Mechanical Function is Normal in Remanent Myocardium During the Healing Period of Myocardial Infarction - Despite Congestive Heart Failure

Alessandra P. O. N. Peron, Roberto M. Saraiva, Ednei L. Antonio, Paulo José Ferreira Tucci
Universidade Federal de São Paulo - UNIFESP - São Paulo, SP - Brazil

Objective

The temporal relation between ventricular dysfunction (VD) after myocardial infarction (MI) and remanent myocardium mechanics is not yet clear. The present work investigated – through Doppler echocardiography (ECHO) – ventricular function in rats with extensive MI, as well as the mechanical function of papillary muscles (PM) at the end of the healing period.

Methods

ECHO and PM of 9 male Wistar rats (MI) were studied against 9 controls (C) three weeks after > 40% LV myocardial infarction. The following were determined: developed tension (DT) and its first negative and positive derivative, time-to-peak tension (TPT), resting tension (RT), and relaxation time at 50% of DT at 0.5, 1.0, 1.5, 2.0 and 2.5 calcium concentrations (mM). Tetanic contractions were carried out after ryanodine administration at 1.5, 2.5 and 5.0 calcium concentrations. Data were analyzed using ANOVA for repeated measures.

Results

VD was clearly characterized by ECHO, with marked abnormality of diastolic volume (C: 0.66±0.04 vs MI: 0.95±0.12 ml; $p<0.05$) and LV and ejection fraction (C: 84±7 vs MI: 44±12%; $p<0.05$), in addition to clear restrictive pattern of blood flow through the mitral valve. Concurrently, no significant difference was found in myocardial mechanics data either for MI or for C rats.

Conclusion

The heart failure (HF) reported by MI rats with > 40% MI at the end of the healing period is not myocardial function dependent. Chamber structural changes and lower population of myocites should base VD and HF.

Key words

myocardial infarction, papillary muscle, ventricular dysfunction, healing period, rats

Mailing Address: Paulo José Ferreira Tucci • Rua Estado de Israel, 181/94 – 04022-000 – São Paulo, SP - Brazil
E-mail: ptucci@cardiol.br
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It is not unusual for post-myocardial infarction ventricular dysfunction to raise the immediate concept of impairment of myocardial intrinsic contraction capacity: myocardial contractility. However, such intuitive interpretation is not always correct. It is possible to consider that ventricular ejection may be depressed, even though the inotropic state of myofibrils may be normal.

When resorting to literature, no unanimous position will be found on the contractile performance of remanent infarcted myocardium. Some works[1-8] that have analyzed myocardial contractility using preparations to focus global systolic function of left ventricle (ejecting or isovolumetric hearts) have reported consistent results in regard to contractile function depression. Most reports resulting from experiments in isolated papillary muscles[9-12] converge to the idea of myocardial contraction depression. One reference[13], however, reports normal systolic function of papillary muscle. When contractile function assessment was carried out in isolated myocyte preparations, results were more inconsistent. Li et al[4] as well as Holt and collaborators[15] have referred to the ability of isolated myocytes to shorten as being depressed in the remote myocardium. In the opinion of Melillo et al[6], the ability to shorten is depressed in isolated cells in regions adjacent to myocardial infarction (MI). Notwithstanding, shortening ability is kept normal by myocytes from the remote myocardium. Anand et al[7] have investigated isolated isovolumetric hearts and isolated myocytes in the remote myocardium. They have found developed pression reduction in isolated hearts, and normal ability to shorten in isolated myocytes. Some authors[18,19] have considered the possibility of some impairment of ventricular chamber systolic function, even when myocardial fibres inotropic state is normal.

Differently from the current controversy on the repercussions of MI on systolic function, the works that have investigated diastolic function in infarcted hearts agree that under such scenario ventricular compliance is restricted concurrently to increased myocardial stiffness[5,7,8,20-23]

The time elapsed as of coronary occlusion, infarction extension, and the type of preparation used to study myocarcial performance may modulate resulting functional repercussions for remanent infarcted myocardium – and they are not consistent in those works. When cardiac overload is kept for a long time, the rule is that myocardial remodelling course compromises contractile state. Post MI late assessment will result in expected decreased inotropism. In general, small size myocardial infarctions result in low repercussion for remanent myocardium; therefore, inotropism is not affected. Studies investigating the systolic function in ventricular chambers do not necessarily reflect the contractile state of subjacent musculature, since changes in ventricular geometry may dissociate ejection capacity from myofibrils contraction status.

