this condition on myocardial ischemia-reperfusion tolerance and on functional vascular reactivity. Wistar male rats were divided in three experimental groups (n = 12 each) subjected to chronic IH (IH group), normoxia (N group), or control conditions (control group). IH consisted of repetitive cycles of 1 min (40 s with inspired O2 fraction 5% followed by 20 s normoxia) and was applied for 8 h during daytime, for 35 days. Normoxic cycles were applied in the same conditions, inspired O2 fraction remaining constant at 21%. On day 36, mean arterial blood pressure (MABP) was measured before isolated hearts were submitted to an ischemia-reperfusion protocol. The thoracic aorta and left carotid artery were also excised for functional reactivity studies. MABP was not significantly different between the three experimental groups. Infarct sizes (in percent of ventricles) were significantly higher in IH group (46.9 ± 3.6%) compared with N (26.1 ± 2.8%) and control (21.7 ± 2.1%) groups. Vascular smooth muscle function was similar in aorta and carotid arteries from all groups. The endothelium-dependent relaxation in response to acetylcholine was also similar in aorta and carotid arteries from all groups. Chronic IH increased heart sensitivity to infarction, independently of a significant increase in MABP, and did not affect vascular reactivity of aorta and carotid arteries.

Potential vascular factors leading to increased cardiovascular morbidity in OSA patients have been documented. During sleep, obstructive apneas are followed by transient peripheral vasoconstriction (1). Recent studies suggest that patients with this syndrome present an altered vascular relaxation (6, 9, 18, 19). Recurrent intermittent hypoxia (IH) is a consequence of sleep apnea that seems to be the key factor involved in both acute and chronic cardiovascular consequences (11). Several animal models have been developed to address the effect of IH on the cardiovascular system. Current experimental protocols vary greatly in cycle length, number of hypoxic episodes per day, and number of exposure days (for review, see Ref. 24). Repeated exposures to IH elicit persistent changes in a variety of physiological responses, in particular vascular reactivity (39). Moreover, sustained chronic hypoxia is known to stimulate angiogenesis and modify vascular integrity, leading to changes in permeability (27, 33), although this has not been studied during IH.

The aim of the present study was first to determine the influence of a 35-day exposure to IH on myocardial ischemia-reperfusion tolerance in the rat. A second time, we assessed the effect of this exposure on the functional reactivity of aorta and carotid arteries.

METHODS

This investigation conformed to the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication no. 85-23, revised 1996) and with French law and local ethical committee guidelines for animal research. The protocol received approval from the Direction des Services Vétérinaires de l’Isère, France. Experiments were conducted on 52 adult male Wistar rats (weight range 220–240 g) from Elevage Janvier (Le Genest-Saint-Isle, France) housed in controlled conditions and provided with standard rat chow.

Intermittent Hypoxia Protocol

Rats were separated randomly into three groups: the first group (IH, n = 12) was exposed to IH, the second group (N, n = 12) was exposed to air, and the third group consisted of unhandled controls (n = 12).

During daily IH, the animals were housed in custom-made identical cylindrical Plexiglas chambers (length 28 cm, diameter 10 cm, volume 2.2 liters) with tightly fitting lids. Timed solenoid valves were used to distribute pure nitrogen to each chamber via a balloon reservoir at a flow rate of 2.2 liters per minute. Nitrogen was distributed at the same flow rate to normoxic chambers, thereby submitting the normoxic groups to the same conditions as IH-exposed rats. A 2.2-liter fresh-air chamber was also used as the control chamber. The IH group consisted of five repetitive cycles of 1 min without inspired O2 (5% inspired O2 for 40 s followed by 20 s normoxia) and was applied for 8 h during daytime, for 35 days. Normoxic cycles were applied in the same conditions, inspired O2 fraction remaining constant at 21%. On day 36, mean arterial blood pressure (MABP) was measured before isolated hearts were submitted to an ischemia-reperfusion protocol. The thoracic aorta and left carotid artery were also excised for functional reactivity studies. MABP was not significantly different between the three experimental groups. Infarct sizes (in percent of ventricles) were significantly higher in IH group (46.9 ± 3.6%) compared with N (26.1 ± 2.8%) and control (21.7 ± 2.1%) groups. Vascular smooth muscle function was similar in aorta and carotid arteries from all groups. The endothelium-dependent relaxation in response to acetylcholine was also similar in aorta and carotid arteries from all groups. Chronic IH increased heart sensitivity to infarction, independently of a significant increase in MABP, and did not affect vascular reactivity of aorta and carotid arteries.

