Obligatory Role of the Endocardial Endothelium in the Increase of Myocardial Distensibility Induced by Endothelin-1

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This study investigated how the endocardial endothelium (EE) and particularly endothelial type B (ET_B) receptors influence the effects of endothelin-1 (ET-1) on diastolic distensibility. ET-1 (0.1, 1, and 10 n*M*) was tested in rabbit papillary muscles (Krebs-Ringer; 1.8 m*M* $CaCl_2$, 35°C) (i) with intact EE ($n = 10$), (ii) with damaged EE (0.5% Triton X-100, $n = 11$), and (iii) in the presence of RES-701-1 (selective endothelial ET_{B1} receptor antagonist, 1 μ*M*, $n = 6$). Additionally, increasing doses (0.1 n*M* to 1 μ*M*) of Sarafotoxin S6c (SRTXc, a selective ET_B receptor agonist) and IRL-1620 (a selective endothelial ET_{B1} agonist) were studied (i) in muscles with intact EE ($n = 7$ and $n = 6$, respectively) and (ii) after damaging the EE ($n = 8$ and $n = 7$, respectively). In papillary muscles with intact EE, ET-1 induced dose-dependent positive inotropic and lusitropic effects. At 10 n*M*, active tension (AT) increased 78% ± 17%, maximum velocity of tension rise (dT/dt_{max}) increased 82% ± 10%, and maximum velocity of tension decline (dT/dt_{min}) increased 77% ± 17%. These effects were maintained when ET-1 was given after damaging the EE (AT increased 70% ± 12%, dT/dt_{max} increased 93% ± 14%, and dT/dt_{min} increased 56% ± 14%), but were significantly reduced in the presence of RES-701-1 (AT increased 30% ± 6%, dT/dt_{max} increased 37% ± 7%, and dT/dt_{min} increased 29% ± 9%). ET-1 reduced resting tension (RT) and increased diastolic distensibility by 3% ± 1%, 5% ± 1%, and 9% ± 2% (at 0.1, 1, and 10 n*M*, respectively) in muscles with intact EE. This effect was abolished after damaging the EE or in the presence of RES-701-1. In muscles with intact EE, SRTXc had no significant effects, whereas, when given after damaging the EE, SRTXc (1 μ*M*) increased inotropy and lusitropy (AT increased 116% ± 24%, dT/dt_{max} 110% ± 28%, and dT/dt_{min} 88% ± 19%) without affecting RT. IRL-1620 dose-dependently decreased AT, dT/dt_{max}, and dT/dt_{min} in muscles with intact EE—effects that were abolished after EE damage. No significant effects were elicited by IRL-1620 in RT. ET-1–induced increase in myocardial distensibility, previously shown to be mediated by ET_A receptor stimulation, requires an intact EE and active endothelial ET_{B1} receptors. Exp Biol Med 231:876–881, 2006

Key words: endothelin; heart; diastolic function; inotropy; endothelium; ET_B receptors

Introduction

Endothelin-1 (ET-1), a potent vasoactive peptide, is synthesized by various cell types including endothelial cells, vascular smooth muscle cells, and cardiac myocytes, and acts in an autocrine/paracrine manner in the mammalian cardiovascular system (1).

ET-1 exerts its diverse effects through the binding to specific receptors, the so-called type A (ET_A) and type B (ET_B) receptors. Both receptors are G-protein–coupled transmembrane proteins, with different molecular and pharmacologic characteristics and functions based on their location. ET_A receptor stimulation elicits vasoconstriction (2) and mitogenesis (3) and increases inotropism (4, 5). ET_B receptor activation promotes vasodilatation and has growth-inhibitory effects (6) associated with apoptosis (7). These receptors also mediate the pulmonary clearance of circulating ET-1 (8) and the reuptake of ET-1 by endothelial cells (9).

