Braz J Cardiovasc Surg 2015;30(1):70-6

Are there gender differences in left ventricular remodeling after myocardial infarction in rats?

Há diferenças entre os gêneros no remodelamento ventricular esquerdo após infarto do miocárdio em ratos?

Ednei Luiz Antonio[1], MD; Andrey Jorge Serra[2], MsC, PhD; Alexandra Alberta dos Santos[3], MD; Stella Sousa Vieira[3], MD; Jairo Montemor Augusto Silva[3], MD; Amanda Yoshizaki[4], MD; Renato Rodrigues Sofia[5], MD; Paulo José Ferreira Tucci[3], MD, PhD

DOI: 10.5935/1678-741.20140093

RBCCV 44205-1616

Abstract

Objective: **An unclear issue is whether gender may influence at cardiac remodeling after myocardial infarction (MI). We evaluated left ventricle remodeling in female and male rats post-MI.**

Methods: **Rats were submitted to anterior descending coronary occlusion. Echocardiographic evaluations were performed on the first and sixth week post-occlusion to determine myocardial infarction size and left ventricle systolic function (FAC, fractional area change). Pulsed Doppler was applied to analyze left ventricle diastolic function using the following parameters: E wave, A wave, E/A ratio. Two-way ANOVA was applied for comparisons, complemented by the Bonferroni test. A $P \leq 0.05$ was considered significant.**

Results: **There were no significant differences between genders for morphometric parameters on first (MI [Female (FE): 44.0±5.0 vs. Male (MA): 42.0±3.0%]; diastolic [FE: 0.04±0.003 vs. MA: 0.037±0.005, mm/g] and systolic [FE: 0.03±0.0004 vs. MA: 0.028±0.005, mm/g] diameters of left ventricle) and sixth (MI [FE: 44.0±5.0 vs. MA: 42.0±3.0, %]; diastolic [FE: 0.043±0.01 vs. MA: 0.034±0.005, mm/g] and systolic [FE: 0.035±0.01 vs. MA: 0.027±0.005, mm/g] of LV) week. Similar findings were reported for left ventricle functional parameters on first (FAC [FE: 34.0±6.0 vs. MA: 32.0±4.0, %]; wave E [FE: 70.0±18.0 vs. MA: 73.0±14.0, cm/s]; wave A [FE: 20.0±12.0 vs. MA: 28.0±13.0, cm/s]; E/A [FE: 4.9±3.4 vs. MA: 3.3±1.8]) and sixth (FAC [FE: 29.0±7.0 vs. MA: 31.0±7.0, %]; wave E [FE: 85.0±18.0 vs. MA: 87.0±20.0, cm/s]; wave A [FE: 20.0±11.0 vs. MA: 28.0±17.0, cm/s]; E/A [FE: 6.2±4.0 vs. MA: 4.6±3.4]) week.**

Conclusion: **Gender does not influence left ventricle remodeling post-MI in rats.**

Descriptors: **Gender and Health. Myocardial Infarction. Ventricular Remodeling.**

Resumo

Objetivo: **A influência do gênero no remodelamento cardíaco após o infarto do miocárdio é uma questão em intenso debate. Nós avaliamos o remodelamento ventricular esquerdo em ratos infartados de ambos os gêneros.**

Métodos: **O infarto do miocárdio foi induzido por oclusão da artéria coronária descendente anterior (fêmeas [FM]; machos [MC]). A ecocardiografia foi realizada na primeira e sexta semana pós-oclusão para determinar o tamanho do infarto do miocárdio e a função sistólica do ventricular esquerdo (mudança na área fracional [FAC]). A função diastólica derivou dos seguintes parâmetros: onda E; onda A; razão E/A. ANOVA duas vias com pós-teste de Bonferroni foi aplicado nas comparações ($P \leq 0,05$).**

Resultados: **Todas variáveis morfométricas foram similares ($P > 0,05$) entre os gêneros com uma (infarto do miocárdio [FM: 44,0±5,0 *vs.* MC: 42,0±3,0, %]; diâmetro diastólico [FM: 0,04±0,003 *vs.* MC: 0,037±0,005, mm/g] e sistólico [FM: 0,03±0,0004 *vs.* MC: 0,028±0,005, mm/g] do VE) e seis (IM**

[1]Laboratório de Fisiologia e Fisiopatologia Cardíacas da Disciplina de Cardiologia da Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil.
[2]Docente da Universidade Nove de Julho (Uninove), São Paulo, SP, Brazil.
[3]Laboratório de Fisiologia e Fisiopatologia Cardíacas da Disciplina de Cardiologia da Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil.
[4]Programa de Pós-graduação em Ciências da Reabilitação da Universidade Nove de Julho (Uninove), São Paulo, SP, Brazil.
[5]Universidade Nove de Julho (Uninove), São Paulo, SP, Brazil.

