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Post-MI left ventricular myocyte remodeling: Are there gender differences in rats?

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Abstract

Background—Previous studies have shown gender differences in left ventricular (LV) remodeling after myocardial infarction (MI). Results are varied, however, and reliable, comprehensive data for changes in cardiac myocyte shape are not available.

Methods—Young adult female and male Sprague-Dawley rats were used in this study and randomly assigned to MI and sham MI groups respectively. MI was produced by ligation of the left descending coronary artery. Four weeks after surgery, LV echocardiography and hemodynamics were performed before isolating myocytes for size determination.

Results—In general, LV functional changes after MI were comparable. Females developed slightly, but significantly, more LV hypertrophy than males and this was reflected by the relative increases in LV myocyte volume. In both males and females, however, myocyte hypertrophy was due exclusively to lengthening of myocytes with no change in myocyte cross-sectional area.

Conclusions—This study demonstrates that post-MI changes in LV function and myocyte remodeling are remarkably similar in young adult male and female rats.

Keywords

myocyte shape; left ventricular dysfunction; gender

1. INTRODUCTION

Left ventricular (LV) remodeling after an acute myocardial infarction (MI) is characterized by infarct expansion, hypertrophy of 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[1,2]. We have shown previously in female rats and a small group of humans that the key cellular change underlying progressive anatomical remodeling of the non-infarcted myocardium is progressive myocyte lengthening with no change in myocyte cross-sectional area[3].

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It is well known that premenopausal women are less likely to develop coronary heart disease than men. Previous studies have also shown post-MI gender differences in LV remodeling. Cavin et al[4] reported that during the acute phase, male mice had more pronounced neutrophil infiltration at the infarct border zone with increased MMP activity, a higher infarct expansion index, and higher rate of cardiac rupture compared to females. Females had more pronounced macrophages infiltration than males. During the chronic phase, males had poorer LV function, more prominent dilatation, and significant myocyte hypertrophy. Litwin et al[5] showed that male rats had greater increases in LV posterior wall thickness, higher average myocyte diameter in the non-infarcted region, and more pronounced restriction of LV diastolic filling compared to female rats 6 weeks after MI. However, neither of these studies provided comprehensive data on changes in myocyte shape. A clinical study published by Crabbe et al[6] showed that women had less myocyte hypertrophy in post MI LV remodeling than men. While their study used isolated myocytes for measurement, normal control subjects were not available for comparison.

Since possible gender differences in post-MI LV myocyte remodeling are not clear, we conducted the current study using a rat MI model using a reliable and comprehensive method. Changes in myocyte shape were similar in both genders. Although there were some relatively small gender differences that reached statistical significance in various hemodynamic and echocardiographic parameters, the overall response for males and females was remarkably similar.

2. METHODS

2.1. Experimental design

Adult female and male Sprague-Dawley rats 10–12 weeks of age were purchased from Harlan Laboratories (Indianapolis, IN) and randomly assigned to sham MI and MI groups, respectively. Rats were anesthetized with ketamine (5mg/100g body weight) plus xylazine (0.2mg/100g body weight) intraperitoneally, intubated, and ventilated with room air. Thoracotomy was performed and MI was produced by ligation of the left descending coronary artery 2–3mm below the aortic root with 5-0 silk suture [7,8]. This typically results in a 30–60% infarct area in our lab. Sham MI was produced with a similar procedure except the suture was tied loosely around the coronary artery. Survivors were assigned to the following groups: (1) Female sham MI (n=15); (2) Female MI (n=15); (3) Male sham MI (n=14); and (4) Male MI (n=17). Animals were housed two per cage and kept on a 12h light/dark cycle with food and water provided *ad libitum*. At termination, cardiac function was assessed by echocardiography and LV catheterization for each animal in the study. All experiments and protocols were performed in accordance with the Guide for the Care and Use of Laboratory Animals (US Department of Health, Education, and Welfare, Department of Health and Human Services, NIH Publication 85-23), and approved by the University of South Dakota Animal Care and Use Committee.