The present work was conducted to investigate myocardial contraction performance at the end of the healing period after large size MI by contrasting results against Doppler-echocardiogram ventricular ejection data obtained.

Methods

Eighteen adult, male, Wistar-EPM rats were under follow-up for three weeks. Nine of them (356 ± 14 g) were studied three weeks after coronary occlusion to promote MI; nine others (366 ± 15 g) made up the control group (C).

The animals were anesthetized with intraperitoneal ketamine (50 mg/kg) and xylazine (10 mg/kg). Following orotracheal intubation, the animal was submitted to mechanical ventilation with Harvard ventilator, model 683 (frequency: 90 m/min, tidal volume: 2.0 mL After shaving, thoracotomy was carried out in left hemithorax, at *ictus cordis*. The heart was rapidly exteriorized. The anterior interventricular branch of left coronary artery was identified and occluded between the left auricular appendix ridges and pulmonary artery using Prolene 6-0 thread. Pulmonary hyperinsuflation was carried out, by a purse-string suture previously done.

After coronary occlusion, the animals were kept at the biotery for three additional weeks. On the third week ECHO was carried out to confirm infarction and to evaluate infarction size.

ECHO was carried out using HP SONOS 5500 (Hewlett Packard, Andover, MA, USA) equipment, a 12 MHz fundamental frequency transductor, with 2 cm deep images.

After anesthesia, following the same anesthetic schedule, the animals were positioned on left lateral decubitus position, with three electrodes placed on paws for electrocardiogram.

Left ventricle (LV) cross-sectional scans were videotaped for later analysis. Left paraesternal (longitudinal and cross-sectional scan) as well as apical views (four chambers and two chambers) were used. Linear measures taken from images obtained through M method, according to Schiller and collaborators[24], were: LV diameters at the end of diastole (LVDD) and at the end of systole (LVSD), as well as left atrium anteroposterior diameter (LAAD). Infarction size (%MI) assessed by the length of akinetic and/or hypokinetic regions (AHR) of ventricular walls was expressed percentually to total perimeter of endocardium perimeter (EP) in three cross-sectional views of LV (ridges of mitral valve leaflets, of papillary muscles, and of apical region), following previous standardization at our laboratory[25], utilizing:

$$\%MI = (AHR / EP)\ 100$$

Systolic function was assessed by ejection fraction (EF). Diastolic (dV) and systolic (sV) ventricular volumes were obtained through Simpson biplane method (apical, four

and two chambers) and EF was calculated as follows:

$$EF = (dV - sV / dV)\ 100$$

Diastolic function was analyzed using indices from mitral diastolic flow velocity curve through pulsatile Doppler technique. Diastolic flow velocity curve was obtained from the four-chamber apical view by positioning volume sample close to mitral valve ventricular face. The following were determined: E wave, A wave and E/A ratio.

After ECHO was completed, the animals whose MI was >40% of LV were referred for the study on the mechanical function of papillary muscles. With animals still anesthetized, thoracotomy was carried out, the heart was rapidly removed and placed in Krebs-Heinseleit (KH) solution previously oxygenated with 100% oxygen, at 28 ºC. After right ventricle musculature was removed, the interventricular septum was scanned so as to expose the two papillary muscles. Anterior papillary muscle was carefully desiccated, and terminations were tied by two stainless steel rings. Muscles were transferred to the glass chamber containing KH solution (mM: NaCl 130; KCl 5.0; $MgCl_2$ 1.2; CaCl2 1.5; glucose 11, insulin 20 U and Hepes 20, as buffer) and kept in vertical position. Solution pH was previously adjusted to 7.3 - 7.4, with sodium hydroxide added at 20% concentration. The lower ring was connected to existing hook on glass chamber inferior end. The upper ring was connected to a force transductor (Grass, modelo FT 03) with a stainless steel wire. Papillary muscle length at resting position was determined by displacing the transductor vertically, with a micromanipulator as support. For 45 minutes the muscles were kept under isotonic contractions activated by 5 ms, 9 mV intensity, and 0.2 Hz frequency square wave electric stimuli from a DV&M stimulator, model ESF-10. The muscles were placed under isometric contractions for 15 minutes. Afterwards, they were progressively stretched to determine the resting length to allow for more intense contraction: Lmax. In order to do that, developed tension values during contractions were evaluated during successive 30 μm stretchings until developed maximal tension was reached.