This study was carried out at Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil and Universidade Nove de Julho (Uninove), São Paulo, SP, Brazil.

Correspondence address:
Andrey Jorge Serra
Postgraduate Program in Biophotonics Applied Health Sciences, Universidade Nove de Julho (UNINOVE)
Rua Vergueiro, 235 - São Paulo, SP, Brazil
Zip code: 01504-001
E-mail: andreyserra@gmail.com

Financial support: Grant number 2009/54225-8, São Paulo Research Foundation (FAPESP).

Article received on September 26th, 2013
Article accepted on June 2nd, 2014

Abbreviations, acronyms & symbols	
FE	Female
LV	Left ventricle
MA	Male
MI	Myocardial infarction

[FM: 44,0±5,0 *vs*. MC: 42,0±3,0, %]; diâmetro diastólico [FM: 0,043±0,01 *vs*. MC: 0,034±0,005, mm/g] e sistólico [FM: 0,035±0,01 *vs*. MC: 0,027±0,005, mm/g] do ventricular esquerdo) semanas. Achado similar ocorreu para os dados funcionais com uma (FAC [FM: 34,0±6,0 *vs*. MC: 32,0±4,0, %]; onda E [FM: 70,0±18,0 *vs*. MC: 73,0±14,0, cm/s]; onda A [FM: 20,0±12,0 *vs*. MC: 28,0±13,0, cm/s]; E/A [FM: 4,9±3,4 *vs*. MC: 3,3±1,8]) e seis (FAC [FM: 29,0±7,0 *vs*. MC: 31,0±7,0, %]; onda E [FM: 85,0±18,0 *vs*. MC: 87,0±20,0, cm/s]; onda A [FM: 20,0±11,0 *vs*. MC: 28,0±17,0 cm/s]; E/A [FM: 6,2±4,0 *vs*. MC: 4,6±3,4]) semanas.

***Conclusão:* O gênero não é determinante para o remodelamento ventricular esquerdo pós-infarto do miocárdio em ratos.**

***Descritores:* Gênero e Saúde. Infarto do Miocárdio. Remodelação Ventricular.**

INTRODUCTION

Myocardial infarction (MI) is an important cause of heart failure and mortality among adults. A number of factors can determine a worsening in prognosis such as infarct expansion, hypertrophy of the non-infarcted myocardium, increased collagen deposition in the infarcted and non-infarcted areas, progressive dilatation, geometric changes in chamber shape, and eventual progression to chronic heart failure.

It is well known that premenopausal women are less likely to develop coronary heart disease than men. Previous studies have also shown that gender can be a key factor in cardiac remodeling post-MI. Thus, studies show gender as a risk factor of unfavorable prognostic[1,2]. Although valuable, these findings cannot be considered as absolute truth. Several issues such as age heterogeneity, drug therapy, associated risk factors, and hemodynamics (e.g., pre- and afterload; blood volume) may cause difficulties in ensuring that the there is differential cardiac remodeling between genders post-MI[2,3]. Moreover, some researchers have found higher survival rates in women[4,5] while others show higher mortality in women due to higher severity of MI[6].

Since possible gender differences in post-MI left ventricle (LV) remodeling are not clear, we conducted the current study using a rat MI model. The MI model by coronary occlusion represented a significant advance to provide accurate control of bias[7-13]. Moreover, coronary occlusion is the most commonly used experimental model to induce MI in rats and somewhat reproduces the findings in humans with cardiac decompensation[14]. We performed paired time evaluations in the LV with transthoracic echocardiography. This approach has been shown to be readily reproducible in longitudinal assessment of morphology and function of LV in rodents[15,16].