2.2. Echocardiographic measurements

Echocardiography was performed in each animal before it was euthanized using a Visualsonics 660 imaging system (Toronto, Canada) with a 20 MHz transducer as described previously[3,8]. Briefly, rats were anesthetized using isoflurane (1.5%) and two dimensional echocardiograms were obtained from short-axis views of the left ventricle at the level of the papillary muscle tips. Two-dimensionally targeted M-mode echocardiograms were used to measure the wall thickness and LV dimensions in systole and diastole as well as fractional shortening (FS).

2.3. Cardiac hemodynamic measurements

Rats were anesthetized using isoflurane (1.5%), LV hemodynamics were obtained by catheterization of the right carotid artery using a Millar Micro-tip catheter (Millar Instruments; Houston, TX) as described before[9]. Data were recorded using a Millar Pressure-Volume System (model MPVS400; Millar Instruments; Houston, TX). The following data were collected: heart rate (HR), LV peak systolic pressure (LVSP), LV end-diastolic pressure (LVEDP), and positive/negative change in pressure over time (dp/dt).

2.4. Cardiac myocyte isolation

Cardiac myocytes were isolated using a standard procedure[9]. After hemodynamic measurements, animals were anesthetized and hearts removed, blotted, and weighed. The aorta was cannulated for retrograde perfusion with an oxygenated prewash solution (calcium-free Joklik media, 37 °C) followed by media containing 0.1% collagenase (Worthington Biomedical). After collagenase perfusion, hearts were divided into LV non-infarcted area + septum, LV infarct area, and RV free wall. Tissue was then minced in calcium-free Joklik media and isolated cells were poured through nylon mesh (250 μ m) into 1.5% glutaraldehyde for cell size measurements.

2.5. Determination of cellular dimensions of isolated myocytes

Myocytes isolated from LV non-infarct area + septum were used for measurements. Cell volume was determined with a Coulter Channelyzer[10]. Profile area and cell length of randomly-selected, undamaged myocytes was determined directly using microscopy and an Image-Pro Plus analysis system (Media Cybernetics, Inc., Bethesda, MD; 50 cells per sample). Cross-sectional area was calculated by dividing cell volume by cell length.

2.6. Statistical analysis

All data are expressed as means (standard deviation) except LVEDP and were compared using Two-way Factorial ANOVA design to determine the effects of gender and MI surgery on specific parameters. If the interaction p value was greater than 0.2, then the interaction effect was dropped from the model, to increase the error degrees of freedom by one. The model assumption (i.e. normality and constant variance) were verified, and response transformation implemented as needed. LVEDP is expressed as median (25th percentile, 75th percentile) and compared using Nonparametric Tests (Kruskal-Wallis Test). In addition, a Mann-Whitney Test was used to compare differences between groups. A p value < 0.05 was considered statistically significant. SPSS 10.0 was used for all analyses.

3. RESULTS

3.1. General data

In this study, there were no gender differences in either early or later mortality rate in rats suffering a MI. All rats survived until the terminal study except for one rat in each MI group that died within 24 hrs after MI. Before harvesting the hearts, we measured cross-sectional infarct length using an electronic caliper. MI rats with small infarcts less than 8mm were excluded from this study. Only one male MI rat and two female MI rats were excluded. The average infarct length for the remaining rats was similar in both genders (9–12.6mm range).

Table 1 and Table 2 show average body weights, body weight changes, heart weights, heart weight-to-body weight ratios, and the statistical results of these parameters, respectively. Male rats had higher body weight than females before surgery. Compared with the female rats, male rats had a greater increase in body and heart size, but slightly lower heart weight/body weight ratio after surgery regardless of MI. Four weeks MI led to increased heart

weight and heart weight/body weight ratio, with no effect on body weight changes. There was no gender difference in heart weight changes after MI.

3.2. Echocardiography

Echocardiographic data are shown in Table 3 with comparison results in Table 4. Male sham MI rats had larger LV chamber dimensions and thicker interventricular septa but tended to have lower FS compared to female sham MI rats. Four weeks MI resulted in decreases in interventricular septal thickness and FS, as well as decreases in LV posterior wall thickness during systole. MI also led to increased LV dimension during both diastole and systole. These changes were similar in both genders. However, male MI rats showed a lesser increase in LV chamber dimension and a lesser decrease in FS compared to female MI rats.