In the vascular bed, ET_A receptors are found in smooth muscle cells, and are involved in the typically long-lasting vasoconstrictor effects of ET-1 (2). In contrast, ET_B receptors are expressed on both endothelial cells (ET_{B1}) and smooth muscle cells (ET_{B2}). ET_{B1} and ET_{B2} receptor stimulation promotes opposite effects on vascular tone: ET_{B1} receptors induce vasodilatation mediated by nitric oxide and prostacyclin release (10), whereas ET_{B2} receptors induce direct vasoconstriction (11).

We have recently demonstrated that the inotropic effect of selective ET_B receptor stimulation is dependent on the functional integrity of the endocardial endothelium (EE), being negative when it is intact and positive when it is damaged. These results had been attributed to the existence of two subtypes of ET_B receptors in the heart, as previously described in the vascular bed (see previous paragraph): ET_{B1} receptors, located on EE and responsible for negative

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inotropism, and ET_{B2} receptors, located on myocardial cells, and responsible for positive inotropism (12).

Unlike its effects on myocardial contractility, the influence of ET-1 on the diastolic properties of the myocardium is still poorly understood. We have recently shown that ET-1 increases diastolic distensibility of human and nonhuman myocardium through ET_A receptor stimulation and Na^+/H^+ exchanger activation (13).

In sequence following these previous studies, in the present work we investigated how the endocardial endothelium and particularly endothelial ET_B receptors influence the effects of ET-1 on diastolic distensibility.

Materials and Methods

The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health and with the Portuguese Law for Animal Welfare.

Experimental Preparation. The study was performed in isolated right papillary muscles ($n = 55$) from male New Zealand White rabbits (*Oryctolagus cuniculus*; 2.0–3.0 kg). Rabbits were anesthetized with intravenous pentobarbital sodium salt (25 mg/kg). A left thoracotomy was performed and beating hearts were quickly excised and immersed in modified Krebs-Ringer (KR) solution (composition in m*M*: NaCl, 98; KCl, 4.7; $MgSO_4 \cdot 7H_2O$, 2.4; KH_2PO_4, 1.2; glucose, 4.5; $CaCl_2 \cdot 2H_2O$, 1.8; $NaHCO_3$, 17; $C_3H_3NaO_3$, 15; CH_3COONa, 5; atenolol, 0.02) at 35°C with cardioplegic 2,3-butanedione monoxime (BDM; 3%) and 5% newborn calf serum and gassed with 95%O_2/5%CO_2, to obtain a pH between 7.38 and 7.42.

After dissection, papillary muscles (length: 3.9 ± 0.1 mm; weight: 3.0 ± 0.2 mg; preload: 4.8 ± 0.2 mN) were mounted vertically in a 10-ml Plexiglas organ bath containing the above-described KR solution and attached to an electromagnetic length-tension transducer (University of Antwerp, Antwerp, Belgium). Preload was estimated according to muscle dimensions and the electrical stimulus (0.6 Hz) was set at 10% above threshold. Twenty minutes later, bathing solutions were replaced by corresponding KR solutions without BDM. During the next 2 hrs, muscles were stabilized. Bathing solutions were then replaced by corresponding KR solutions without calf serum and maximum physiologic length (L_{max}) was calculated. Protocols were initiated after obtaining two similar isotonic and isometric control twitches separated by a 10-min interval.

Experimental Protocols. Myocardial effects of increasing doses of ET-1 (0.1, 1, and 10 n*M*) were studied in rabbit papillary muscles (i) in the presence of intact EE ($n = 10$); (ii) after damaging EE ($n = 11$); and (iii) in the presence of RES-701-1 (selective endothelial ET_{B1} receptor antagonist, 1 μ*M*, $n = 6$; Refs. 14, 15).

In addition, increasing doses of an ET_B receptor agonist, Sarafotoxin S6c (SRTXc; 0.1–1 μ*M*; Ref. 16) and of an endothelial ET_{B1} receptor agonist (IRL-1620; Refs. 12, 15, 17) were studied (i) in muscles with intact EE ($n = 7$ and $n = 6$, respectively) and (ii) after damaging the EE ($n = 8$ and $n = 7$, respectively).