After higher developed tension value was defined, muscle length was measured with the support of a Mitutoyo pakimeter. The muscles were then left for isometric contraction for 15 minutes.

The following variables values were analyzed: maximum developed tension (DT), resting tension (RT), maximum positive (+dT/dt) and negative (-dT/dt) values of first temporal tension variation, time-to-peak tension (TPT), and time for developed tension to lower 50% from its maximum value (TR50%).

After 15 minutes, when the muscles were left to reach functional equilibrium state, experimental protocol application was actually started.

The KH containing 1.5 mM of $CaCl_2$ was changed by another that contained 0.5 mM of the same salt and a new state of equilibrium was awaited. After variables were recorded, the nutrient solution was again changed for KH, with 1.5 mM of $CaCl_2$. Successive evaluations of variables were carried out with KH solutions at 1.0 mM, 1.5 mM, 2.0 mM, 2.5 mM $CaCl_2$ concentrations. Among the different solutions used, the muscle was always left to reach equilibrium in KH solution at $CaCl_2$ de 1.5 mM concentration.

Afterwards, procedures for tetanic contractions were carried out. The standard 1.5 mM $CaCl_2$ KH solution was replaced by another at the same salt concentration, added with 1.0 μM ryanodine The muscles were kept in that solution for 45 minutes to reach a new steady state. Stimuli frequency was increased to 1 Hz; after new stabilization, it was increased to 10 Hz for 10 seconds, thus producing tetanic contraction. Other tetanic contractions were produced in KH solutions, with 2.5 and 5.0 mM of $CaCl_2$. Between one tetanus episode and the next, the muscle was kept at 1 Hz contraction frequency for 5 minutes.

After myocardial mechanics evaluation was completed, the muscles were removed from the system and weighed in a Fisher Scientific scale, model OCCU-124. Considering muscular density equal to 1, muscle cross-sectional area was estimated by dividing its weight by length at rest as shown in L_{max}.

Data were organized as means ± stardard deviation (SD); results comparisons were carried out using Student "t" test for independent data while comparing C vs MI. Significance values obtained in the five calcium concentrations was defined by ANOVA, followed by Student-Newman-Keuls tests for multiple comparisons whenever significance was detected by ANOVA. Statistical significance was $p < 0.05$.

Results

Body and cardiac chambers weight recorded for C and MI can be found in Figure 1. It is interesting to notice that although no difference was shown ($p > 0.05$) for body weight (BW) in the two groups at the point in time the animals were included in the protocol (C: 366 ± 14 g vs MI: 356 ± 37 g; $p > 0.05$), MI group rats body weight (385 ± 50 g) showed to be lower ($p < 0.05$) when compared to controls (433 ± 29 g) by protocol closing; which is to say, infarcted animals gained less weight when compared to controls in the three weeks following coronary occlusion. Concurrently, no statistical significance was shown between heart weight values (HW: C: 1,040 ± 373 mg vs MI: 1.093 ± 442 mg), LV (HW: C. 632 ± 179 mg; MI: 698 ± 208 mg) and right ventricle (RV): C: 407 ± 210 mg; MI: 392 ± 263

mg). MI: Non-significance was kept when the different cardiac weights were considered for their respective body weights: H/HW: C: 2,42 ± 0.92 mg/g vs MI: 2.94 ± 1.42 mg/g; LV/HW: C: 1.47 ± ±0.43 mg/g vs MI: 1.72 ± 0.85 mg/g and LV: C: 0.95 ± 0.51 mg/g vs MI: 1.07 ± 0.81 mg/g. Neither were papillary muscles section area values statistically different in the groups (C: 0.89 ± 0.15 mm^2; MI: 0.92 ± 0.18 mm^2).