3.3. Hemodynamics

Hemodynamic data and comparison results are summarized in Tables 5 and 6 respectively. LVEDP results are presented in Table 7. Male rats had higher $-dp/dt$ compared to females regardless of MI. MI led to a decrease in LVSP and $\pm dp/dt$ in both genders. LVEDP increased significantly in males while females showed a marginally significant increase. No gender difference was seen in hemodynamic changes at 4 weeks after MI.

3.4. Myocyte measurements

Table 8 and Table 9 show LV cardiac myocyte measurements and comparison results respectively. Compared with female rats, male sham MI rats had higher cell volume and cross-sectional area, but had similar profile area and cell length. Four weeks after MI, both female and male rats showed an increase in cell volume, profile area and length, but no change in cross-sectional area. There were no gender differences in myocyte dimensional changes in response to MI.

4. DISCUSSION

As expected, male rats were larger than age-matched female rats, with bigger hearts, but slightly lower heart weight/body weight ratio, indicating the heart weight difference was related to lean body mass. Four weeks after MI, both female and male rats showed a similar increase in heart weight and heart weight/body weight.

Female MI rats showed more prominent LV dilatation by 4 weeks compared to male MI rats. Although both male and female MI rats showed impaired LV function, male rats had better diastolic function as they had higher $-dp/dt$ to begin with and tended to have better systolic function. The functional results are similar to reports in mice where Shioura et al[11] found that female mice had lower $\pm dp/dt$ than males at 4 weeks post MI with similar ejection fraction (EF) and Bridgman et al[12] found that female mice had lower $+dp/dt$ than males at 6 week post MI. Conversely, Cavašin and colleagues have reported that male mice had lower EF and more prominent dilatation at 2 week after MI[4]. The use of gonadectomized mice, a different observation time point, and the different ages of mice used in Cavašin's study may be responsible for the different findings. It should also be pointed out that the EF reported by Shioura et al[11] was measured with pressure-volume loop, and the EF shown by Cavašin et al[4] was based on echocardiographic 2-dimensional short-axis views which should be interpreted with caution as LV shape alterations after MI should be taken into account. The functional changes observed here offer some explanation for the more prominent dilatation in LV chamber in female MI rats.

The animals used in this study were young adults with normal ovarian and testes function. This study was not designed to investigate the role of sex hormones in post-MI LV

remodeling and we did not monitor the serum sex hormone changes after MI in these animals. Since serum sex hormones in females vary during the menstrual cycle, minor effects of sex hormones on LV functional and echocardiographic parameters can not be excluded. Researchers have revealed conflicting sex hormonal effects so far regarding gender differences after MI. In ovariectomized female mice, Van Eickels et al[13] reported that long term treatment with 17-beta-estradiol further increased LV chamber dimension and impaired LV function after MI. Smith et al[14] and Cavaşin et al[15] found that long term estrogen treatment can reduce LV cavity size and wall stress in rats and mice. In addition, Beer et al[16] reported that high dose estrogen treatment can almost completely prevent LV dilatation and dysfunction after MI. However, Hügel et al showed that physiological concentration of estrogen did not have any major effects on post-MI cardiac hypertrophy, LV dysfunction, and dilatation in rats[17]. Although males are more likely to suffer from MI, testosterone seems to have no detrimental effects on post-MI LV remodeling. Its pro-hypertrophic effect may even reduce wall stress and LVEDP and improve long-term outcome in males[18].

Unlike Litwin's report[5], we did not see an increase in LV posterior wall thickness in either gender after MI. On the contrary, we observed only a tendency for decrease in LV posterior wall thickness and a significant decrease in interventricular septal thickness, which is consistent with volume-overload induced LV remodeling. In patients, however, no change in wall thickness after MI was seen by McKay et al[19] and Kramer et al[20].

In this study, we found that male rats had bigger myocytes than females. The difference was mainly in cross-sectional area. After MI, both female and male rats showed increase in myocyte size by cell lengthening, without a significant change in cross-sectional area, indicating both genders have a similar pattern of myocyte remodeling in response to MI. Our results are different from what Litwin et al[5] reported previously, in which they found that male rats had greater myocyte diameter in the LV non-infarcted area than females at 6 weeks after MI. However, their study used a method that provides only a crude estimation of a single parameter without appropriate corrections for well-known sources of error.