EE was damaged by briefly (1 sec) exposing the isolated papillary muscle to a weak solution (0.5%) of the detergent Triton X-100 (18).

Chemicals were obtained from Sigma Chemical Company, St. Louis, Missouri.

Data Analysis. Isotonic and isometric twitches were recorded and analyzed. Selected parameters include: resting tension (RT) at the beginning (RT_{beg}, mN/mm^2) and at the end (RT_{end}, mN/mm^2) of the twitch; active tension (AT, mN/mm^2); maximum velocity of tension rise (dT/dt_{max}, $mN/mm^2/sec$); maximum velocity of tension decline (dT/dt_{min}, $mN/mm^2/sec$); peak isotonic shortening (PS, $\%L_{max}$); maximum velocity of shortening (dL/dt_{max}, L_{max}/sec), maximum velocity of lengthening (dL/dt_{min}, L_{max}/sec); and time to half relaxation (tHR).

Notwithstanding, only data obtained from isometric twitches will be described, as the analysis of isotonic twitches yielded globally similar results. In the various protocols, results are given as percentage change from baseline. For the parameters that are expressed as negative values (e.g., dT/dt_{min}) such percentage change refers to the absolute values.

When a pharmacologic inhibitor (RES-701-1) was used, the term baseline refers to the condition in the presence of this inhibitor before the addition of ET-1. Analysis of the effects of RES-701-1 *per se* on myocardial performance revealed that it did not significantly alter any of the myocardial parameters studied.

Statistical Methods. Values are means ± SEM. Effects of a single concentration of an individual drug on the various contractile parameters were analyzed by a paired *t* test, and the effects of increasing concentrations were analyzed by one-way repeated measures ANOVA. When significant differences were detected with the latter, the Student-Newman-Keuls test was selected to perform multiple comparisons. $P < 0.05$ was accepted as significant.

Results

Mean values of the contractile parameters in papillary muscles with an intact EE ($n = 29$) were similar in all experimental protocols. Removal of the EE ($n = 26$) resulted in a negative inotropic effect (Table 1).

Myocardial Effects of ET-1. Myocardial effects of ET-1 in the several experimental conditions are illustrated in Figures 1 and 2. In the presence of an intact EE, this agent promoted concentration-dependent positive inotropic and lusitropic effects: AT increased 12% ± 6%, 39% ± 9%, and 78% ± 17%; dT/dt_{max}, 11% ± 5%, 33% ± 6%, and 82% ± 10%; and dT/dt_{min}, 10% ± 6%, 35% ± 8%, and 77% ± 17% (at 0.1, 1, and 10 n*M*, respectively). These effects were maintained after damaging the EE (AT increased 15% ± 4%, 43% ± 10%, and 70% ± 12%; dT/

Table 1. Mean Values of the Contractile Parameters in Papillary Muscles with an Intact or Damaged EE[a]

Contractile parameter	Intact EE ($n = 29$)	Damaged EE ($n = 26$)
AT (mN/mm^2)	24 ± 3	16 ± 2*
dT/dt_{max} ($mN/mm^2/sec$)	149 ± 18	121 ± 15*
dT/dt_{min} ($mN/mm^2/sec$)	−114 ± 11	−79 ± 9*
PS (% of L_{max})	12 ± 0.1	8 ± 0.1*
dL/dt_{max} (L_{max}/sec)	0.8 ± 0.06	0.5 ± 0.04*
dL/dt_{min} (L_{max}/sec)	−3 ± 0.3	−2 ± 0.2*
tHR (ms)	418 ± 16	394 ± 14

[a] Values are means ± SEM. EE, endocardial endothelium; AT, active tension; dT/dt_{max}, maximum velocity of tension rise; dT/dt_{min}, maximum velocity of tension decline; PS, peak isotonic shortening; dL/dt_{max}, maximum velocity of shortening; L_{max}, maximum physiologic length; dL/dt_{min}, maximum velocity of lengthening; tHR, time to half relaxation.
* $P < 0.05$ vs. intact EE.

dt_{max}, 11% ± 3%, 45% ± 9%, and 93% ± 14%; and dT/dt_{min}, 7% ± 3%, 35% ± 14%, and 56% ± 14%), but were significantly reduced in the presence of RES-701-1 (AT increased 0.1% ± 0.2%, 1.0% ± 0.5%, and 30% ± 6%; dT/dt_{max} increased 1.0% ± 0.7%, 1.7% ± 0.8%, and 37% ± 7%; and dT/dt_{min} increased 1.0% ± 0.5%, 1.6% ± 0.8%, and 29% ± 9%).