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bances. A dampening device at the chamber intake was used to dissipate the air-stream arriving on the animals.

The level of \(F_{\text{O}_2}\) in the chambers was controlled throughout the hypoxia protocol by using a Beckman OM11 \(O_2\) analyzer (Fullerton, CA).

**Mean Arterial Blood Pressure Measurement**

The day after the completion of the 35-day IH period, the rats were anesthetized by intraperitoneal injection of pentobarbital sodium (60 mg/kg, Sanofi, Libourne, France). Heparin (500 U/kg, Sanofi Winthrop, Gentilly, France) was injected intravenously and mean arterial blood pressure (MABP) was measured as previously described (35, 37). The right carotid artery of the rats was cannulated with polyethylene tubing (PE-50) connected to a pressure transducer (Statham), and arterial blood pressure was recorded on a data-acquisition system (PowerLab, ADInstruments). Hematocrit was measured by collecting blood in a specific glass tube (Brand, Finland) and centrifuging for 2 min at 1,000 rpm.

**Tissue Preparation**

After MABP and hematocrit measurements, hearts were rapidly excised and immediately immersed in 4°C Krebs-Henseleit buffer solution (NaCl 118, CaCl\(_2\) 1.8, MgSO\(_4\) 1.2, KH\(_2\)PO\(_4\) 1.2, NaHCO\(_3\) 25.2, and glucose 11 mM). The thoracic aorta and left carotid artery were excised, transferred to a dish filled with Krebs bicarbonate buffer, cleared of periadventitial tissue, and cut into ring segments (3.0 mm in length). Care was taken not to touch the inner surface of the blood vessels.

**Isolated Heart Preparation**

*Ischemia-reperfusion on isolated heart, after chronic IH exposure.*

The aortic stump was then cannulated and hearts were perfused retrogradely by the Langendorff technique at a constant pressure (75 mmHg) with oxygenated Krebs-Henseleit buffer, as previously described (20). Water-filled latex balloon (Hugo Sachs, no. 4), coupled to a pressure transducer, was inserted in the left ventricular cavity via the left atrium for pressure recording. Left ventricular end-diastolic pressure (LVEDP) was adjusted to 5 mmHg. Myocardial temperature, measured by a thermoprobe inserted into the left ventricle, was maintained constant close to 37°C. After 20 min of stabilization, global ischemia was induced by stopping the perfusion for 30 min. Thereafter the heart was reperfused for 120 min. Coronary flow (CF) was measured throughout the experiment, by collecting the effluent. Heart rate and left ventricular developed pressure (LVDP = difference between left ventricular systolic pressure and LVEDP) were continuously recorded.

Only hearts with CF within 10–16 ml/min and LVDP > 70 mmHg at the end of the stabilization period were included in this study. Hearts that developed ventricular fibrillation during reperfusion, which could not be restored to normal sinus rhythm within 2 min, were excluded. Three hearts per group were excluded because of nonconformity with these criteria.

At the end of the ischemia-reperfusion protocol, the atria were removed and the heart was frozen at −20°C for 10 min. It was then cut into 2-mm transverse sections from apex to base (6–7 slices/heart). Once thawed, the slices were incubated at 37°C with 1% triphenyltetrazolium chloride in phosphate buffer (pH 7.4) for 10 min and fixed in 10% formaldehyde to clearly distinguish stained viable tissue from unstained necrotic tissue. Infarct size was determined by a computerized planimetric technique (Scion Image for Windows) and expressed as a percentage of the ventricular size.

