ORIGINAL ARTICLE

Cerebral Ischemia and Reperfusion-Induced Changes in Left Ventricular Function and Electrocardiogram in Mice

Modificaciones en la función ventricular izquierda y el electrocardiograma en ratones debidas a isquemia y reperfusión cerebral

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ABSTRACT

Background: Stroke may produce functional and electrical heart disturbances. The underlying characteristics and mechanisms have not been fully elucidated.
Objectives: To evaluate whether acute cerebral ischemia (I) and reperfusion (R) may cause cardiac dysfunction and electrocardiographic alterations in an experimental mice model.
Methods: Male mice that underwent cerebral ischemia and reperfusion (I/R) were evaluated by electrocardiography (ECG) and echocardiography. Heart rate, corrected QT (QTc) interval, T-wave peak to T-wave end (Tp-Te) interval, left ventricular ejection fraction (LVEF), shortening fraction (SF) and isovolumetric relaxation time (IVRT) were analyzed. Cerebral infarct size was calculated, and neurological deficit was assessed with the Longa scale.
Results: Twenty-four hours after R, a statistically significant decrease in LVEF (I/R: 66.5±1.5% vs. sham: 74.3±0.9%; p=0.002) and in SF (I/R: 42.9±1.7% vs sham: 52.3±1.7%; p=0.004) was observed. QTc interval prolongation was observed during I/R (baseline: 125.1±4.3 ms; 60 min after I: 143.8±5.2 ms; 24 h after R: 170.3±5.8 ms; p=0.002). Tp-Te interval was not prolonged during I (baseline: 25.9±1.3 ms vs. 60 min after I: 23.8±1.4 ms; p=0.999) but it was prolonged during R (24 h after R: 32.0±2.3 ms; p=0.049). Cerebral infarct size was 34.9±2.5% and survival in the I/R group was 43.3%.
Conclusion: Acute cerebral ischemia induces mild left ventricular dysfunction and disturbances in ventricular repolarization which intensify within the first 24 hours after reperfusion.

Key words: Cerebral ischemia - Ventricular dysfunction - Electrocardiogram - arrhythmias

RESUMEN

Introducción: El accidente cerebrovascular (ACV) puede generar perturbaciones funcionales y eléctricas del corazón. Las características y mecanismos subyacentes no están completamente elucidados.
Objetivo: Evaluar si la isquemia (I) y reperfusión (R) cerebral agudas ocasionan disfunción cardíaca y alteraciones electrocardiográficas en un modelo experimental en ratones.
Material y Métodos: Ratones macho sometidos a isquemia y reperfusión cerebral (I/R) fueron evaluados mediante electrocardiografía (ECG) y ecocardiografía. Se analizó la frecuencia cardíaca, el intervalo QT corregido (QTc) y el intervalo entre el pico de la onda T – fin de la onda T (Tp-Te), la fracción de eyección ventricular izquierda (FEVI), la fracción de acortamiento (FA) y el tiempo de relajación isovolumétrica (TRIV). Se cuantificó el tamaño del infarto cerebral (TI), y el déficit neurológico se evaluó con la escala de Longa (EL).
Resultados: Encontramos una disminución estadísticamente significativa de la FEVI a las 24 horas de R (I/R: 66,5 ± 1,5 % vs. *sham*: 74,3 ± 0,9 %; p=0,002) y la FA (I/R: 42,9 ± 1,7 % vs. *sham*: 52,3 ± 1,7 %; p=0,004). Se observó una prolongación del QTc durante la I/R (basal: 125,1 ± 4,3 ms; 60 min I: 143,8 ± 5,2 ms; 24 horas R: 170,3 ± 5,8 ms; p=0,002), sin una prolongación del Tp-Te en la I (basal: 25,9 ± 1,3 ms vs. 60 min I: 23,8 ± 1,4 ms; p=0,999) pero sí en la R (24 horas R: 32,0 ± 2,3 ms; p=0,049). El tamaño del infarto cerebral fue de 34,9 ± 2,5 % y la supervivencia del grupo I/R fue del 43,3 %.
Conclusión: La isquemia cerebral aguda induce una disfunción ventricular izquierda leve y trastornos en la repolarización ventricular que se intensifican en las primeras 24 horas de reperfusión.