Concerning the effects of ET-1 on myocardial distensibility, we found that RT significantly decreased after an isometric twitch in the presence of ET-1. Such a decrease was not significant at baseline and became progressively larger with increasing doses of ET-1 in muscles with intact EE. In fact, compared with its value at the beginning of the twitch (RT_{beg}), RT at the end of an isometric twitch (RT_{end}) decreased 3.1% ± 1.0%, 5.4% ± 1.4%, and 9.0% ± 2.4% in the presence of 0.1, 1, and 10 n*M* of ET-1, respectively. Such a decrease in RT reflects an increase in myocardial distensibility, because restoring the value of RT to its initial value results in an increase in the resting length of the muscle. No significant differences between RT_{end} and RT_{beg} were found when ET-1 was given after damaging the EE or in presence of RES-701-1.

Myocardial Effects of Selective ET_B Receptor Stimulation by SRTXc. Concentration-response curves to SRTXc for AT, dT/dt_{max}, dT/dt_{min}, and RT in the various experimental conditions are illustrated in Figure 3.

When given alone to muscles with an intact EE, SRTXc did not significantly alter myocardial performance. In contrast, when the EE was damaged, SRTXc induced positive inotropic and lusitropic effects, which were highly significant at 10^{-6} *M*. At this concentration, SRTXc increased AT 116% ± 24%, dT/dt_{max} 110% ± 28%, and dT/dt_{min} 88% ± 19%.

No significant differences between RT_{end} and RT_{beg} were induced by SRTXc in any of the experimental conditions.

Myocardial Effects of Selective ET_B Receptor Stimulation by IRL-1620. Concentration-response curves to IRL-1620 for AT, dT/dt_{max}, dT/dt_{min}, and RT in the various experimental conditions are illustrated in Figure 4.

When the EE was intact, this agent promoted concentration-dependent negative inotropic and lusitropic effects. At 10^{-6} *M*, it decreased AT by 23% ± 3%, dT/dt_{max} by 15% ± 2%, and dT/dt_{min} by 15% ± 5%. These effects were abolished when the EE was damaged.

As for SRTXc, no significant differences between RT_{end} and RT_{beg} were induced by IRL-1620 in any of the experimental conditions.

Discussion

The present study showed that the increase in myocardial distensibility induced by ET-1 and previously shown to be mediated by ET_A receptor stimulation requires

