Effects of Beta-Adrenoceptor Blocking Agents on Isolated Atrial and Papillary Muscles from Experimentally Diabetic Rats

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Abstract—Effects of propranolol and atenolol on isoproterenol-induced responses of isolated atrial and papillary muscles from experimentally diabetic rats were examined. Male Sprague-Dawley rats were divided into the diabetic group (DM) which received streptozotocin 60 mg/kg, i.v. and the control group (C) which received vehicle i.v. At 6 weeks after, the right atrial or right ventricular papillary muscle was isolated, and the beating rate (R) in the atrium or isometric force development (F) and its first derivatives (±dF/dt) in the papillary muscle under pacing were recorded. Basal R was less frequent in DM than in C, but ED50 values for isoproterenol-induced chronotropy were not different between the two groups. Basal F and basal ±dF/dt were not different between the two groups, but isoproterenol-induced increases in F and ±dF/dt were less in DM than in C. ED50 values in F and +dF/dt were not different between the two groups. Propranolol and atenolol shifted the concentration-response curves in R, F and ±dF/dt for isoproterenol to the right in both groups. pA2 values of propranolol and atenolol for each parameter were not different between the two groups. Results indicate that propranolol and atenolol exert the same beta-adrenoceptor blocking potency in both diabetic and non-diabetic hearts of rats.

It has been known that diabetes mellitus is frequently associated with atherosclerotic diseases such as hypertension or ischemic heart diseases (1–4), and recently, there have been reports of patients with diabetic cardiomyopathy having no obvious genesis that is accompanied by chronic congestive heart failure (5, 6). In experimentally diabetic animals, it has been noted that the chronotropic and inotropic actions of beta-adrenoceptor stimulating agents (beta-agonists) in isolated myocardium diminished (7–9), and a concomitant decrease in the number of beta-adrenoceptors might be responsible for these reduced myocardial functions (7–9). On the other hand, in the therapy of the hypertension and ischemic heart diseases that accompanied diabetes mellitus, beta-adrenoceptor blocking agents (beta-blockers) have generally been used (10, 11). When beta-blockers are administered to patients with diabetes mellitus, influences on lipid metabolism, hypoglycemia and/or secretion of insulin have been taken into account (12, 13), but those on myocardial function have not. If the decrease in the number of beta-adrenoceptors is related to reduced myocardial function, great attention must be paid in the use of beta-blockers on diabetic patients. Therefore in the present study, we evaluated experimentally the influence of beta-blockers on diabetic myocardium by examining the effects of propranolol with beta₁- and beta₂-blocking activity as a standard beta-blocker and atenolol with beta₁-blocking activity as a cardioselective beta-blocker on isoproterenol-induced responses of both atrial and papillary muscles isolated from experimentally diabetic rats.

Materials and Methods

Induction of experimental diabetes: Male Sprague-Dawley rats (Clea Japan, Tokyo,
Japan), weighing 200–260 g, were randomly separated into two groups: the control group (n=18) and the diabetic group (n=17). In approximately half of the rats of each group (n=9 in control group and n=8 in diabetic group), the effects of propranolol were examined. In the remaining rats (n=9 in both control group and diabetic group), effects of atenolol were examined. After an overnight fast, the diabetic group was treated with a single intravenous injection of streptozotocin (60 mg/kg, Sigma, St. Louis, MO, U.S.A.) which was dissolved in NaCl solution (154 mM) immediately before use, and the control group was injected with buffered vehicle. Animals were assessed to be in a diabetic state when the nonfasting blood glucose value was more than 350 mg/dl at 3 days after streptozotocin injection. Animals were fed on ordinary rat chow (Clea Japan, CE-2) and given water ad libitum for 6 weeks.