Palabras clave: Isquemia cerebral - Disfunción ventricular - Electrocardiograma - Arritmias

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INTRODUCTION

Cerebrovascular disease is one the four leading causes of mortality worldwide and affects both high- and low-income countries. (1) According to recent data, it is the second leading cause of death and the leading cause of disability in Argentina. Factors worsening the prognosis of these patients include several cardiac complications collectively known as neurocardiogenic syndrome. The consequences of this syndrome, which include coronary syndromes, arrhythmias, Takotsubo syndrome and heart failure, result in more than 1.5 million deaths each year. (2, 3)

Some pathophysiological mechanisms involved in the brain-heart axis deterioration have been identified in several studies, both basic and clinical. One of the most relevant is the imbalance in the autonomic nervous system in favor of an exaggerated sympathetic discharge and parasympathetic impairment. (4, 5) Although not exclusive, research in humans and several animal species associates insular ischemic involvement with dysautonomia. (4, 6) Coincidentally, a proinflammatory state is triggered both locally and systemically, which increases cytokines and leukocyte migration that, if the stimulus persists, may induce fibrotic changes in the myocardium. (7) More recently, the role of the release of glial microvesicles with mRNA-carrying capacity, which carry distant transcriptional messages and induce myocardial injury, has been demonstrated. (8)

Although myocardial dysfunction and electrical changes, such as atrial fibrillation, atrioventricular conduction disturbances, and QT interval prolongations, have been well documented, (4, 9) their relationship and temporal evolution in acute stages have not been sufficiently studied. Thus, this work aimed to investigate cardiac functional and electrical impairment during ischemia (I) and reperfusion (R) of the right cerebral hemisphere in a male mouse model.

METHODS

Cerebral ischemia model

The experiments were carried out following the guidelines of the "Guide for the Care and Use of Laboratory Animals" of the United States National Academy of Sciences, updated by the American Physiological Society (10), and in accordance with the regulations of the Institutional Committee for the Care and Use of Laboratory Animals (CICUAL) of the School of Medicine, Universidad of Buenos Aires (Resolution CD 4081/04). The present project has been approved by CICUAL (RESCD-2023-913-E-UBA-DCT#FMED).

Eighteen FVB strain male mice aged between 8 and 12 weeks were used. Cerebral ischemia (I) and reperfusion (R) were induced using the technique described by Koizumi. (11) For this purpose, the mice were anesthetized with a ketamine-xylazine solution (100 mg/10 mg) at a dose of 4.4 μL/g intraperitoneally (IP). After cervical dissection, an intraluminal filament was inserted in the common carotid artery, advancing through the internal carotid, to obstruct the flow of the middle cerebral artery for 60 minutes. To perform reperfusion, the filament was removed. The results of this I/R mice group were compared to those of sham mice group, or surgery without cerebral ischemia. For this purpose, 5 mice underwent the same operation as the I/R mice group, except for the intraluminal filament which was not inserted in the artery and, therefore, cerebral artery occlusion did not occur. During procedure, body temperature was maintained constant at 36.5±0.5°C with a rectal thermocouple and a heat lamp.

After reperfusion, the animals recovered from anesthesia in a temperature-controlled chamber and, then, in the biotherium, they were monitored for 24 hours. Analgesics (tramadol, 5μL/g subcutaneously) and antibiotics (cefazolin, 5μL/g intramuscularly) were administered as part of postoperative care.

Neurological evaluation and mortality records

At 4 and 24 hours post-reperfusion, neurological deficits were assessed using the Longa scale. (12) On this scale, no neurological deficit was assigned 0 points; inability to flex the contralateral limbs, 1 point; circular movements toward the side of the lesion, 2 points; barreling or longitudinal axis movements, 3 points; and coma or lack of response to external stimuli, 4 points.

Survival records were carried out and plotted using Kaplan-Meier curves to analyze the temporal evolution of the mice according to neurological deficits evaluated.

Electrocardiographic recording

To obtain the electrocardiographic recordings, subcutaneous electrodes (ADinstruments®) were used together with the LabChart 8® software. Recordings were made throughout the 60 minutes of I, the first 10 minutes of R and, finally, at the end of this period. Heart rate (HR), QT interval, HR-corrected QT interval (using the Bazett formula) and the interval between the peak and end of the T wave (Tp-Te) were measured. For the statistical analysis, the values at baseline (prior to the onset of ischemia), 60 minutes after I and 24 hours after R were used.