Infarctions identified in animals submitted to coronary occlusion were expressive in size: 50 ± 8% of LV circumference were taken by MI.

ECHO results – Figure 1 – clearly illustrate infarcted animals' structural and functional cardiac abnormality: left auricle (C: 0.38 ± 0.03 mg vs MI: 0.63 ± 0.15 cm), diastolic diameter (C: 0.66 ± 0.07 cm vs 0.95 ± 0.12 cm) and systolic diameter (C: 0.26 ± 0.08 mg vs MI: 0.80 ± 0.14 cm) of LV associated to reduced EF (C: 84 ± 7% vs MI: 44 ± 12%) characterize severe compromising of LV. Concurrently, the restrictive diastolic pattern shown by atrial functional can be noticed: increase of E wave (C: 66 ± 10 cm/s vs MI: 90 ± 16 cm/s) and E/A ratio (C: 1.92 ± 0.31 vs MI: 5.90 ± 3.90). The lowest numeric value for A wave (C: 35 ± ±5 cm/s vs MI: 24 ± 17 cm/s) did not show to be at significance level.

Systolic and diastolic results for myocardial mechanics can be found in Table 1 and in Figures 2 and 3.

As for variables that show contractile function (DT and +dT/dt, Figures 2A and 2B), it is clear that calcium concentration increase in nutrient solution ($[Ca^{2+}]_o$) was followed by increased myocardial contractile performance in both groups. However, statistical significance of data was not reported for all $[Ca^{2+}]_o$ changes. $[Ca^{2+}]_o$ 0.5 mM were lower than all others. The other differences were not significant. While comparing DT and +dT/dt values both for C and MI for the different $[Ca^{2+}]_o$ levels data analogy is clear, thus indicating no differences between contractile performance in the two groups. Systole duration (TPT, Figure 2C) was not affected either by MI or by $[Ca^{2+}]_o$.

Table 2 shows diastolic function results, which are also illustrated in Figure 2.

Resting tension (Fig. 2D) did not report changes after MI or under the different $[Ca^{2+}]_o$. The same behavior was reported for TR50% (Fig. 2E) – no change. Tension decrease rate (-dT/dt, Figure 2F) was enhanced with $[Ca^{2+}]_o$ increase; statistical significances were identified while comparing data found for $[Ca^{2+}]_o$ at 0.5 mM and all the others, both in C as in MI.

Tetanic contractions reported no differences in C and MI data (Fig. 3). Values found for tetanus were numerically higher in higher $[Ca^{2+}]_o$; however, significance was found only when comparing 1.5 and 5.0 mM in the two groups. No significance was found for data obtained in C (1.5 mM: 2.22 ± 0.81 g/mm^2; 2.5 mM: 2.71 ± 0.91 g/mm^2; and 5.0 mM: 3.22 ± 0.84 g/mm^2) and in MI (1.5 mM: 2.00 0.42 – g/mm^2; <2.5 mM: 2.56 ± 0.54 g/mm^2; and 5.0 mM: 2.87 ± 0.53 g/mm^2).

Discussion

Weight data were not seen to identify differences between C and MI myocardial masses, whether considering absolute values or cardiac weight relatively to body weight. Since myocardial necrosis and subsequent scar reduce left ventricle weight, the lack of difference between C and MI leads to the conclusion that infarcted rats reported left ventricle musculature hypertrophy with the ability to restore chamber weight. Additionally, the same weights reported for RV suggest that MI hemodynamic repercussion – in that time period – did not result in pulmonary hypertension that would induce expressive hypertrophy of RV myocardial mass. Such interpretation does not, however, rule out pulmonary congestion. The clear reduction of EF characterized the ventricular systolic depression associated to expressive enlargment of LV and LA in our animals, which suggests left trial hypertension and resulting pulmonary