*Isolated heart after chronic IH exposure without ische- mia-reperfusion.* To investigate the effect of chronic IH exposure per se on cellular necrosis, independently of the ischemia-reperfusion sensitivity, additional hearts (from N and IH groups, \(n = 8\) in each group) were perfused in the same conditions (during 170 min) without ischemia. At the end of perfusion, potential necrosis was assessed as described above by triphenyltetrazolium chloride staining and computerized planimetric technique.

**Vascular Reactivity**

Studies of tension development were performed on rings from aorta and carotid arteries by using a previously reported method (35). Rings were suspended horizontally between two stainless steel wires in organ chambers containing 6 ml of Krebs solution (37°C) aerated with 95% \(O_2\) and 5% \(CO_2\). The lower wire was fixed to a micrometer (Mitutoyo) and the upper wire was attached to a force transducer (UF-1, Pioden UK) for recording of isometric force.

For aortic rings, a normalization procedure was performed in preliminary experiments to standardize the baseline resting internal circumference (calculated from the distance between the wires) of each ring as previously described (17). Briefly, the rings were stretched with the micrometer in progressive steps to determine the wall tension–internal circumference exponential curve for each ring. On the basis of this relationship, the distance between the wires was set at a normalized internal circumference corresponding to 90% of the internal circumference the vessel would have at a transmural pressure of 100 mmHg. The average vessel internal diameters at an equivalent transmural pressure of 100 mmHg were 2.721 ± 0.086 mm (\(n = 6\)), 2.676 ± 0.069 mm (\(n = 9\)), and 2.854 ± 0.019 mm (\(n = 6\)) on aortic rings from IH, N, and control rats, respectively. Resting forces were 1.6 ± 0.1, 1.6 ± 0.1, and 1.7 ± 0.1 g on aortic rings from IH, N, and control rats, respectively. This degree of passive force was then applied on all aortic rings throughout the experiments. Rings from carotid arteries were initially stretched to a given preload of 1.5 g as previously described (4). After a 60-min equilibration period, experiments were initiated by inducing a reference contraction in response to KCl (90 mM) in each ring.

The contractile effects of norepinephrine (1 nM–3 \(\mu M\)) were assessed in aortic rings from all rat groups. The contribution of cysteinyl leukotrienes (CysLT) to the contractile response to norepinephrine was assessed by prior incubation of the preparations for 30 min with either the 5-lipoxygenase inhibitor AA861 (10 \(\mu M\)) (40), the specific 5-lipoxygenase-activating protein inhibitor MK-886 (10 \(\mu M\)) (30), or the specific CysLT; receptor antagonist MK571 (1 \(\mu M\)). For all experiments, appropriate controls (incubation with vehicle) were run under similar experimental conditions in rings obtained from the same aorta.

Endothelial function was assessed by testing the relaxant effect of acetylcholine (1 nM–0.1 mM) on rings from aorta and carotid artery precontracted with phenylephrine (30 nM-0.1 \(\mu M\)). To investigate the basal release of endogenous nitric oxide (NO), aortic rings were pretreated with the NO synthase inhibitor N\(^\text{ono}\)-nitro-L-arginine (L-NNA, 0.1 mM for 30 min) (34).

Only one cumulative concentration-response curve was established for each drug in each ring.

**Drugs**

KCl (Prolabo Normapur grade), acetylcholine, norepinephrine, AA861 [2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadienyl)-1,4-benzquinone], and L-NNA were from Sigma. MK571 [propanoic acid, 3-[[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl][3-(dimethylamino)-3-oxopropyl]thio]methyl][thio]-(E)-, sodium salt] was purchased from Cayman. MK-886 [3-[[1-(4-chlorobenzyl)-3-hydroxy-thio-5-isopropyl-indol-2-yl]-2,2-dimethylpropanoic acid] was kindly provided by Merck Frosst. Drugs were kept at −20°C and freshly dissolved in distilled water to the appropriate concentration expressed as the final molar concentration in the organ bath.
Statistical Analysis

All data are presented as means ± SE. MABP, hematocrit, and infarct size values were compared by one-way ANOVA. Hemodynamic data were analyzed by two-way ANOVA. Post hoc multiple comparisons were performed by Tukey tests.

