Changed Duration of Ventricle Repolarization in Dog Heart under Conditions of Increased Preload

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The duration of repolarization of subendocardial, intramural, and epicardial layers of dog ventricles was studied under conditions of volume overload of the heart *in situ*. Increased preload was modeled by rapid intravenous infusion of saline and rheopolygluquine. The activation-recovery interval was measured by flexible intramural electrodes inserted into the right and left ventricles. The level of preload was evaluated by the increase in left-ventricular end-diastolic pressure. The increase in preload from 11±6 to 26±10 mm Hg led to a significant ($p<0.05$) prolongation of the activation-recovery interval in the subepicardial layers of apex, all layers of the lateral wall, and subepicardial and intramural layers of the base of the left ventricle and in subendocardial layers of the apex and base of the right ventricle. Further elevation of the end-diastolic pressure to 34±11 mm Hg led to shortening of the activation-recovery interval ($p<0.05$) in the subepicardial layers of the apex and lateral wall of the left ventricle and in the subepicardial layers of right-ventricular base and left-ventricular lateral wall. Hence, different areas of the myocardium differently react to volume overload of the heart. Changes in repolarization length in response to preload increase are biphasic.

Key Words: *repolarization; preload; activation-recovery interval*

Ventricular arrhythmias are the main cause of sudden death in patients with chronic cardiac failure. The relationship between heart distention and risk of fatal arrhythmias is a proven fact [9]. The physiological mechanism of arrhythmias induced by stretching of the myocardium remains little studied. It is hypothesized that the key role belongs to triggering activity of myocytes and the re-entry phenomenon, which, in turn, results from uneven changes in repolarization duration in different sites and layers of the myocardium [1]. Studies of repolarization process in the myocardium subjected to mechanical stretching were carried out mainly on isolated myocytes [5,10], myocardial strips and isolated heart [2,4,7], and patient's heart *in situ* [3,8]. The duration of repolarization was evaluated by action potentials in one or several points of the left ventricle (LV) in the majority of studies; this could provide an incomplete picture of electrophysiological changes in different layers and areas of the myocardium. We hypothesized that changes in the duration of heart repolarization during volume overload *in situ* depended on the degree and duration of exposure and on electrophysiological heterogeneity of different areas and layers of the myocardium.

MATERIALS AND METHODS

The study was carried out on 8 adult mongrel dogs of both sexes (18-35 kg). The animals were narcotized intramuscularly with zoletil (drug containing tiletamine and zolazepam; 10 mg/kg) and xylazine (4 mg/kg). Body temperature was maintained at 38-39°C.

The left ventricle was catheterized through the femoral artery for monitoring of the end-diastolic pres-

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sure (EDP). Hemodynamic parameters were measured with a Prucka Mac Lab 2000 hemodynamic device (General Electric).

Flexible intramural electrodes were inserted into the ventricular myocardium for recording unipolar electrograms. Each electrode had 4 contact points (macroelectrodes) fixed to a silk thread. The total number of macroelectrodes was 48 in all experiments. The electrodes were inserted perpendicularly to myocardial surface in the apical area, lateral wall, and base of LV and in the base and apex of the right ventricular (RV). Hence, electrograms of subepicardial, subendocardial, and intramural layers of the myocardium were recorded from one intramural thread. The electric potentials of the heart were recorded using a multichannel system for synchronous recording of electric field of the heart, de-