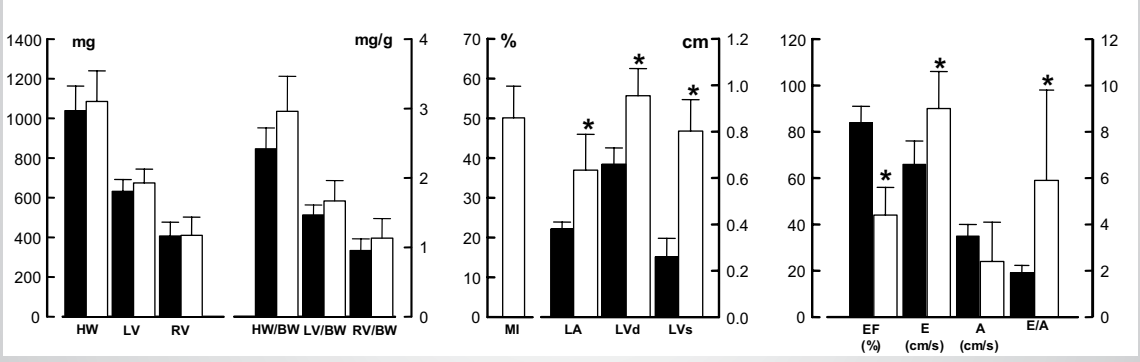

*Fig. 1 – Data (x ± sd) on C weights (filled columns) and myocardial infarction (transparent). Values presented refer to heart weight (HW), LV weight (LVW), RV weight (RVW), heart weight and body weight ratio (HW/BW), left ventricle weight and body weight ratio (LV/BW), right ventricle weight and body weight (RV/BW), MI: MI size, systolic diameters of left atrium (LA), diastolic diameter of LV (LVd) and systolic diameter of LV (LVs),ejection fraction (EF), E wave (E), A wave (A), and E/A ratio (E/A). *: p < 0.05 when comparing C x IM*

Table 1 – Means ± stardard deviations of systolic function variables in control animals (C) and those submitted to myocardial infarction (MI)

$[Ca^{2+}]_o$	DT (g/mm²)		+dT/dt (g/mm²/s)		TPT (ms)	
	C	IM	C	IM	C	IM
0.5 mM	2.87±1.47^{a1}	3.03±1.37^{a1}	27±11^{a1}	30±8^{a1}	229±35^{a1}	222±31^{a1}
1.0 mM	4.79±1.92^{a12}	5.23±1.8^{a2}	48±17^{a2}	50±14^{a2}	217±20^{a1}	211±37^{a1}
1.5 mM	6.17±2.2^{a2}	6.32±1.9^{a2}	63±22^{a2}	62±16^{a23}	212±29^{a1}	207±39^{a1}
2.0 mM	7.01±2.4^{a2}	7.12±2.0^{a2}	71±25^{a2}	71±20^{a3}	196±28^{a1}	207±40^{a1}
2.5 mM	7.01±2.5^{a2}	7.39±2.1^{a2}	75±26^{a2}	74±23^{a3}	195±21^{a1}	201±41^{a1}

DT: developed tension; +dT/dt: maximum positive value of first temporal derivative of developed tension; TPT: time-to-peak tension. Non-capitalized letters by standard deviations show values that are not statistically significant when comparing C vs MI. Equal numbers indicate values that are not statistically different in comparisons of data under different calcium concentrations