METHODS

Animal MI model

The study was approved by the Committee on Ethics from the Federal University of São Paulo and use the "Principles of Laboratory Animal Care formulated by the National Institutes of Health (National Institutes of Health publication number 96-23, revised, 1996; http://bioethics.od.nih.gov/animals.html)". The MI was induced in three-month-old female Wistar-EPM rats weighing between 180 to 220g. The animals were housed at regular temperature (22°-24°C) on a 12h dark/light cycle with food and water provided ad libitum. Rats were anesthetized with ketamine (50 mg/kg) plus xylazine (10 mg/kg) intraperitoneally, intubated, and ventilated with room air (rate: 90 breaths/minute; tidal volume: 2.5 ml on a Harvard rodent respirator [model 683, Harvard Apparatus Co., South Natik, MA, USA]). After thoracotomy, the MI was produced by ligation of the left descending coronary artery as previously described[17,18]. Sham surgery was performed with a similar process except the suture was tied loosely around the coronary artery. Afterward MI or Sham surgery, the rats returned to their plastic boxes and were kept under observation without any drug therapy. Survivor animals were assigned to the following groups: (1) Female sham (n=8); (2) Female MI (n=11); (3) Male sham (n=9); (4) Male MI (n=12).

Echocardiographic measurements

Echocardiography has been shown accurate in evaluating cardiac remodeling post-MI[16,19-20]. Echocardiographic analysis was applied on the first and sixth week post-MI. The rats were anesthetized as described above and measurements were performed using a 12-MHz transducer connected to an HP Sonos-5500 echocardiograph (Hewlett-Packard, California, USA)[11]. MI size was evaluated by transversal LV two-dimensional view on the basal, mid-transversal, and apical planes. In the diastolic phase, measurements of the endocardial perimeter (EP) and length of the infarcted segment (ISe) for each view were taken. MI size for each segment (ISi), expressed as the proportion of the LV perimeter for each view, was calculated by the following equation: ISi (%) = ISe/EP x 100. MI was defined as a segment with increased echogenicity and/or change in myocardial thickening or systolic movement.

Only rats with large infarctions (≥ 40% of LV) were included for evaluation since this is the group that shows the highest severity of the disease[8]. The diastolic (DA) and systolic (SA) transverse areas of the LV were measured by two-dimensional

images on the basal, middle and apical parasternal transverse planes. The final value was the arithmetic mean of the measurements of the three views. Systolic function was analyzed by the fractional area change (FAC=DA - SA/DA, %) in the three transverse planes (basal, middle, and apical). Pulsed Doppler at the LV side of the mitral valve provided the flow velocity curve to analyze the diastolic function parameters (E and A waves and E/A ratio). Echocardiographic images for cardiac effects of MI are shown in Figure 1.

Statistical analysis

Data were analyzed with GraphPad Prism software 4.0 (San Diego, CA, USA) and values are expressed as mean ± S.D. The Shapiro-Wilk and Levene tests were applied to verify normal statistic distributions and error variances, respectively. To determine the effect of time and infarction on the echocardiographic parameters of respective genders, two-way analysis of variance (ANOVA) with repeated measures was performed. To evaluate the difference between genders at each respective time point, regular two-way ANOVA was performed. The Bonferroni post-hoc was carried out for all analyses and level of significance was set at 5%.

RESULTS

To characterize the MI repercussions in both genders, echocardiography analyses were taken into account over six weeks after coronary occlusion. LV morphology and function were evaluated in the first and sixth week after ischemic insult. The sham group was evaluated at the same time.

LV morphology data are shown in Table 1. None of the evaluated parameters changed for female and male sham-operated rats during follow-up. MI size was similar between female and male rats, and we did not see expansion of MI in either gender during follow-up. Left atrium size was significantly higher in the infarcted rats regardless of gender; moreover, there was not difference in the left atrium size between female and male rats on any assessment time. There was LV dilatation with only a week post-MI; therefore, female and male rats showed a significant increase in diastolic and systolic LV diameter when comparing the first and sixth week. For all follow-ups, LV dilatation level was similar between genders. When LV diameters were indexed by body weight, LV dilation post-MI was similar comparing first to sixth week for both genders.

The LV performance data are shown in Table 2.

Table 1. Echocardiographic morphology parameters for female and male rats post-MI.