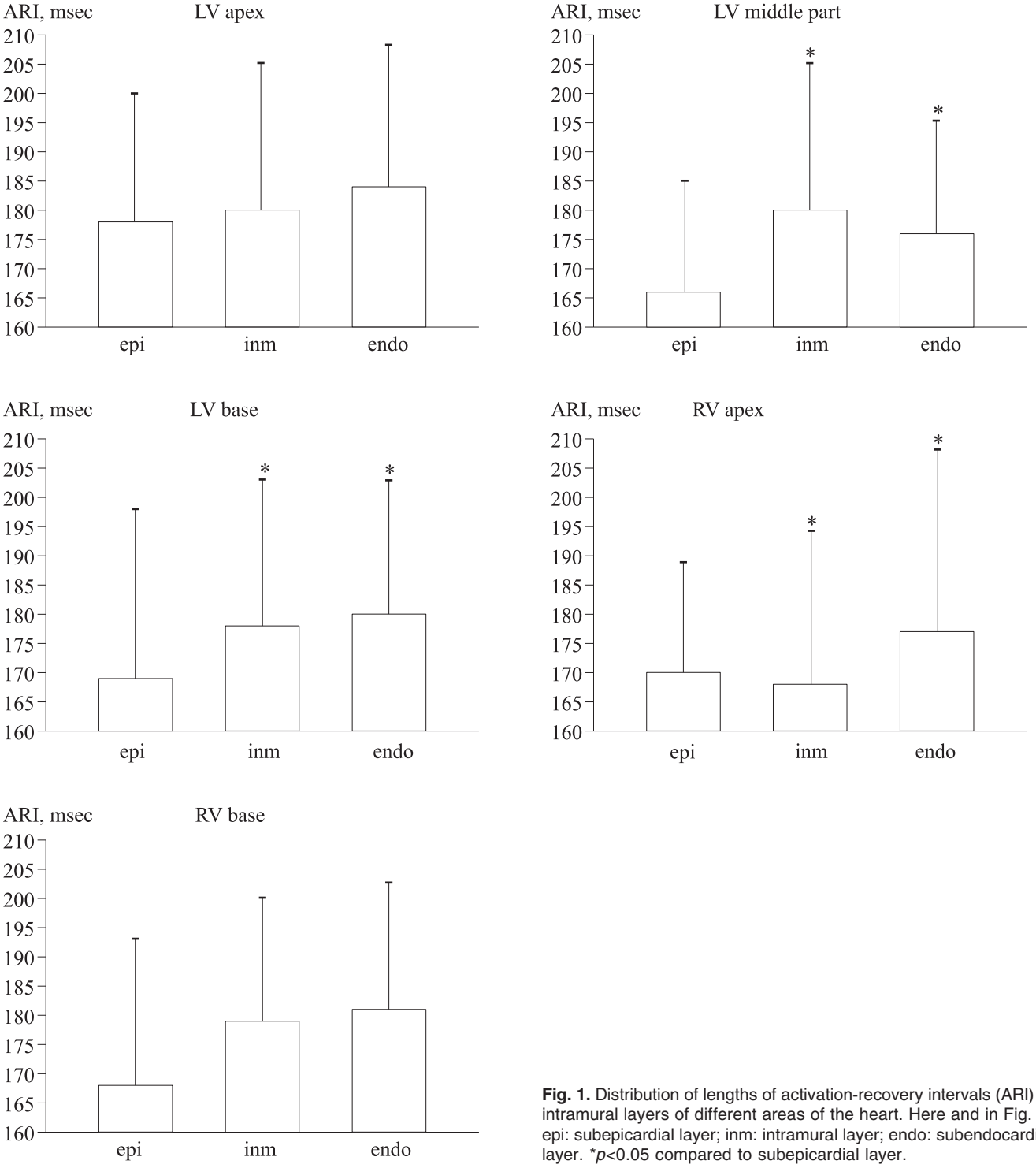

Fig. 1. Distribution of lengths of activation-recovery intervals (ARI) in intramural layers of different areas of the heart. Here and in Fig. 2: epi: subepicardial layer; inm: intramural layer; endo: subendocardial layer. *$p<0.05$ compared to subepicardial layer.

veloped by the Geosoft-Eastlink (Geolink) Joint Venture in collaboration with Institute of Physiology and VITA Company. The moment of entry of the depolarization wave into the potential lead area was evaluated by the dV/dt_{min} index during the *QRS* complex, repolarization moment by the dV/dt_{min} during the *ST-T* complex, and activation-recovery intervals (ARI) by the interval between depolarization and repolarization moments, action potential duration at the level of 90% repolarization [6].