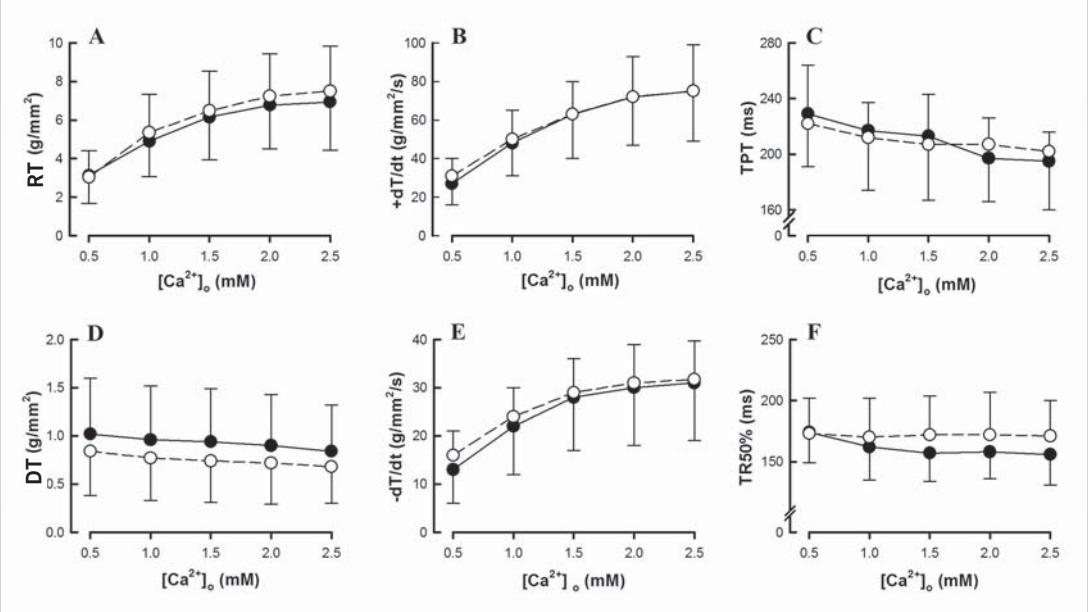

***Fig. 2** – Means (symbols) ± SD (vertical lines) of values of developed tension (DT) (A); highest positive value of first DT temporal derivative (+dT/dt) (B); time to peak tension (TPT) (C), resting tension (RT) (D); highest negative value of first DT temporal derivative(–dT/dt) (E); and time for DT to reduce 50% from maximum value (TR50%) (F) for control groups (in black) and myocardial infarction (transparent)*

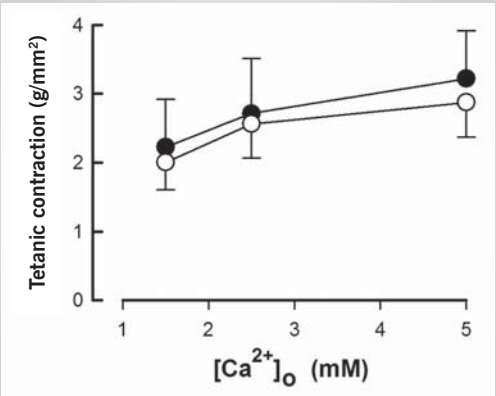

***Fig. 3** – Values (x ± SD) for tetanic contractions of control groups (filled columns) and myocardial infarction (transparent)*

congestion. The clear flow changes seen in mitral valve – which characterized ventricular filling restrictive pattern – consolidate the assumption of pulmonary congestion in our infarcted animals. Additionally, laboratory data[26] have shown that pulmonary water content is high in rats reporting such echo Doppler characteristics, thus emphasizing the assumption that the animals under study at the end of MI healing period reported heart failure (HF) condition. The assumption is supported by evidence in literature, thus confirming that rats with MI of equivalent size as our animals' report established HF immediately after coronary occlusion[27,28]. Consolidated interpretation of such information is based on the assumption that infarcted rats reported pulmonary congestion, and that the level of hypertension in RV and the brief period of evolution were not enough for RV mass increase to be manifested.

Table 2 – Means ± standard deviations of diastolic function variables for control animals (C) and those submitted to myocardial infarction (MI)