	Female				Male			
	Week 1 Sham	Week 1 MI	Week 6 Sham	Week 6 MI	Week 1 Sham	Week 1 MI	Week 6 Sham	Week 6 MI
MI size(%)	----	44±5	----	42±9	----	42±3	----	42±7
SLA (mm)	4±0.5	4.9±1*	4±0.2	6±1*#	3±0.5	5±1*	3±0.4	6±1*#
SLA/BW(mm/g)	0.02± 0.001	0.02±0.0005*	0.02±0.002	0.03±0.003*	0.01±0.002	0.02±0.0005*	0.01±0.0003	0.02±0.002*
LVDD(mm)	5±0.5	8±0.5*	5±1	9±1*#	4±1	9±1*	5±1	10±0.01*#
LVDD/BW(mm/g)	0.03± 0.002	0.04±0.003*	0.03±0.001	0.04±0.01*	0.03±0.001	0.04±0.005*	0.03±0.002	0.03±0.005*
LVSD(mm)	2±0.3	6±1*	3±1	7±1*#	2±1	7±0.3*	3±1	8±0.3*#
LVSD/BW(mm/g)	0.02± 0.002	0.03±0.0004*	0.02±0.0001	0.03±0.01*	0.02±0.0001	0.03±0.005*	0.02±0.0002	0.03±0.005*

MI=myocardial infarction; BW=body weight; SLA=left atrium size; LVDD=left ventricle diastolic diameter; LVSD=left ventricle systolic diameter. Data are shown as means±SD. Two-way ANOVA and Bonferroni tests were applied for comparisons.
**P<0.05 vs. Sham on first and sixth week.*
 # P<0.05 vs. MI on first week

Table 2. Echocardiographic functional parameters for female and male rats post-MI.

	Female				Male			
	Week 1 Sham	Week 1 MI	Week 6 Sham	Week 6 MI	Week 1 Sham	Week 1 MI	Week 6 Sham	Week 6 MI
FAC (%)	63±4	34±6*	67±3	29±7*	66±7	32±4*	63±4	31±7*
E (cm/s)	69±2	70±2	73±6	85±2*	59±2	73±1	67±4	87±2*
A (cm/s)	24±1	20±1	29±5	20±1	30±5	28±1	30±6	28±2
E/A ratio	3±1	5±3	3±1	6±4*	1±0.5	3±2	2±0.2	5±3*

FAC=fractional area change; E=E wave; A=A wave; Data are shown as means±SD. Two-way ANOVA and Bonferroni tests were applied for comparisons.
**P<0.05 vs. Sham on first and sixth week*