In order to monitor the heart rate, the heart was passed at supraventricular rhythm of 130 min^{-1} (double diastolic stimulation threshold, 2.5 msec). The increase in preload was induced by rapid intravenous infusion of 200-ml doses of rheopolygluquine and saline to a total volume of 1.5-2.0 liters, depending on animal's body weight. The temperature of solution was maintained at 39-40°C. The level of preload was evaluated by LV EDP.

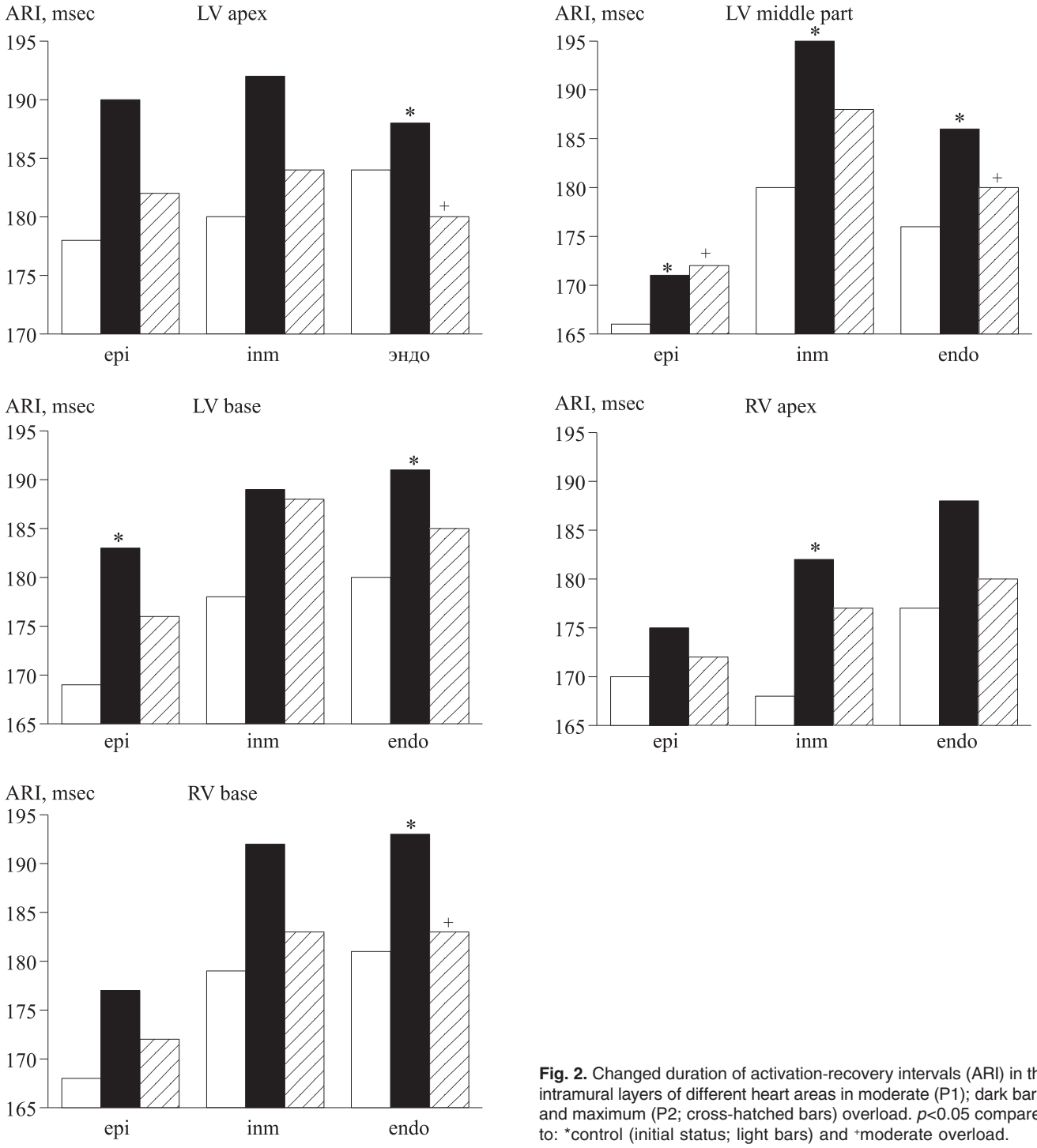

Fig. 2. Changed duration of activation-recovery intervals (ARI) in the intramural layers of different heart areas in moderate (P1); dark bars) and maximum (P2; cross-hatched bars) overload. $p<0.05$ compared to: *control (initial status; light bars) and +moderate overload.

Differences in the time parameters were evaluated by Friedman and Newman—Keuls tests. The differences were considered significant at $p<0.05$. The data are presented as the arithmetic means±standard deviations ($M\pm\sigma$).

RESULTS

The initial LV EDP was 11±6 mm Hg. The duration of repolarization in the middle part and base of LV and in the apex of RV was significantly lower in the subepicardial compared to intramural and subendocardial layers. No appreciable differences in transmural ARI were detected in the LV apical and RV basal (Fig. 1).

A trend to ARI prolongation was observed in all layers and areas of the myocardium in moderate overload (EDP 26±10 mm Hg). Significant changes in the LV ARI were recorded in the subepicardial layers of apical myocardium, all layers of the middle myocardium, and in the subepicardial and intramural layers of the basal myocardium; in the RV significant shifts were recorded in the intramural layers of the apex and in the subendocardial layers of the base (Fig. 2). Transmural differences in the ARI lengths disappeared for the middle part of LV, but emerged for the RV base (between the subepicardium and subendocardium).