Echocardiography

Echocardiographic studies were performed in mice under anesthesia with 290mg/kg of a 2.5% solution of 2,2,2,2 tribromoethanol (AVERTIN, Sigma Aldrich®) IP. (13) An Acuson® Sequoia C512 ultrasound machine equipped with a 14 MHz linear ultrasound transducer was used. Recordings were made 24 hours after reperfusion, during which the left ventricular ejection fraction (LVEF), shortening fraction (SF) and isovolumetric relaxation time (IVRT) were calculated.

Evaluation of cerebral infarction

To visualize the cerebral infarct area 24 hours after reperfusion, the mice were sacrificed by an overdose of ketamine and xylazine, (14) the brain was removed and frozen to obtain 2-mm-thick coronal sections. These sections were incubated in a 1% 2,3,5-triphenyltetrazolium (TTC) solution for 20 minutes at 37°C. Non-infarcted cerebral tissue was stained red, whereas the infarcted area remained white. To document the cerebral infarct area, images were acquired using an HP® scanner, and the area was subsequently quantified using ImageJ® software. Using Swanson's formula [(contralateral hemisphere - ipsilateral hemisphere/contralateral hemisphere) x 100], the value of the edema-adjusted infarct area was obtained. (15)

Statistical analysis

Graphical representations of all values were carried out using GraphPad Prism 9® software. The results were ex-

pressed as the mean ± standard error. Statistical tests were applied, including one-way analysis of variance (ANOVA), followed by Student's t-test for comparison between two groups. In addition, the log-rank test was used to analyze the Kaplan-Meier curves. A 2-tailed p-value <0.05 was considered statistically significant

RESULTS

Cerebral infarct size, neurological involvement and survival

The cerebral infarct size after 60 minutes I and 24 hours after R was 34.9±2.5% (Figure 1A and 1B). The infarct area affected territories supplied by the middle cerebral artery, including the cerebral cortex and white matter of the frontal, parietal and temporal lobes, as well as the caudate and putamen nuclei (Figure 1A).

According to the Longa scale, 67.9% of mice scored 2 and 28.6% scored 3. Only 3.6% scored 0, while no mice scored 1 or 4. At 24 hours, the survival of mice with a score of 0 was 100%, with a score of 2 was 77.8%, while only 37.5% with a score of 3 survived.

Ventricular function

Twenty-four hours after reperfusion, a statistically significant decrease in LVEF was observed in I/R group compared to the sham group (I/R: 66.5±1.5% vs. sham: 74.3±0.9%; p=0.002), as well as in the shortening fraction (SF) (I/R: 42.9±1.7% vs. sham: 52.3±1.7%; p=0.004). (Figure 2) In contrast, there were no statistically significant changes in the isovolumetric relaxation time (IVRT) between the two groups (I/R: 20.1±0.7 ms vs. sham: 19.4±0.4 ms; p=0.450) (Figure 2).

Electrocardiographic changes

During cerebral ischemia, a progressive increase in HR (baseline: 252±10 bpm, after 60 min I: 317±24 bpm; p=0.182) and a gradual prolongation of the QTc interval (baseline: 125.1±4.3 ms, after 60 min I: 143.8±5.2 ms; p=0.008) were observed (Figure 3). Twenty-four hours after reperfusion, an even more significant prolongation of the QTc interval was observed (170.3±5.8 ms; p=0.002) (Figure 3B), as well as a notable increase in HR (384± 30 bpm; p=0.034 vs. baseline).

On the contrary, the Tp-Te interval was not prolonged during ischemia (baseline: 25.9±1.3 ms, after 60 min I: 23.8±1.4 ms; p=0.999) but it was prolonged during reperfusion (32.0±2.3 ms; p=0.049 vs. after 60 min I; p=0.068 vs. baseline) (Figure 3C).

DISCUSSION

Our findings show that, in this experimental model, left ventricular dysfunction and cardiac electrical changes occur in early stages after cerebral reperfusion. Furthermore, we emphasize that the electrocardiographic changes observed during cerebral ischemia may be intensified during reperfusion. Although the aim of this work was not to make a comparative analysis with the involvement of other areas of the central nervous system, cardiac involvement is the result of a cerebral lesion that involves an extensive territory supplied by the middle cerebral artery, one of the most affected areas in ischemic stroke. (16) Right frontal cortical lesions are reflected in the type of motor dysfunction in mice, and the extent of the lesion causes different degrees of dysfunction that correlate with mortality.