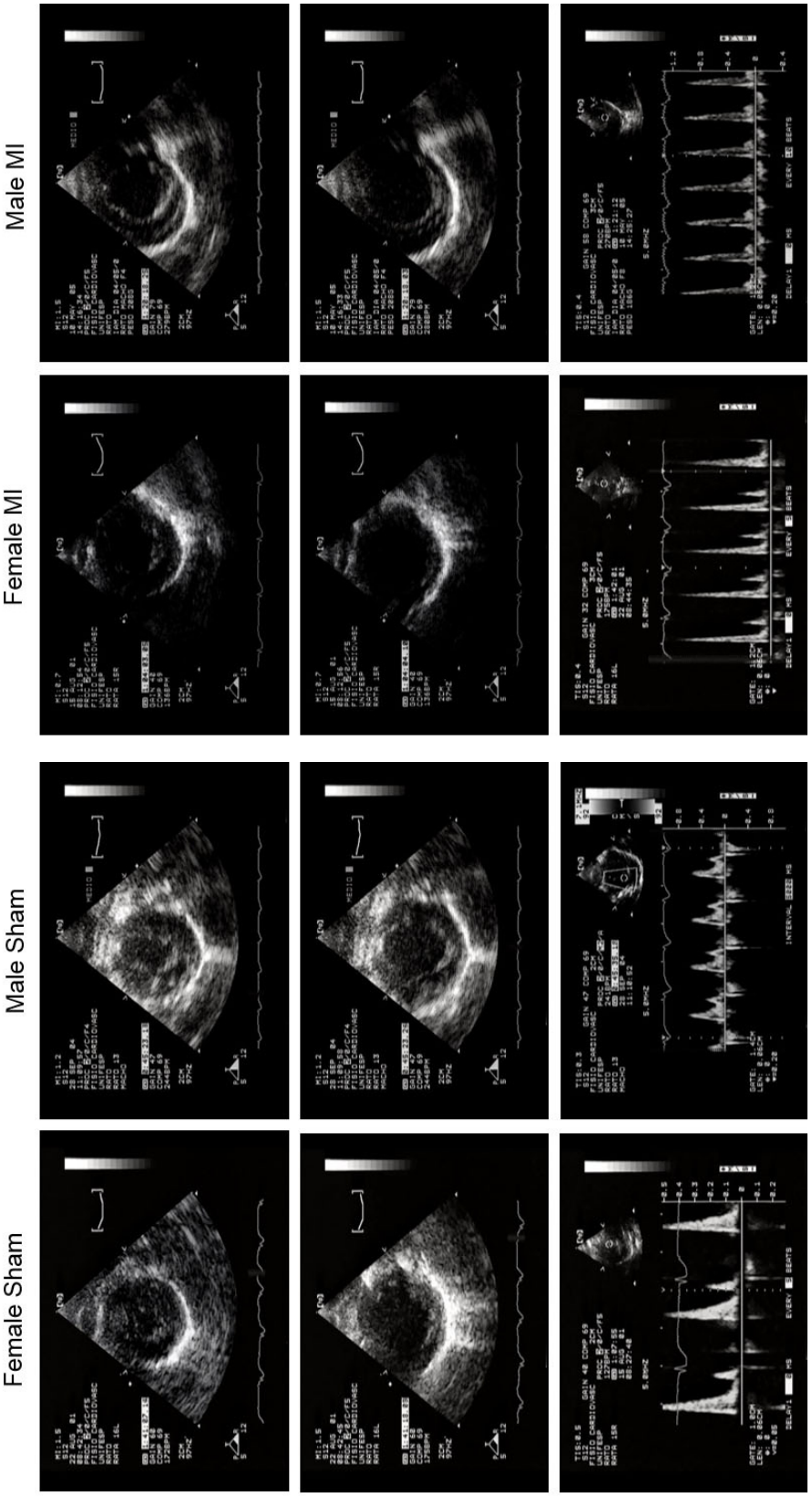

Fig. 1 - Illustrative example of two-dimensional mode traces of the left ventricle (LV) of the female and male rats. Images for mitral inflow velocity profile determined by pulsed wave Doppler are also shown. Sham rats are placed on the left, and infarcted rats are placed on the right

The MI resulted in a significant reduction of LV systolic function within a week of coronary occlusion. The systolic dysfunction level was not significantly different compared to the sixth week post-MI. Our findings indicate that gender did not influence the deleterious MI effects on LV systolic function. Both genders showed significant increases in E wave in the sixth week post-MI, whereas the A wave remained unchanged. Thus, female and male rats had a restrictive LV filling pattern defined as an increased ratio of early (E) to late (A) filling velocities and rapid deceleration of the early filling wave with six weeks post-MI. There were no significant differences between genders for these parameters (Table 2).

DISCUSSION

We performed this study to evaluate if there are gender-related differences in the LV remodeling post-MI. Echocardiography serial analyses were performed including sham non-operated rats for paired comparisons. We have included in the study only animals with large infarcts, and this was based on the issue that large infarcts are representative of notable cardiac remodeling[8,21].

The current study showed that several indicators for poor prognosis were seen with only one week of coronary occlusion[22-25]. Except for restrictive LV filling pattern (increased in the sixth week), the left atrium size, LV end-systolic and end-diastolic dimensions as well as depressed LV systolic function were increased. These findings are consistent with previous studies in rats on similar MI sizes and follow-up analysis[3].

As the main interest was the comparison between genders, we directly compared male and female rats with similar infarction sizes. The negative effects of MI on LV morphology and function were similar for both genders. Therefore, gender was not decisive for LV remodeling post-MI. In respect to LV dilatation and systolic dysfunction, we have shown similar results to other studies[3]. On the other hand, our results do not corroborate results reported by Litwin et al.[3] in regards to restrictive LV filling pattern. Although Litwin et al.[3] showed a higher increase of E wave and E/A ratio in male rats, we have shown that there was a similar increase in these variables for both genders.

In terms of gender as a determinant of LV remodeling after MI, the reasons for the different patterns in male and female are not clear. Better remodeling of noninfarcted regions in female than in male animals can result in lower operating chamber stiffness; thus female rats may have attenuated the development of a restrictive LV filling pattern[3]. Lines of evidence have attributed a key role for sex hormones. This is based, for example, in observations that testosterone is a potent inducer of LV hypertrophy while estradiol has an inhibitory action[26,27]. There is evidence that estrogen reduces collagen content[28,29] as well as wall stress in late MI[30]. Moreover, studies showed that estrogen may favor remodeling by preventing apoptosis[31] and increasing angiogenesis in female[32]. It is also possible that sexual hormones may indirectly regulate myocardial adaptation by vascular or endocrine effects. For example, cardiac preload or afterload may be different between males and females with MI as a result of differences in blood volume regulation, venous or arterial tone[13].