Preparation of right atrial and papillary muscles and measurement of parameters: At 6 weeks after vehicle or streptozotocin injection, animals were anesthetized with intraperitoneal injection of sodium pentobarbital (30 mg/kg). The abdomen was opened, and 3–5 ml blood were collected rapidly from the inferior vena cava. Immediately after thoracotomy, the heart was removed and placed in a beaker containing oxygenated Krebs-Henseleit solution of following composition: 120 mM NaCl, 4.8 mM KCl, 1.25 mM CaCl₂, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 25.0 mM NaHCO₃, and 11.0 mM glucose. The right ventricular papillary muscle was carefully dissected from the ventricles, and one end of the papillary muscle was attached to a stimulating electrode assembly and the other end was connected to a force-displacement transducer (Nihon Kohden, TB-611T). The atrium was carefully dissected from the right ventricle, and the remaining fat and aorta were trimmed off. One end of the atrium was connected to a force-displacement transducer (Nihon Kohden, TB-611T). These isolated myocardial preparations were suspended in a 20 ml organ bath filled with Krebs-Henseleit solution (pH 7.4) that was maintained at 37°C and continuously aerated with a gas mixture of 95% O₂ and 5% CO₂. 

Krebs-Henseleit solution in the organ bath was replaced every 15 min, and these preparations were allowed to equilibrate for 1 hr. Resting tension in the right atrial and papillary muscles was adjusted to 300 mg and maintained throughout the experiment. Beating rate (R) in the right atrium and isometric force development (F) and its first derivatives (±dF/dt) in the papillary muscle under pacing (voltage: 10–15% above threshold, duration: 1–5 msec) at a constant rate of 3.3 Hz (200 beats/min) using an electronic stimulator (Nihon Kohden, SEN-3201) were recorded. R was counted continuously by a cardiotachometer (Nihon Kohden, AT-600G) triggered by the developed force of the right atrium. ±dF/dt of the papillary muscle were derived from differentiating the force development signal using an electronic differentiator (Nihon Kohden, ED-601G). All the parameters were recorded on a heat-pen writing polygraph (Nihon Kohden, WT-685G) and were stored on a tape using a data-recorder (Sony Magnescale, A-47, Sony, Tokyo, Japan).

The drugs used in the present study were as follows: dl-isoproterenol hydrochloride (Nikken Kagaku, Tokyo, Japan), dl-propranolol hydrochloride (ICI Pharma, Osaka, Japan) and atenolol (ICI Pharma, Osaka, Japan).

Experimental protocol and calculation of ED50 values and pA₂ values: After all the parameters were equilibrated, an experiment was started. Isoproterenol was dissolved in NaCl solution (154 mM) and added cumulatively to the organ bath in a volume of less than 0.2 ml. Chronotropic and inotropic effects of isoproterenol on right atrial and papillary muscles were observed and expressed as percent changes in R, F and ±dF/dt when the maximum increases in each parameter were defined as 100%. Thus, cumulative concentration-response curves for R, F and ±dF/dt were obtained. As an index of affinity, values of the mean effective dose (ED50) for R, F or ±dF/dt were geometrically derived from these concentration-response curves. Muscle preparations were then washed out several times and equilibrated for 1 hr. Thereafter, beta-blockers at a certain concentration were added, and concentration-response
curves in each preparation for isoproterenol were again obtained 30 min after addition of these beta-blockers. Furthermore, preparations were once again washed out, and concentration-response curves for isoproterenol were taken after adding beta-blockers of 10-fold higher concentration than the first addition. pA2 values were calculated from these concentration-response curves after confirming the same slope (±1) of the line for beta-agonist and beta-blocker. At the end of the experiment, right atrial and papillary muscles were removed from the organ bath, and their wet weights were measured.

**Blood analysis:** Plasma glucose levels were measured by the glucose oxidase method (14), and plasma glycosylated hemoglobin levels were measured by the affinity column method (15, 16).

**Statistical analysis:** The data were expressed as the mean±S.E.M., and the statistical analysis of the data was done with the non-paired Student's t-test. A P value less than 5% was defined as a significant difference.