We have also observed involvement of the insular cortex, which could have pathophysiological implications in this study. Previous studies have shown that insular damage produces cardiac lesions as a consequence of the autonomic imbalance. (17-19) The physiological role of this cortical area has been documented in the differential regulation of the parasympathetic nervous system associated with the left hemisphere, and the sympathetic regulation associated with the right hemisphere. (20) The greater association of the side of the insula lesion with cardiac damage is not entirely clear; while some studies associate greater involvement with right lesions, (14) others do so with contralateral lesions. (21) Although we have not yet directly or indirectly evaluated the possible association between cardiac involvement and catecholaminergic discharge, it is plausible that the increases in HR observed in our experiments show an increase in sympathetic activity, possibly due to right insular damage. This hypothesis is supported by previous research in several species, which has shown an increase in sympathetic activity during right insula ischemia. (19-23) In addition, studies on cerebral hemorrhage have shown an increase in noradrenaline, without alterations in adrenaline or plasma cortisol levels. The authors attribute this phenomenon to a response not mediated by the adrenal glands. (24) The possibility of a direct discharge of catecholamines in the sympathetic terminals of the heart was also suggested in studies in rats, where greater damage was observed at the base of the atria, an area where cardiac nerve density is higher. (4)

Interestingly, we observed a prolongation of QTc interval during cerebral ischemia, which became even greater during reperfusion, but we did not observe a prolongation of the Tp-Te interval during ischemia, which was only modified during reperfusion. This finding indicates the early onset of electrical changes suggestive of disturbances in ventricular repolarization, which became more pronounced within the first 24 h post-reperfusion. QT interval prolongation has been well documented in other neurological pathologies, such as subarachnoid hemorrhage (25) or epilepsy, (26) and in both cases, it has been associated with severe ventricular arrhythmias and sudden death. (27) These electrical disturbances have also been observed in experimental models, following selective electrical stimulation of the insular cortex, but not of surrounding areas. (19) Although we have not specifically evaluated the arrhythmias, they may be partly responsible for the mortality rate observed in mice in

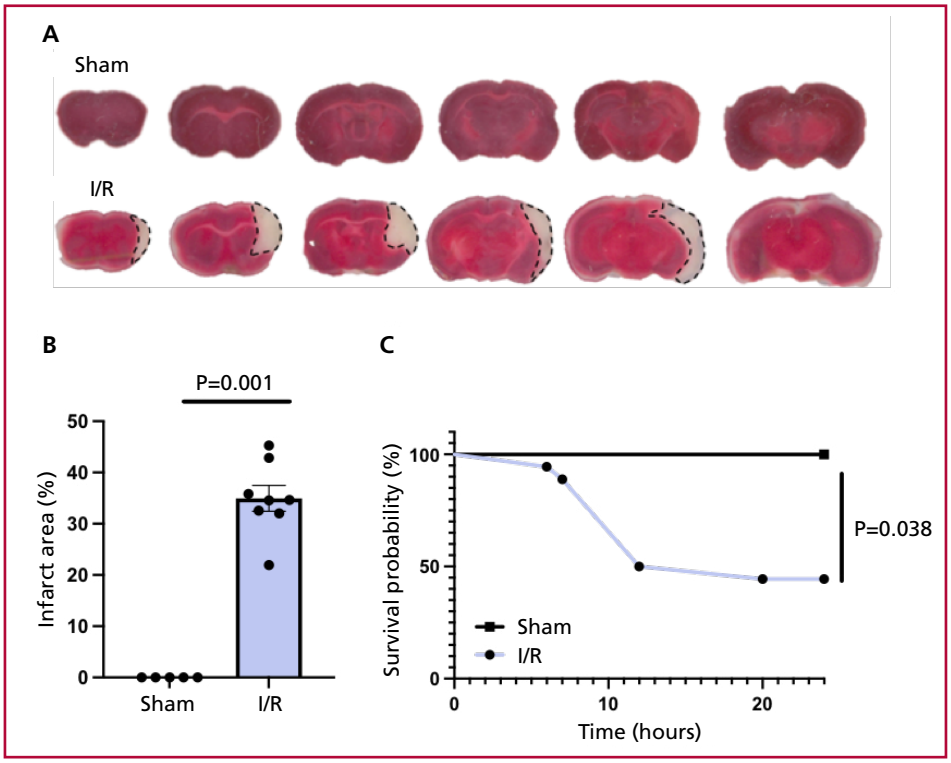

Fig. 1. A. Coronal sections of the brain stained with TTC corresponding to the sham group and ischemia and reperfusion (I/R) group are shown. The infarct area (indicated by a dotted line) is observed in the middle cerebral artery territory and affects both the cortex and the caudo-putamen. **B.** Quantification of the infarct area. Sham n=5; I/R n=8. **C.** Kaplan-Meier curve representation for survival. Survival rate at 24 hours was on average 43% for the I/R group. I/R: ischemia/reperfusion