The widespread use and acceptance of less precise techniques to assess myocyte size has led to some confusion about myocyte remodeling patterns in heart disease. For instance, it is common to see reports of myocyte cross-sectional area doubling or tripling after MI. This, of course, is extremely unlikely since wall thickness is minimally changed if at all in the non-infarcted myocardium. A common approach used by most labs is to measure myocyte diameter or cross-sectional area using routine histological slides without appropriate consideration of the many sources of error involved with such measurements (e.g. difficulty in identifying "true" cross-sections, tissue preparation artifacts, variation in contractile phase, etc). This approach can be improved by sampling only from fields with circular capillaries and using a cell membrane marker, such as wheat germ agglutinin, to better identify myocyte boundaries. Myocyte length is also underestimated from histological sections because of the stair-stepped nature of the intercalated disc and the difficulty in knowing if the maximum cell length lies outside the plane of section for a given myocyte. We recognized these limitations many years ago and devoted considerable effort to developing and validating a more reliable approach[9]. In that study, three independent cell sizing methods were compared to validate the method that was used in this study. After applying appropriate corrections for all known sources of error, a precise correlation was observed between all three methods. The precision of the Coulter Channelyzer-isolated myocyte sizing method used in the current study has led to a clear and consistent understanding of myocyte remodeling patterns in cardiac growth, hypertrophy, and dilated heart failure[21]. Importantly, data collected in this manner are comprehensive (length, cross-sectional area, volume) and can be directly compared to data from any other study

using the same method. The requirement for high quality isolated myocyte preparations that yield a distinct myocyte peak when assessing volume by Coulter Channelyzer is likely the reason this method has not been more widely incorporated. In the case of post-MI remodeling of LV myocyte shape, data reported here from female rats are virtually identical to those reported in a collaborative study done in 1990 using the same method[3]. Using this method, post-MI remodeling of myocyte shape in humans has been reported by our lab and that of Ken Margulies with virtually identical results[6,22]. The only difference between the results of the rat and human MI studies is a greater increase in myocyte length in humans due to greater progression of the disease. Gender differences in post-MI mean myocyte cross-sectional area from the human study by Crabbe et al. (males, 263 μm ; females, 223 μm) are remarkably similar to those from the rats reported here (males, 281 μm ; females, 224 μm). It is worth noting that individuals with established hypertension prior to developing a MI have increased myocyte cross-sectional areas prior to the initiation of myocyte lengthening from series addition of sarcomeres. Indeed, we could reliably identify the hypertensive sub-group of ischemic patients based on comprehensive evaluation of isolated myocyte shape from explanted hearts (AM Gerdes, unpublished observation).

The pattern of cardiac myocyte remodeling has been shown to correlate well with changes in LV chamber anatomy in different models of heart failure from our previous studies[23–25]. However, the molecular regulation of myocyte shape is poorly understood. LV remodeling is a complex process involving the myocyte, myocardial extracellular matrix (ECM), and vasculature changes. ECM remodeling is modulated by multiple matrix metalloproteinases (MMPs) and a group of four endogenous proteins, tissue inhibitors of matrix metalloproteinases (TIMPs). There are highly regulated interactions between fibroblasts, smooth muscle cells, endothelial cells, infiltrating inflammatory cells, and cardiomyocytes. Among these, TIMPs have been shown to influence myocyte hypertrophy during cardiac remodeling independent of their ability to influence MMP activity[26].

It should be noted that the animals used in this study were young adult rats with no atherosclerotic disease. It is unlikely that humans have MI at such a young age. However, this animal model has been widely accepted in studying post-MI LV remodeling, and we have observed that the myocyte remodeling pattern in this model is identical to that of patients with ischemic heart diseases. So, the results observed are likely to be relevant to humans.

5. CONCLUSIONS

This study demonstrates that changes in LV function and myocyte remodeling after MI in young adult male and female rats are remarkably similar. The observed gender differences were due to rather subtle changes occurring in the same direction.

6. SUMMARY

Using a young adult rat MI model, we found that there was no significant difference in the myocyte remodeling pattern between males and females at 4 weeks post MI. Myocyte lengthening alone, from series addition of sarcomeres, was the major finding.