**Results**

**Values of plasma glucose and plasma glycosylated hemoglobin, body weight and wet heart weight:** Values of plasma glucose and plasma glycosylated hemoglobin, body weight and wet weights of the heart, right atrial muscle and papillary muscle of the control and diabetic groups at 6 weeks after vehicle or streptozotocin i.v. are summarized in Table 1. Plasma glucose and glycosylated hemoglobin levels were significantly higher in the diabetic group than in the control group (P<0.01). Body weight and wet weights of the heart and right atrium were significantly lower in the diabetic group than in the control group (P<0.01). Although the wet weight of the right papillary muscle was lower in the diabetic group than in the control group, this was not statistically significant.

**Basal values of R, F, +dF/dt and −dF/dt in steady state:** Basal values of R, F, +dF/dt and −dF/dt in the steady state are 326.8±4.1 beats/min, 278.8±32.2 mg, 6.9±0.6 g/sec and −5.9±0.6 g/sec in the control group and

![Graph of isoproterenol concentration and response](image)

**Fig. 1.** Effects of isoproterenol on beating rate (R) of isolated right atria from control (open circles, n=18) and diabetic (closed circles, n=17) rats. Each point represents the mean±S.E.M. ***P<0.001 versus the corresponding control value. The values at “before” show the basal beating rate.

**Table 1.** General features of control and diabetic rats

|                          | C group (n=18) | DM group (n=17) |
|--------------------------|---------------|-----------------|
| Plasma glucose (g/dl)    | 146.6±2.9     | 552.7±17.7**    |
| Plasma glycosylated hemoglobin (%) | 5.0±0.1 | 14.2± 0.3**  |
| Body weight (g)          | 468.7±7.9     | 287.7±10.4**    |
| Heart weight (g)         | 1.1±0.0       | 0.9± 0.0**      |
| Right atrium weight (mg) | 86.2±2.4      | 71.4± 2.6**     |
| Papillary muscle weight (mg) | 41.4±2.4 | 35.5± 1.9  |

C: control. DM: diabetes mellitus. Each value represents the mean±S.E.M. n=number of rats. **P<0.01 versus the corresponding control value.
290.6±8.2 beats/min, 297.2±27.8 mg, 6.4±
0.5 g/sec and -5.8±0.5 g/sec in the diabetic
group, respectively. The basal value of R was
significantly lower in the diabetic group than
in the control group (P<0.001). Basal F and
basal ±dF/dt were not different between the
two groups.

Chronotropic effects in right atrium and
inotropic effects in right ventricular papillary
muscle of isoproterenol: Concentration-re-
response curves for R by cumulative adminis-
trations of isoproterenol are shown in Fig. 1.
Increases in R by isoproterenol were concen-
tration-dependent in both control and dia-
betic groups. The maximum response of R to
isoproterenol was significantly lower in the
diabetic group than in the control group
(control group: 436±10 beats/min, diabetic
group: 375±9 beats/min, P<0.001). In-
creases in F and ±dF/dt by isoproterenol were
concentration-dependent, and increases of
±dF/dt by isoproterenol (10⁻⁷–10⁻⁶ M) in
the diabetic group were significantly smaller
than those in the control group (Fig. 2, P<
0.05). The maximum responses of +dF/dt
(control group: 15.1±1.4 g/sec, diabetic
group: 11.2±1.0 g/sec, P<0.05) and −dF/dt
(control group: −15.7±1.3 g/sec, diabetic
group: −11.8±0.9 g/sec, P<0.05) to isopro-
terenol (10⁻⁶ M) were significantly smaller
in the diabetic group than in the control group.
The maximum response of F to isoproterenol

![Graphs](https://example.com/graphs)

Fig. 2. Effects of isoproterenol on myocardial force development (F, panel a) and first derivatives of F
(+dF/dt, panel b and −dF/dt, panel c) of isolated papillary muscle from control (open circles, n=13) and
diabetic (closed circles, n=15) rats. Each point represents the mean±S.E.M. *P<0.05 versus the cor-
responding control value. The values at “before” show the basal force development, the basal +dF/dt
and the basal −dF/dt, respectively.
(10⁻⁶ M) was also smaller in the diabetic group than in the control group, but there was no significant difference between these two groups. ED50 values of −dF/dt for isoproterenol were significantly greater in the diabetic group than in the control group. However, ED50 values of R, F and +dF/dt tended to be greater in the diabetic group, but were not statistically different between the two groups (Table 2).