$[Ca^{2+}]_o$	TR (g/mm²)		-dT/dt (g/mm²/s)		TR50% (ms)	
	C	IM	C	IM	C	IM
0.5 mM	1.02±0.57^{a1}	0.84±0.46^{a1}	12±7^{a1}	15±4^{a1}	173±24^{a1}	172±28^{a1}
1.0 mM	0.96±0.56^{a1}	0.77±0.44^{a1}	22±10^{a12}	23±6^{a12}	161±27^{a1}	170±31^{a1}
1,5 mM	0.93±0.55^{a1}	0.73±0.43^{a1}	27±11^{a12}	28±7^{a12}	156±23^{a1}	171±32^{a1}
2.0 mM	0.90±0.53^{a1}	0.71±0.43^{a1}	30±11^{a2}	31±8^{a2}	158±22^{a1}	172±35^{a1}
2.5 mM	0.84±0.47^{a1}	0.67±0.38^{a1}	30±11^{a2}	32±9^{a2}	156±24^{a1}	171±29^{a1}

RT: resting tension; -dT/dt: maximum negative of first temporal derivative of developed tension; TR50%: time to relaxation for DT level to be reduced 50% from maximum value. Non-capitalized letters by standard deviations show values that are not statistically significant when comparing C vs MI. Equal numbers indicate values that are not statistically different in comparisons of data under different calcium concentrations

Our results come forward as unquestionable indicators of non-compromising of contraction and relaxation functions in MI remanent myocardium in the early period of cardiac overload. Data from the two groups under study were analogous and overlapping for all indicators under analysis.

Literature available on the analysis of early myocardial mechanical properties in the infarction healing period is not abundant.

Stuver and collaborators[18], while studying the papillary muscles of rats with 38±1% of LV MI size three weeks after coronary occlusion, have detected increase of RV mass, thus characterizing left ventricular dysfunction. While studying LV papillary muscles, the authors have not identified differences in DT, +dT/dt, -dT/dt, TPT or TR50%. Such results show considerable left ventricular dysfunction, concurrent to normal myocardial contractile state. Similar results have been described by Cheung and collaborators[3], who have found expressive left ventricular dysfunction three weeks after MI produced in rats, associated to normal shortening of isolated myocites in physiologic levels of calcium concentration.

Results by Li and collaborators[14] disagree from those described above. While studying mechanical properties of isovolumetric contracting LV and myocite calcium transient of rats 6 hours, two to three days, one week, and one month after MI, the authors have found that at all periods LV +dP/dt and –dP/dt were much lower when compared to that of non-infarcted, control animals. The same result was found for shortening peak and for shortening velocity of isolated myocites. Systolic calcium intracellular concentration values were lower, and diastolic calcium values were higher in infarcted group.

Anand and cols[17] have studied *in situ* hemodynamics, isolated isovolumetric LV, and isolated myocites of rats one, two, four and six weeks after MI. The authors have found systolic function parameters to be depressed both hemodynamically as in isolated ventricle analyses. Notwithstanding, contractile function data were normal in isolated myocites submitted to increasing concentrations of extracellular calcium.

Mill and collaborators[11], while studying the papillary muscles of normotensive rats, spontaneously hypertensive rats (SHR), and rats submitted to MI thirty days before have found that SHR developed higher forces, while infarcted rats developed lower force if compared to controls when submitted to increasing calcium concentrations.

Those results agree in pointing out ventricular chamber contraction impairment, and disagree as to the conclusions on myocardial function. Reports by other authors[3,17,18] point towards the non-existence of myocardial dysfunction in that early period of myocardial infarction healing. Mill and collaborators[11] and Li and collaborators[14] have referred results that show contractile impairment of remanent myocardium. Our data have not characterized changes in the contractile performance of infarcted rats in the post-MI period under study.

LV dysfunction associated to normal myocardial function is understandable. Ventricular ejection performance is inversely related to ventricular afterload. With Laplace[1] implications taken into account, dilated ventricular cavities imply increased afterload. The interactions between cavity radius/ejection function characterize cavity diameter as an internal component of afterload and point out large cavities as of little efficiency in converting the variable that regulates muscular contraction (force) in the variable regulating ventricular ejection (pressure). The increased afterload explains impaired ventricular ejection associated to normal contractile function in myocardium remanent to MI. Additionally, the possibility of a lower number of contractile units in the LV of infarted animals may contribute for ventricular contraction impairment.

To conclude, our results have shown that at the end of the healing period of large myocardial infarctions there is significant impairment of ventricular ejection ability, even though intrinsic mechanical properties may be normal.

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