Further elevation of LV EDP to 34±11 mm Hg led to ARI shortening in the subepicardial layers of the apex and subendocardial layers of the middle part of LV, as well as in the subendocardial layers of RV base (Fig. 2). Significant difference in ARI duration was again detected in the subepicardial *vs.* intramural and subendocardial layers of the middle part of LV. Significant differences in ARI lengths persisted for RV basal subepicardium and subendocardium.

Hence, changes in the duration of myocardial repolarization during volume overload *in situ* are biphasic. Moderate overload leads to prolongation of local repolarization in the majority of ventricular myocardial areas, while further increase in EDP results in their shortening in comparison with moderate overload.

REFERENCES

1. L. Eckardt, P. Kirchof, G. Breithardt, and W. Haverkamp, *Basic Res. Cardiol.*, **96**, No. 4, 369-380 (2001).
2. B. B. Lerman, E. D. Engelstein, and D. Burkhoff, *Circulation*, **104**, No. 4, 486-490 (2001).
3. K. Nanthakumar, P. Dorian, M. Paquette, *et al.*, *Cardiovasc. Res.*, **45**, No. 2, 303-309 (2000).
4. M. J. Reiter, M. Landers, Z. Zetelaki, *et al.*, *Circulation*, **96**, No. 11, 4050-4056 (1997).
5. N. Sasaki, T. Mitsuiye, Z. Wang, and A. Noma, *Circ. Res.*, **75**, No. 5, 887-895 (1994).
6. B. M. Steinhaus, *Circ. Res.*, **64**, No. 3, 449-462 (1989).
7. D. Sung, R. W. Mills, J. Schettler, *et al.*, *J. Cardiovasc. Electrophysiol.*, **14**, No. 7, 739-749 (2003).
8. P. Taggart, P. Sutton, R. John, *et al.*, *Br. Heart J.,* **67**, No. 3, 221-229 (1992).
9. P. Taggart, *Cardiovasc. Res.*, **32**, No. 1, 38-43 (1996).
10. E. White, J. Y. Le Guennec, J. M. Nigretto, *et al., Exp. Physiol.*, **78**, No. 1, 65-78 (1993).