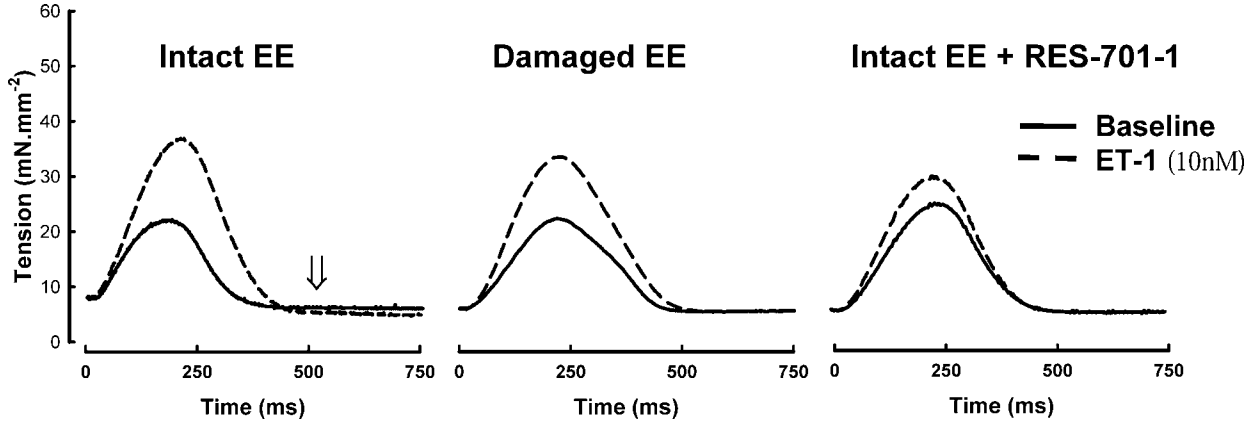

Figure 1. Representative examples of the effects of endothelin-1 (ET-1, 10 n*M*) on isometric twitches of rabbit papillary muscles, in the various experimental conditions: intact endocardial endothelium (EE, left); damaged EE (middle); and intact EE and endothelial ET_{B1} receptor blockade with RES-701-1 (right). ET-1 increased active tension and decreased resting tension (arrow) after the isometric twitch in muscles with intact endocardial endothelium. The effect on active tension was maintained after damaging endocardial endothelium, but was reduced after blocking endothelial ET_{B1} receptors. The effect on resting tension was completely abolished when ET-1 was given after damaging endocardial endothelium or after blocking endothelial ET_{B1} receptors.