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Table 1

General data

Groups	N	Body Wt1 (g)	Body Wt Changes (g)	Heart Wt (mg)	Heart Wt/Body Wt2 ratio
Female					
Sham	15	232.3 (12.6)	20.6 (11.0)	881 (85)	3.5 (0.3)
MI	15	226.3 (9.6)	22.4 (18.4)	1032 (131)	4.2 (0.7)
Male					
Sham	14	307.0 (25.9) ^{***‡}	57.0 (20.5)	1180 (137)	3.2 (0.3)
MI	17	305.9 (25.7) ^{***‡}	57.5 (18.1)	1289 (109)	3.6 (0.3)

Data presented as means (SD).

N, number of rats; Body Wt1, body weight before surgery; Body Wt changes, body weight changes=body Wt2-body Wt1; Body Wt2, body weight before sacrifice; Heart Wt, heart weight; Heart Wt/Body Wt2 ratio, heart weight/body weight before sacrifice.

^{***} $p < 0.01$ vs. Female Sham

[‡] $p < 0.01$ vs. Female MI (one-way ANOVA).

Table 2

Model Results of Two-way Factorial ANOVA for general data

Baseline Data	Male	MI	Interaction
Body Wt Changes (g)	35.7 (26.7, 44.7) ($p<0.001$)	1.23 (-7.5, 10.3) ($p=0.786$)	$p=0.893$
Heart Wt (mg)	277 (218, 337) ($p<0.001$)	130 (70, 189) ($p<0.001$)	$p=0.483$
Heart Wt/Body Wt ratio [§]	-0.29 (-0.44, -0.15) ($p<0.001$)	0.42 (0.22, 0.69) ($p<0.001$)	$p=0.416$

[§] the inverse ratio was tested to satisfy model assumptions.

Table 3

Echocardiographic data

Groups	N	IVSd (mm)	IVSs (mm)	LVIDd (mm)	LVIDs (mm)	LVPWd (mm)	LVPWs (mm)	FS (%)
Female								
Sham	15	1.6 (0.4)	2.5 (0.5)	7.3 (0.6)	4.4 (0.8)	1.5 (0.4)	2.4 (0.7)	40.8 (7.1)
MI	15	1.2 (0.4)	1.7 (0.8)	9.6 (0.8)	7.6 (1.1)	1.5 (0.4)	2.1 (0.5)	21.4 (7.2)
Male								
Sham	14	1.9 (0.5)	2.7 (0.6)	7.9 (0.7)	5.0 (0.6)	1.8 (0.5)	2.6 (0.4)	36.1 (3.7)
MI	17	1.4 (0.4)	2.1 (0.5)	9.5 (0.8)	7.6 (1.0)	1.5 (0.4)	2.0 (0.5)	20.3 (5.5)

Data presented as means (SD).

N, number of rats; IVSd and IVSs, interventricular septum thickness during diastole and systole, respectively; LVIDd and LVIDs, left ventricular dimension during diastole and systole, respectively; LVPWd and LVPWs, left ventricular posterior wall thickness during diastole and systole, respectively; FS, fractional shortening.

Table 4

Model Results of Two-way Factorial ANOVA for echocardiographic data

Baseline Data	Male	MI	Interaction
IVSd (mm)	0.24 (0.04, 0.45) ($p<0.05$)	-0.46 (-0.67, -0.26) ($p<0.001$)	$p=0.970$
IVSs (mm)	0.27 (-0.05, 0.58) ($p=0.09$)	-0.74 (-1.06, -0.43) ($p<0.001$)	$p=0.538$
LVIDd (mm)	0.58 (0.03, 1.13) ($p<0.05$)	2.33 (1.78, 2.88) ($p<0.001$)	$P=0.08$
LVIDs (mm)	0.68 (-6.80, 1.36) ($p=0.05$)	3.21 (2.53, 3.90) ($p<0.001$)	$P=0.184$
LVPWd (mm)	0.17 (-0.05, 0.39) ($p=0.12$)	-0.17 (-0.38, 0.05) ($p=0.13$)	$p=0.229$
LVPWs (mm)	0.01 (-0.27, 0.29) ($p=0.94$)	-0.44 (-0.71, 0.16) ($p<0.01$)	$p=0.205$
FS (%)	-2.8 (-6.0, -0.4) ($p=0.08$)	-17.5 (-20.7, -14.3) ($p<0.001$)	$P=0.254$