For organ bath experiments, contractile responses to norepinephrine were expressed as a percentage of the contraction induced by 90 mM KCl. Relaxant responses to acetylcholine were expressed as percentage of phenylephrine-induced tone. The maximal effect was the greatest response obtained with the agonist. The EC_{50} was determined from each curve by using a logistic curve-fitting equation. The pD_{2} value is the negative logarithm of the EC_{50}. Statistical analyses were performed using ANOVA followed by Bonferroni-corrected t-tests.

Statistical significance was set at P < 0.05.

RESULTS

Body Weight, MABP, and Hematocrit

After the 35-day IH period, body weight was significantly lower in hypoxic than in normoxic and control groups (Table 1). Hematocrit was significantly higher in hypoxic than in normoxic and control groups (Table 1). MABP was not significantly different between IH compared with N groups, although there was a significant difference between IH group compared with controls (Table 1).

Isolated Heart Preparation

Myocardial infarction and ventricular function after ischemia-reperfusion. Figure 1 shows myocardial infarct size, expressed as the percentage of the ventricular area in the three different groups (N = 9 per group). The infarct size was significantly higher in the hypoxic group (46.9 ± 3.6%) than in the normoxic (26.1 ± 2.8%) and control (21.7 ± 2.1%) groups.

As shown in Table 2, after the 30-min global ischemia, LVDP and its derivative (dP/d_{max}, an index of contractility) decreased markedly at reperfusion in all hearts. No difference in functional ventricular recovery was seen between the three groups during reperfusion. CF, heart rate, and LVEDP were not significantly different between the three groups throughout the ischemia-reperfusion protocol.

Myocyte viability after chronic IH exposure, without ischemia-reperfusion. No cellular necrosis was seen in the hearts from animals chronically exposed to IH or N, after a 170-min perfusion without ischemia.

Organ Chamber Experiments

Vascular smooth muscle function. KCl 90 mM induced a similar contraction in aorta and carotid artery from all rat groups: aortic rings, 3,962 ± 180 mg (IH rats, n = 32 rings), 3,861 ± 204 mg (N rats, n = 31 rings), and 4,429 ± 200 mg (control rats, n = 21 rings); rings from carotid artery, 1,288 ± 108 mg (IH rats, n = 13 rings), 1,191 ± 78 mg (N rats, n = 12 rings), and 1,276 ± 56 mg (control rats, n = 8 rings).

Norepinephrine induced a concentration-dependent contraction in aorta and carotid artery from hypoxic, normoxic, and control rats. In terms of potency (pD_{2}) or efficacy (maximal effect), the contractile response to norepinephrine was similar in aorta and carotid arteries from the three rat groups (Table 3). Pretreatment with either the 5-lipoxygenase inhibitor AA861, the specific 5-lipoxygenase-activating protein inhibitor MK-886, or the CysLT_{1} receptor antagonist MK571 did not modify the contraction elicited by norepinephrine in aortic rings from each rat group (Table 4).

Endothelial function. Acetylcholine induced concentration-dependent relaxations of phenylephrine precontracted aorta and carotid arteries that were similar in aorta and carotid arteries from the three rat groups (Table 3).

The addition of a single dose of L-NNA (0.1 mM) on the basal tone resulted in vasoconstriction that was similar in aortas from all groups. The L-NNA-induced increases in tone were (% of KCl-induced contraction) 6.0 ± 1.6 (n = 20), 4.2 ± 1.5 (n = 17), and 5.5 ± 2.4 (n = 6) on aortic rings from hypoxic, normoxic, and control rats, respectively.

DISCUSSION

This study first shows that chronic IH in the rat results in an enhanced myocardial susceptibility to ischemia as shown by the significantly higher infarct size in hypoxic hearts compared with normoxic and control hearts. This effect appears independently of any significant change in MABP. The second and independent observation supported by this study is that chronic IH exposure does not affect peripheral vascular reactivity, as seen in aorta and carotid arteries.

Effect of Chronic IH on Blood Pressure and Hematocrit

Chronic exposure to IH can cause moderate increases in blood pressure in the rat (13, 16, 39). This was not observed in...
of the contraction elicited by 90 mM KCl. The expressed as percentage of phenylephrine-induced tone pD2, apparent affinity.