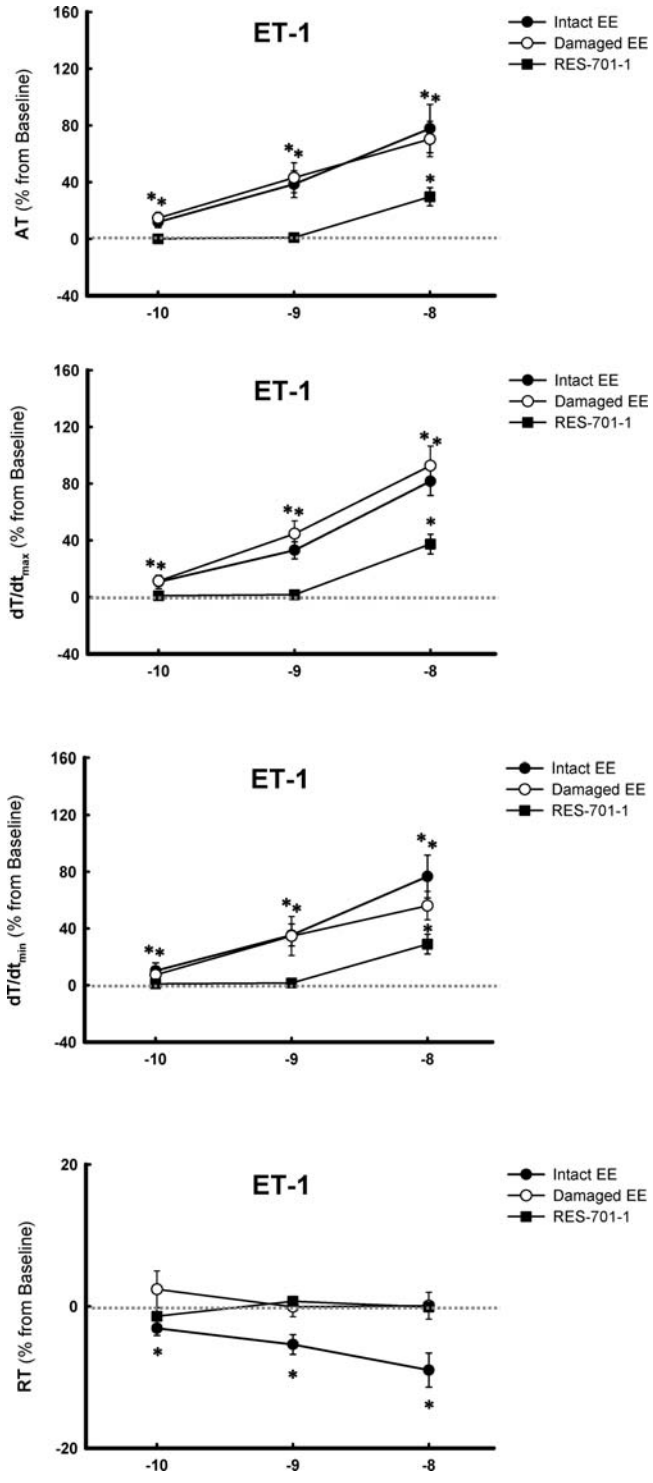

Figure 2. Concentration-response curves for the effect of ET-1 on the contractile parameters of rabbit papillary muscles in various experimental conditions: intact endocardial endothelium (EE; full circles, $n = 10$); damaged EE (open circles, $n = 11$); and intact EE and endothelial ET_{B1} receptor blockade with RES-701-1 (full squares, $n = 6$). AT, active tension; dT/dt_{max}, maximum velocity of tension rise; dT/dt_{min}, maximum velocity of tension decline; RT, resting tension. Mean ± SEM; percentage of baseline. $^*P < 0.05$ vs. baseline.

an intact endocardial endothelium (EE) and active endothelial ET_{B1} receptors.

Positive inotropic and lusitropic effects of ET-1 and their dependence on ET_A receptor activation have been previously described by several authors in various experimental preparations, although the magnitude of the effects varied among distinct animal species (19). Rabbits are one of the most sensitive animals to ET-1, which was one of the reasons for carrying out the experiments in this species. The magnitude of positive inotropic and lusitropic effects obtained in the present study is consonant with previously published data in rabbit papillary muscles (13, 20).

With regard to the effects of ET-1 on the diastolic properties of the myocardium, we found that the decrease in resting tension (increase in myocardial distensibility) observed after an afterloaded twitch in presence of ET-1 was not observed when the EE was previously damaged. The effects of ET-1 on myocardial contractility (inotropy) and relaxation (lusitropy) were, however, not significantly altered by the presence of an intact EE. Cardiac endothelium, both vascular and endocardial, regulates performance of underlying cardiac muscle. We have recently reported that the inotropic and lusitropic effects of selective ET_B receptor stimulation are dependent on the integrity of the EE, being negative when it is intact and positive when it is damaged (12). These differential effects were attributed to the existence of two ET_B receptor subtypes: ET_{B1}, located on endothelial cells, promotes negative inotropic and lusitropic effects, and ET_{B2}, located on myocardial cells, promotes positive inotropic and lusitropic effects (12). The present study revealed that endothelial ET_B (ET_{B1}) receptors also influence the effects of ET-1 on myocardial distensibility, even if the direct stimulation of either endothelial ET_{B1} or myocardial ET_{B2} receptors does not elicit any effect on this parameter. In a previous study we have shown that this effect of ET-1 on myocardial distensibility was mediated by ET_A receptor stimulation and not affected by myocardial ET_B receptor inhibition with BQ-788 (13), which is considered to predominantly block the ET_{B2} receptor subtype (15, 21). Taken together, these data suggest that the effects of ET-1 on myocardial distensibility may result from an interaction between ET_A and endothelial ET_{B1} receptors. This possibility is further reinforced by the attenuation of the positive inotropic and lusitropic effects of ET-1 in the presence of selective endothelial ET_{B1} receptor blockade.