Table 5

Hemodynamic data

Groups	N	HR (beat/min)	LVSP (mm Hg)	+dp/dt (mmHg/s)	-dp/dt (mmHg/s)
Female					
Sham	15	354 (28)	123 (11)	8484 (1848)	7647 (2015)
MI	15	328 (51)	106 (11)	5945 (965)	4708 (862)
Male					
Sham	14	357 (32)	126 (14)	8427 (1612)	9363 (2397)
MI	17	350 (38)	108 (13)	6468 (991)	5442 (1009)

Data presented as means (SD).

N, number of rats; HR, heart rate; LVSP, left ventricular end-systolic pressure; +dp/dt and -dp/dt, maximal rate of pressure development and decline, respectively.

Table 6

Model Results of Two-way Factorial ANOVA for hemodynamic data

Baseline Data	Male	MI	Interaction
HR (beat/min)	13 (-7, 33) ($p=0.19$)	-17 (-36, 3) ($p=0.10$)	$P=0.919$
LVSP (mmHg)	2.3 (-4.0, 8.5) ($p=0.47$)	-18 (-23.9, -11.5) ($p<0.001$)	$P=0.965$
$+dp/dt$ (mmHg/s) [§]	2.7 (-5.4, 31.4) ($p=0.41$)	-168.2 (-286.8, -81.0) ($p<0.001$)	$p=0.381$
$-dp/dt$ (mmHg/s) [§]	50.2 (5.3, 140.9) ($p<0.01$)	-421.1 (-640.7, -247.4) ($p<0.001$)	$p=0.394$

[§] the square root was tested to satisfy model assumptions.

Table 7

Left Ventricular End Diastolic Pressure (mmHg)

	Sham	MI
Female	4.5 (3.7, 6.3)	9.0 (7.2, 14.2)**
Male	5.4 (4.7, 6.1)	7.3 (6.5, 10.2) [‡]

Data presented as median (25th percentile, 75th percentile).**
 $p < 0.01$ vs. female sham[‡]
 $p < 0.01$ vs. male sham.

Table 8

Left ventricular plus septum myocyte dimensions

Groups	N	CV (μm ³)	Profile area (μm ²)	Cell length (μm)	CSA (μm ²)
Female					
Sham	15	29693 (3399)	3613 (343)	135 (5)	220 (25)
MI	15	36601 (3565)	4301 (470)	157 (8)	234 (24)
Male					
Sham	14	38171 (3762)	3833 (397)	135 (6)	283 (31)
MI	17	43083 (6188)	4364 (395)	153 (7)	283 (42)

Data presented as means (SD). N, number of rats; CV, cell volume; CSA, cross-sectional area.

Table 9

Model Results of Two-way Factorial ANOVA for myocyte dimensions

Baseline Data	Male	MI	Interaction
CV (μm^3) [§]	29% (18%, 40%) ($p<0.001$)	23% (13%, 34%) ($p<0.001$)	$P=0.119$
Profile area (μm^2) [§]	137 (−69, 344) ($p=0.19$)	608 (401, 815) ($p<0.001$)	$p=0.450$
Adjusted CL (μm)	−2.4 (−5.8, 1.0) ($p=0.17$)	19.5 (16.7, 23.0) ($p<0.001$)	$P=0.236$
CSA (μm^2)	56 (39.9, 72.2) ($p<0.001$)	6.8 (−9.4, 22.9) ($p=0.41$)	$p=0.381$
A dimension (μm)	0.5 (−0.7, 1.7) ($p=0.38$)	0.5 (−0.7, 1.7) ($p=0.43$)	$p=0.640$
B dimension (μm)	2.0 (1.1, 2.8) ($p<0.001$)	0.2 (−0.7, 1.0) ($p=0.71$)	$p=0.509$
A/B ration	−0.4 (−0.6, −0.1) ($p<0.01$)	−0.03 (−0.2, 0.3) ($p=0.81$)	$p=0.779$

[§]the natural logarithm was tested to satisfy model assumptions.