The female rats used in this study were young adults with normal ovaries. This study was not designed to assess the role of sex hormones in post-MI LV remodeling, and we did not monitor the serum hormone changes. Although we can not exclude that there were minor effects of sex hormones on LV functional and echocardiographic parameters, our data do not support the view that the positive effects of the sexual hormones may spread for a beneficial LV remodeling in female rats with MI.

CONCLUSION

The current study had a preset end point of 6 weeks in which male and female rats showed similar morphological and functional abnormalities. Therefore, we cannot draw conclusions about gender differences in the LV remodeling post-MI. It should be noted that the rats were young adults with no atherosclerotic disorder. It is unlikely that humans would have MI at such a young age. However, this experimental model has been widely accepted in studying post-MI LV remodeling.

ACKNOWLEDGMENTS

This study was funded by grant number 2009/54225-8, São Paulo Research Foundation (FAPESP).

Authors' roles & responsibilities	
ELA	Data collection and analysis, experimental design and manuscript writing
AJS	Experimental design, statistical analysis and manuscript writing
AAS	Collection and analysis of data
SSV	Collection and analysis of data
JMAS	Collection and analysis of data
AY	Collection and analysis of data
RRS	Study design and manuscript writing
PJFT	Experimental design, getting funding for research, critical review of the manuscript

REFERENCES

1. Klein HH, Hengstenberg C, Peuckert M, Jürgensen R. Comparison of death rates from acute myocardial infarction in a single hospital

in two different periods (1977-1978 versus 1988-1989). Am J Cardiol. 1993;71(7):518-23.

2. Marschner IC, Colquhoun D, Simes RJ, Glasziou P, Harris P, Singh BB, et al.; Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study. Long-term risk stratification for survivors of acute coronary syndromes. Results from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study. LIPID Study Investigators. J Am Coll Cardiol. 2001;38(1):56-63.

3. Litwin SE, Katz SE, Litwin CM, Morgan JP, Douglas PS. Gender differences postinfarction left ventricular remodeling. Cardiology. 1999;91(3):173-83.

4. Brett KM, Madans JH. Long-term survival after coronary heart disease. Comparisons between men and women in a national sample. Ann Epidemiol. 1995;5(1):25-32.

5. Heer T, Schiele R, Schneider S, Gitt AK, Wienbergen H, Gottwik M, et al. Gender differences in acute myocardial infarction in the era of reperfusion (the MITRA registry). Am J Cardiol. 2002;89(5):511-7.

6. Marrugat J, Sala J, Masiá R, Pavesi M, Sanz G, Valle V, et al. Mortality differences between men and women following first myocardial infarction. RESCATE Investigators. Recursos Empleados en el Síndrome Coronario Agudo y Tiempo de Espera. JAMA. 1998;280(6):1405-9.

7. Fishbein MC, Maclean D, Maroko PR. Experimental myocardial infarction in the rat: qualitative and quantitative changes during pathologic evolution. Am J Pathol. 1978;90(1):57-70.

8. Pfeffer MA, Pfeffer JM, Fishbein MC, Fletcher PJ, Spadaro J, Kloner RA, et al. Myocardial infarct size and ventricular function in rats. Circ Res. 1979;44(4):503-12.

9. Fletcher PJ, Pfeffer JM, Pfeffer MA, Braunwald E. Left ventricular diastolic pressure-volume. Relations in rats with healed myocardial infarction. Effects on systolic function. Circ Res. 1981;49(3):618-26.

10. Baily RG, Lehman JC, Gubin SS, Musch TI. Non-invasive assessment of ventricular damage in rats with myocardial infarction. Cardiovasc Res. 1993;27(5):851-5.

11. Moisés VA, Ferreira R, Nozawa E, Kanashiro RM, Campos O, Andrade JL, et al. Structural and functional characteristics of rat hearts with and without myocardial infarct. Initial experience with Doppler echocardiography. Arq Bras Cardiol. 2000;75(2):125-36.

12. Kanashiro RM, Nozawa E, Murad N, Gerola LR, Moisés VA, Tucci PJ. Myocardial infarction scar plication in the rat. Cardiac mechanics in an animal model for surgical procedures. Ann Thorac Surg. 2002;73(5):1507-13.