Although such interaction has not previously been described in the heart, cross talk between ET-1 receptors has been reported in vascular (22–25) and nonvascular tissues (26). For instance, in the rabbit basilar artery, ET_{B2} receptor–mediated constriction seems to be dependent on prior ET_A receptor blockade (24). On the other hand, other studies have documented that concomitant ET_B stimulation decreases the effectiveness of ET_A receptor stimulation (22, 23, 25, 26). The underlying mechanisms for such cross talk remain, however, speculative. Although the results are

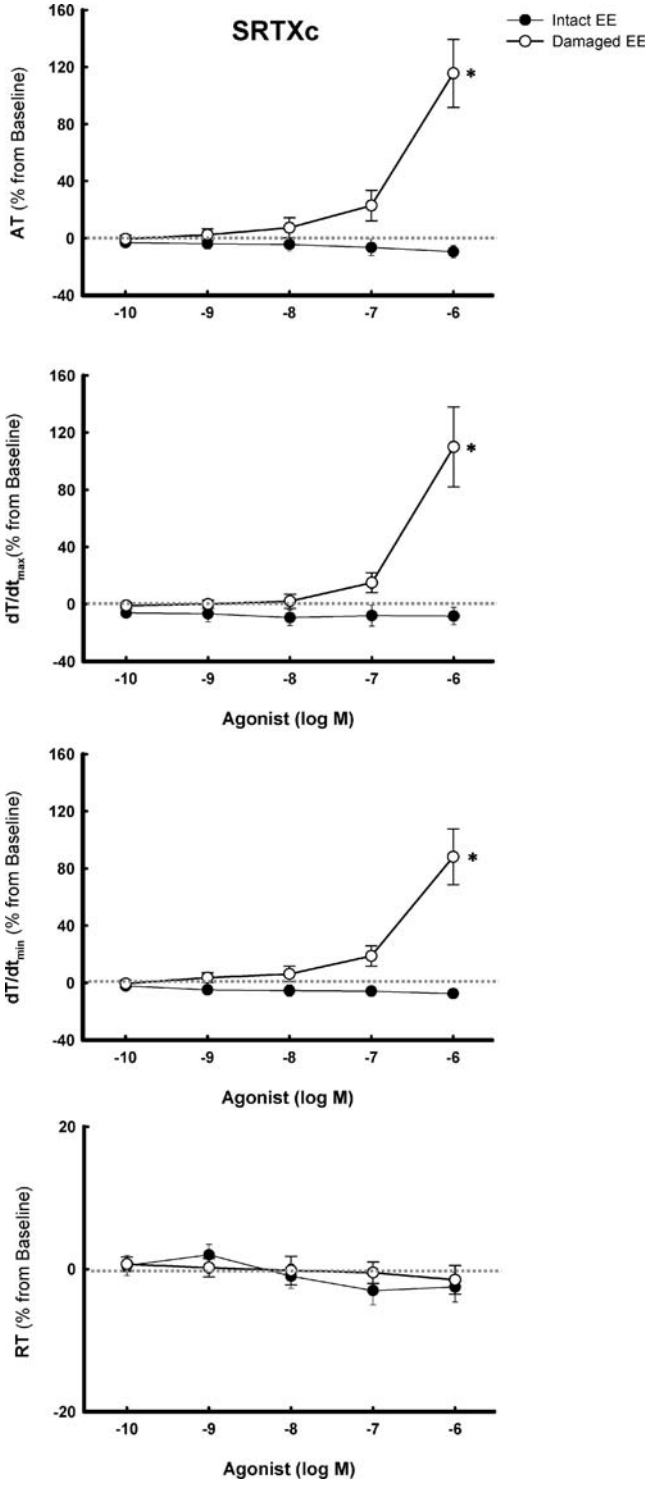

Figure 3. Concentration-response curves for the effect of Sarafotoxin S6c (SRTXc, selective ET_B receptor agonist) on the contractile parameters of rabbit papillary muscles with intact (full circles, $n = 7$) or damaged (open circles, $n = 8$) endocardial endothelium (EE). AT, active tension; dT/dt_{max}, maximum velocity of tension rise; dT/dt_{min}, maximum velocity of tension decline; RT, resting tension. Mean ± SEM; percentage of baseline. $^*P < 0.05$ vs. baseline.