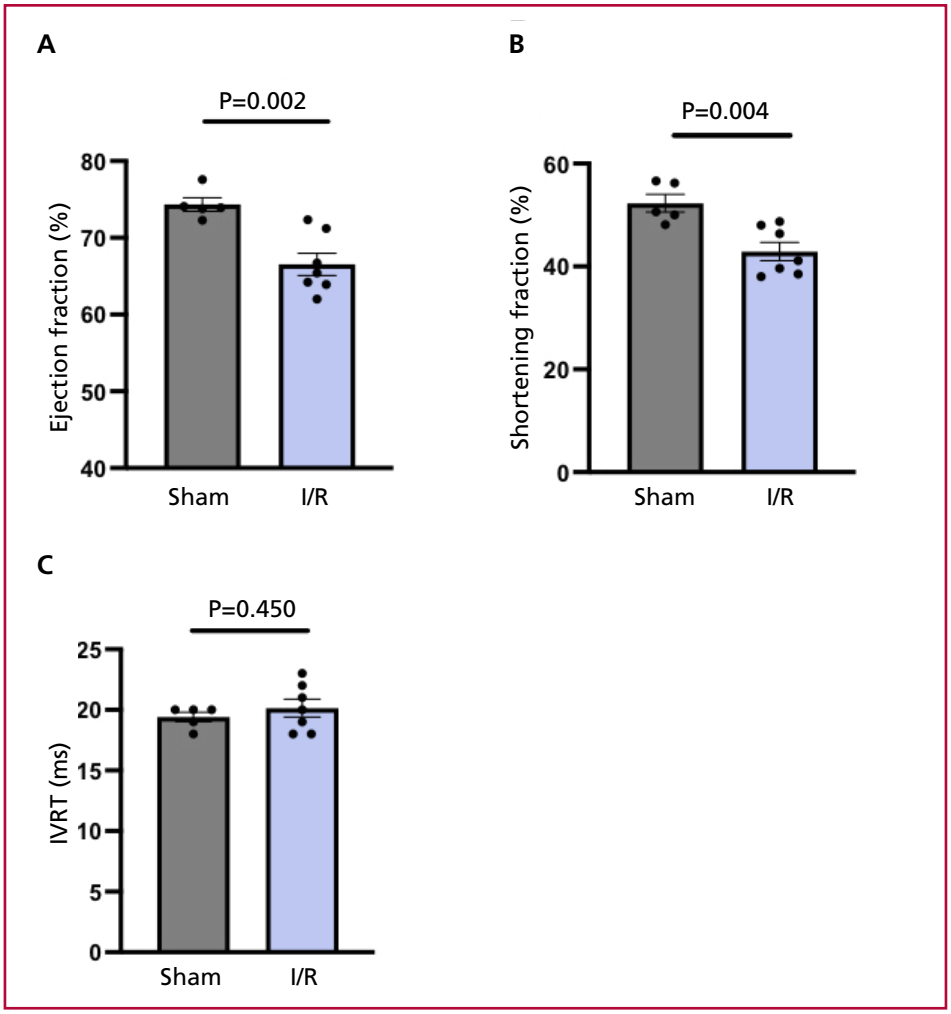

Fig. 2. Echocardiographic variables calculated 24 hours after cerebral reperfusion. Ischemia/reperfusion (I/R) group experienced a statistically significant decrease in ejection fraction (**A**) and in shortening fraction (**B**), with no changes in isovolumetric relaxation time (IVRT) (**C**). Sham n=5; I/R n=7.