13. Cavasin MA, Tao Z, Menon S, Yang XP. Gender differences in cardiac function during early remodeling after acute myocardial infarction in mice. Life Sci. 2004;75(18):2181-92.

14. Tucci PJ. Pathophysiological characteristics of the post-myocardial infarction heart failure model in rats. Arq Bras Cardiol. 2011;96(5):420-4.

15. Litwin SE, Katz SE, Morgan JP, Douglas PS. Serial echocardiographic assessment of left ventricular geometry and function after large myocardial infarction in the rat. Circulation. 1994;89(1):345-54.

16. Santos AA, Helber I, Flumignan RL, Antonio EL, Carvalho AC, Paola AA, et al. Doppler echocardiographic predictors of mortality in female rats after myocardial. J Card Fail. 2009;15(2):163-8.

17. Cosmo S, Francisco JC, Cunha RC, Macedo RM, Faria-Neto JR, Simeoni R, et al. Effect of exercise associated with stem cell transplantation on ventricular function in rats after acute myocardial infarction. Rev Bras Cir Cardiovasc. 2012;27(4):542-51.

18. dos Santos AA, Helber I, Antonio EL, Franco MF, Tucci PJ. Severity of the cardiac impairment determines whether digitalis prolongs or reduces survival of rats with heart failure due to myocardial infarction. Int J Cardiol. 2013;167(2):357-61.

19. Nozawa E, Kanashiro RM, Murad N, Carvalho AC, Cravo SL, Campos O, et al. Performance of two-dimensional Doppler echocardiography for the assessment of infarct size and left ventricular function in rats. Braz J Med Biol Res. 2006;39(5):687-95.

20. dos Santos L, Mello AF, Antonio EL, Tucci PJF. Determination of myocardial infarction size in rats by echocardiography and tetrazolium staining: correlation, agreements, and simplifications. Braz J Med Biol Res. 2008;41(3):199-201.

21. Jain M, Liao R, Podesser BK, Ngoy S, Apstein CS, Eberli FR. Influence of gender on the response to hemodynamic overload after myocardial infarction. Am J Physiol Heart Circ Physiol. 2002;283(6):H2544-50.

22. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation, 1987;76(1):44-51.

23. St John Sutton M, Pfeffer MA, Plappert T, Rouleau JL, Moyé LA, Dagenais GR, et al. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. Circulation. 1994;89(1):68-75.

24. Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. J Am Coll Cardiol. 1994;24(1):132-9.

25. Meris A, Amigoni M, Uno H, Thune JJ, Verma A, Køber L, et al. Left atrial remodelling in patients with myocardial infarction

complicated by heart failure, left ventricular dysfunction, or both: the VALIANT Echo study. Eur Heart J. 2009; 30(1):56-65.

26. Cabral AM, Vasquez EC, Moysés MR, Antonio A. Sex hormone modulation of ventricular hypertrophy in sinoaortic denervated rats. Hypertension. 1988;11(2 Pt 2):I93-7.

27. Pelzer T, Loza PA, Hu K, Bayer B, Dienesch C, Calvillo L, et al. Increased mortality and aggravation of heart failure in estrogen receptor-beta knockout mice after myocardial infarction. Circulation. 2005;111(12):1492-8.

28. Fischer GM, Swain ML. Effect of sex hormones on blood pressure and vascular connective tissue in castrated and noncastrated male rats. Am J Physiol. 1977;232(6):H617-21.

29. Dubey RK, Gillespie DG, Jackson EK, Keller PJ. 17Beta-estradiol, its metabolites, and progesterone inhibit cardiac fibroblast growth. Hypertension. 1998;31(1 Pt 2):522-8.

30. Smith PJ, Ornatsky O, Stewart DJ, Picard P, Dawood F, Wen WH, et al. Effects of estrogen replacement on infarct size, cardiac remodeling, and the endothelin system after myocardial infarction in ovariectomized rats. Circulation. 2000;102(24):2983-9.

31. Patten RD, Pourati I, Aronovitz MJ, Baur J, Celestin F, Chen X, et al. 17beta-estradiol reduces cardiomyocyte apoptosis in vivo and in vitro via activation of phospho-inositide-3 kinase/Akt signaling. Circ Res. 2004;95(7):692-9.

32. Chen Q, Williams R, Healy CL, Wright CD, Wu SC, O'Connell TD. An association between gene expression and better survival in female mice following myocardial infarction. J Mol Cell Cardiol. 2010;49(5):801-11.