Also, in our study, MABP was measured under pentobarbital anesthesia, whereas in the above-mentioned studies it was recorded either under urethane anesthesia (16) or in conscious animals (13, 39). Overall, the impact of IH on blood pressure is limited in rodents. The pressor response may vary from one experiment to another depending on the intensity of the stimulus. In any case, it underscores the fact that cardiovascular changes may occur in response to IH before any increase in blood pressure is observed. This is true in humans with OSA who can present with vascular dysfunction in the absence of hypertension (9, 19) and may be applicable to our results on myocardial sensitivity to ischemia.

Finally, our model of chronic IH appears to induce an adaptive response to hypoxia, because hematocrit values were increased to 69%. A wide range of hematocrit levels is ob-

<table>
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<tr>
<th>Hemodynamic data in isolated hearts from control, normoxic, and hypoxic rats</th>
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<td>Control</td>
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<tr>
<td>HR, beats/mm</td>
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<td>LVDP, mmHg</td>
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<td>dP/dt max, mmHg/s</td>
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<td>LVEDP, mmHg</td>
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Table 3. Potency and efficacy of norepinephrine and acetylcholine in aorta or carotid artery from control, normoxic, and hypoxic rats

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<th></th>
<th>Control</th>
<th>Normoxic</th>
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<tr>
<td>Norepinephrine</td>
<td>pD2</td>
<td>6.4±0.1 (8)</td>
<td>6.4±0.2 (8)</td>
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<td></td>
<td>Acetylcholine</td>
<td>pD2</td>
<td>7.0±0.1 (12)</td>
</tr>
<tr>
<td>Carotid artery</td>
<td>Norepinephrine</td>
<td>pD2</td>
<td>6.4±0.1 (6)</td>
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<tr>
<td></td>
<td>Acetylcholine</td>
<td>pD2</td>
<td>6.6±0.2 (6)</td>
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Table 4. Potency and efficacy for noradrenaline-induced contractions in aorta from control, normoxic, and hypoxic rats, in the absence (vehicle) or the presence of AA861 (10 μM), MK-886 (10 μM), and MK571 (1 μM)

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<th>Control</th>
<th>Normoxic</th>
<th>Hypoxic</th>
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<tr>
<td>Vehicle</td>
<td>pD2</td>
<td>6.4±0.1 (6)</td>
<td>6.4±0.2 (8)</td>
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<tr>
<td>AA861</td>
<td>pD2</td>
<td>6.6±0.2 (5)</td>
<td>6.6±0.2 (8)</td>
</tr>
<tr>
<td>MK-886</td>
<td>pD2</td>
<td>6.4±0.1 (5)</td>
<td>6.3±0.1 (7)</td>
</tr>
<tr>
<td>MK571</td>
<td>pD2</td>
<td>6.3±0.2 (5)</td>
<td>6.6±0.2 (8)</td>
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</table>

Values are means ± SE of n aortic rings as indicated in parentheses. The maximal effect (Emax) values of norepinephrine are expressed as a percentage of the contraction elicited by 90 mM KCl. The Emax values of acetylcholine are expressed as percentage of phenylephrine-induced tone pD2, apparent affinity. There was no significant difference between the 3 rat groups.
served in chronic IH models under normobaric conditions, with values varying from normal to almost 70% (5, 7).

Effect of Chronic IH on Peripheral Vascular Function

The endothelium-dependent relaxation in response to acetylcholine was similar in aorta and carotid arteries from all rat groups. These data were consistent with a similar release of endogenous NO, as measured by the increase in tone induced by the NO synthase inhibitor, observed in aorta from all rat groups. In contrast, Tahawi and collaborators (39) showed that 35 days of IH induced an alteration of the endothelium-dependent relaxation in response to acetylcholine in resistance arteries of the cremaster muscle. They suggested that chronic elevation in blood pressure, as produced by IH in their model, involves increased peripheral resistance from decreased basal release of NO.