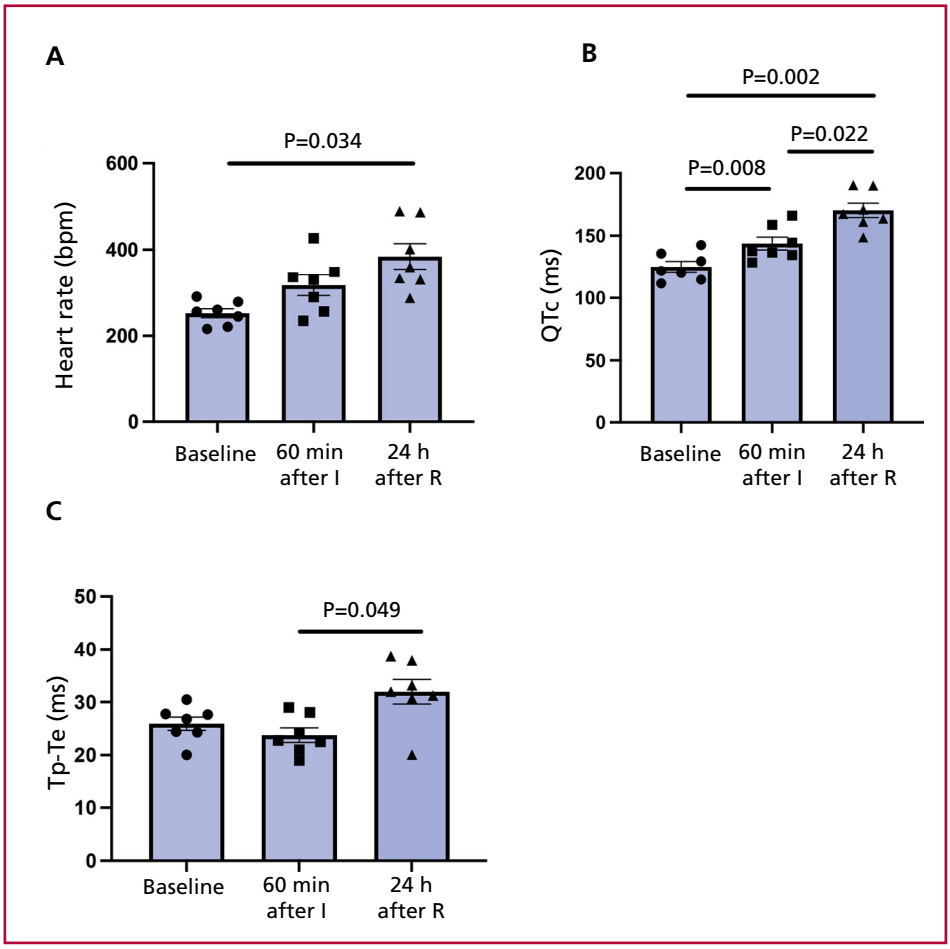

Fig. 3. Electrocardiographic changes evaluated at baseline before ischemia, at the end of ischemia and at the end of reperfusion. (**A**) Twenty-four hours after reperfusion, there is evidence of an increase in heart rate compared to baseline and 60 minutes after ischemia. (**B**) A prolongation of the QTc interval (Bazzet) is observed after 60 minutes ischemia and 24 hours after cerebral reperfusion. (**C**) There are no differences in the TpTe interval during ischemia, but there are differences at the end of reperfusion. I: ischemia; R: reperfusion; Tp-Te: interval from the peak to the end of T wave. n=7.

our study. It is known that prolongation of both intervals is an index of greater arrhythmogenicity (26) than the isolated prolongation of the QTc interval. These electrical alterations may be associated with intense sympathetic activation. This encourages us to continue studying repolarization disorders in other experimental groups.

Another potential mechanism associated with cardiac involvement in cerebral ischemia is the local and systemic inflammatory response. Inflammation plays a crucial role in the pathogenesis and progression of various cardiovascular pathologies. (28,29) The increase in proinflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α), is linked to both myocardial functional damage and alterations in electrical potentials, thus predisposing to the appearance of arrhythmias. (28) Increased expression of these cytokines can lead to the recruitment of macrophages and fibroblasts, generating a local inflammatory environment with acute functional damage and long-term fibrotic compromise. (30) Several experimental and clinical studies have shown the increase of cytokines at local and systemic levels, as well as the mobilization of leukocytes following cerebral ischemia. (7, 14) In addition, the dynamic and bilateral association between the increase in the sympathetic response and in inflammation is recognized. (31) Therefore, it is likely that both possible mechanisms are involved in the pathophysiology of cardiac damage in our model.

CONCLUSION

In our experimental model, acute ischemia with cerebral reperfusion in the right hemisphere affecting the insular cortex induces functional and ventricular repolarization disorders that could be responsible for the increased mortality rate observed.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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