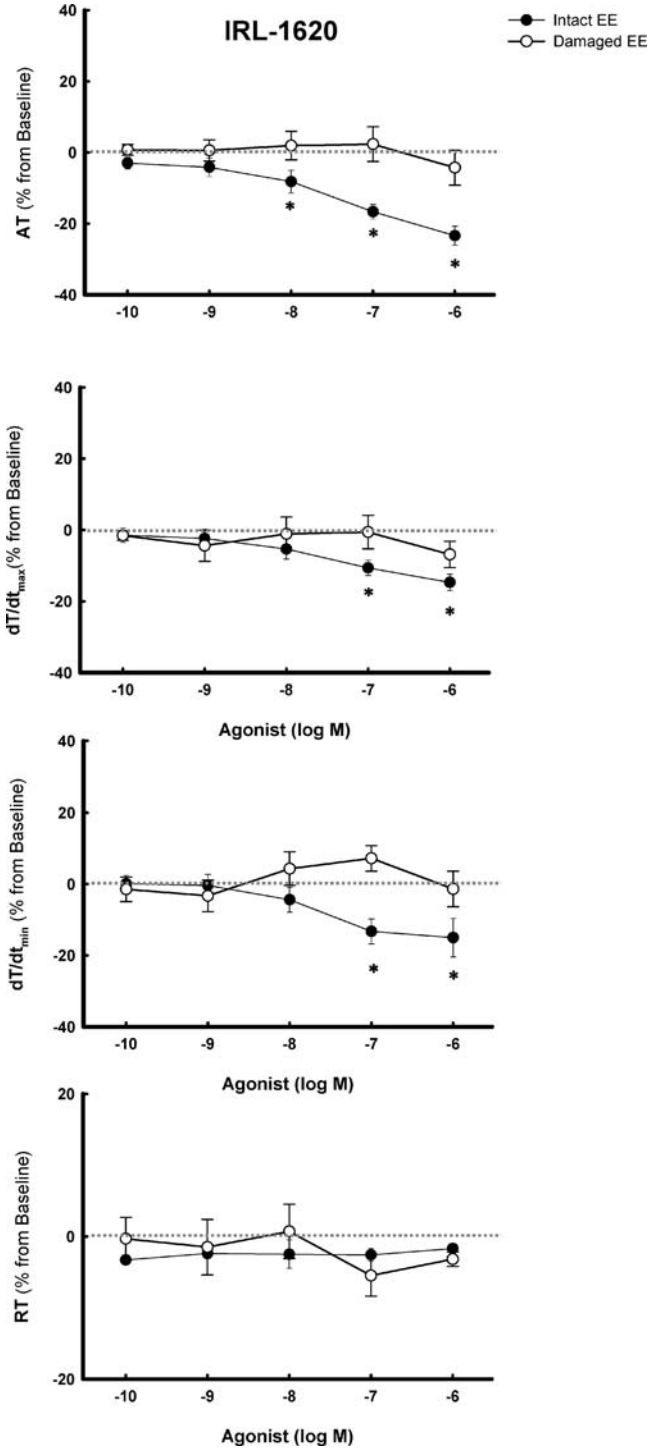

Figure 4. Concentration-response curves for the effect of IRL-1620 (selective endothelial ET_{B1} receptor agonist) on the contractile parameters of rabbit papillary muscles with intact (full circles, $n = 6$) or damaged (open circles, $n = 7$) endocardial endothelium (EE). AT, active tension; dT/dt_{max}, maximum velocity of tension rise; dT/dt_{min}, maximum velocity of tension decline; RT, resting tension. Mean ± SEM; percentage of baseline. $^*P < 0.05$ vs. baseline.

suggestive of potential occurrence of receptor cross talk, the present study is not designed to provide significant additional information with regard to this issue, which is a limitation that we have to point out.

In conclusion, ET-1–induced increase in myocardial distensibility, previously shown to be mediated by ET_A receptor stimulation, requires an intact EE and active endothelial ET_{B1} receptors. These results reflect that ET-1 activity is likely to depend on a complex balance of ET_A- and ET_B-mediated effects with factors such as functional endothelial integrity and efficiency of receptor subtype or receptor-effector coupling determining the overall response. These findings might improve our understanding about the role of ET-1, namely on diastolic function, which has been greatly overlooked in most studies.

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