In aortic and carotid artery (present study), chronic IH induced no change in endothelial function and no change of the contractile response to norepinephrine. These findings are in line with the absence of effect of IH on blood pressure. Moreover, leukotriene biosynthesis inhibition or CysLT1 receptor blockade did not change norepinephrine contractile response. These findings suggest that, in contrast with established experimental models of hypertension (36), CysLT are not involved in the contractile response to norepinephrine in aorta from IH rats.

Effect of Chronic IH on Myocardial Ischemia-Reperfusion Sensitivity

Chronic IH is known as a preconditioning stimulus inducing cardioprotection against ischemic injury (42). Indeed, several studies have previously shown that chronic IH adaptation may be beneficial in protecting heart against ischemia-reperfusion-induced apoptosis (8), necrosis (23), or arrhythmias (2). However, in these studies, the type of IH was entirely different, with only one hypoxic event per day. In the present study, the stimulus was clearly different, with repetitive sequences of hypoxia-reoxygenation. Although all the physiological pathways are not fully understood, the excess in O₂ species production may be a key factor in the cardiovascular response to IH exposure (29).

Our study is the first to show that chronic IH makes the heart more sensitive to ischemic injury. Indeed, the infarct size was significantly larger in hypoxic than in normoxic and control groups. This effect does not involve a circulating agent because it was observed in the isolated heart from hypoxic rats. Moreover, the enhanced infarct size seen in the IH group after ischemia-reperfusion was in fact due to an aggravated sensitivity to ischemia because no necrosis was induced by chronic IH exposure alone.

OSA is commonly associated with cardiovascular disease and remains as a significant predictor of coronary disease after adjustment for age, body mass index, hypertension, smoking habits, and diabetes (28). Sleep apnea is accompanied by myocardial ischemia, demonstrated by ST-segment depression in patients with ischemic heart disease (15). Therefore, it is conceivable that recurrent IH, as occurring during sleep apnea, increases the heart’s sensitivity to infarction and may be responsible, at least in part, for the increased morbidity and mortality observed in OSA patients. It should be noted that the increased sensitivity to infarction reported in this study occurred after a short-term exposure to IH and without major changes in MABP, suggesting a direct effect on myocytes. This hypothesis is reinforced by the fact that the increased infarct size induced by IH occurred without modification of coronary artery dilation (i.e., CF was not different between IH, N, and control groups). This issue will be addressed in future experiments on coronary vascular reactivity. Finally, the increase in hematocrit induced by IH could not be involved in the increased sensitivity to infarction reported here because this effect appeared on isolated heart (perfused without blood).

One of the underlying mechanisms that may be involved in the development of cardiovascular disease in OSA patients is the formation of hypoxia-related free radicals and increased oxidative stress due to IH (10). Free O₂ radicals or proinflammatory mediators such as leukotrienes, which are released from polymuclear neutrophils, are known to be important contributors to the development of ischemia-reperfusion injury (3). Free radical generation is increased in OSA (32) and could be one of the mechanisms whereby IH increases myocardial susceptibility to infarction. Reinforcing this hypothesis, it has been observed that plasma antioxidant status was significantly reduced in IH rats compared with N and control rats (P. Faure, unpublished observations). In contrast, because leukotrienes are not involved in the contractile response to norepinephrine on aorta from IH rat, their involvement in the cardioprotectivity to infarction induced by IH appears unlikely. However, this does not rule out the potential contribution of other cytokines or proinflammatory factors. Another possible underlying mechanism could be the activation of adhesion molecules such as intracellular adhesion molecule 1 (ICAM-1). Indeed, the deleterious role of ICAM-1 in the inflammatory response associated with myocardial infarction has been clearly established (14). Because increased levels of circulating ICAM-1 have been reported in OSA patients, it has been suggested that this activation could increase the risk factor for cardiovascular disorders (25). These different hypotheses remain, however, to be confirmed experimentally, as well as by investigations in patients with OSA. Overall, this experimental model of chronic IH appears useful for studying cardiovascular consequences of OSA syndrome. It may allow us to elucidate some of the mechanisms responsible for the higher sensitivity to coronary artery disease seen in patients with OSA.

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