**Effects of beta-blockers on isoproterenol-induced responses in isolated right atrial and papillary muscles:** Concentration-response curves of R for isoproterenol after administration of propranolol (10⁻⁸ M and 10⁻⁷ M) and atenolol (10⁻⁷ M and 10⁻⁶ M) are shown.

|               | R       | F       | +dF/dt   | −dF/dt  |
|---------------|---------|---------|----------|---------|
| **C group**   | 5.31 × 10⁻⁹ | 2.92 × 10⁻⁹ | 4.24 × 10⁻⁸ | 4.37 × 10⁻⁸ |
| (n=18)        | (4.40–6.41) | (2.12–4.03) | (3.69–4.86) | (3.60–5.25) |
| **DM group**  | 5.73 × 10⁻⁹ | 3.97 × 10⁻⁹ | 4.92 × 10⁻⁸ | 6.17 × 10⁻⁸* |
| (n=17)        | (4.73–6.89) | (3.24–4.86) | (4.04–6.00) | (4.84–7.85) |

Table 2. ED50 values (M) of right atrial and papillary muscles to isoproterenol

C: control. DM: diabetes mellitus. Each value represents the geometric mean ED50 and their 95% confidence intervals (in parentheses). n=number of preparations. *P<0.05 versus the corresponding control value. R: beating rate of right atrium. F: myocardial force development of papillary muscle. +dF/dt: positive first derivative of force development. −dF/dt: negative first derivative of force development.

**Fig. 3.** Effects of propranolol (panels a and b, circles: control, triangles: 10⁻⁸ M, squares: 10⁻⁷ M) and atenolol (panels c and d: circles: control, triangles: 10⁻⁷ M, squares: 10⁻⁶ M) on isoproterenol-induced percent increases in beating rate (R) of right atri of control (open symbols, propranolol and atenolol: n=9) and diabetic (closed symbols, propranolol: n=8, atenolol: n=9) rats. Each point represents the mean±S.E.M. S.E.M. values are included in each symbol since they are smaller than the size of the symbol.
Table 3. pA₂ values of beta-blockers

|            | R       | F       | +dF/dt  | -dF/dt  |
|------------|---------|---------|---------|---------|
| Propranolol-treated |         |         |         |         |
| C group    | 8.72±0.23 | 8.36±0.26 | 8.79±0.17 | 8.73±0.08 |
| (n=9)      | (n=9)   | (n=5)   | (n=5)   | (n=5)   |
| DM group   | 8.71±0.08 | 9.00±0.19 | 8.45±0.09 | 8.40±0.17 |
| (n=8)      | (n=9)   | (n=5)   | (n=6)   | (n=5)   |
| Atenolol-treated |       |         |         |         |
| C group    | 7.11±0.11 | 7.27±0.10 | 7.24±0.08 | 7.25±0.09 |
| (n=9)      | (n=9)   | (n=7)   | (n=7)   | (n=7)   |
| DM group   | 7.19±0.08 | 7.12±0.06 | 7.21±0.05 | 7.19±0.08 |
| (n=9)      | (n=9)   | (n=9)   | (n=9)   | (n=9)   |

C: control group. DM: diabetes mellitus. Each value represents the geometric mean pA₂ value±S.E.M. Value of slope of the line for beta-agonist and beta-blocker is given in parentheses. n=number of preparations. R: beating rate of right atrium. F: myocardial force development of papillary muscle. +dF/dt: positive first derivative of force development. -dF/dt: negative first derivative of force development.

Fig. 4. Effects of propranolol (panels a and b, circles: control, triangles: 10⁻⁶ M, squares: 10⁻⁷ M) and atenolol (panels c and d, circles: control, triangles: 10⁻⁷ M, squares: 10⁻⁸ M) on isoproterenol-induced percent increases in myocardial force development (F) of right ventricular papillary muscle from control (open symbols, propranolol: n=5, atenolol: n=7) and diabetic (closed symbols, propranolol: n=5, atenolol: n=9) rats. Each point represents the mean±S.E.M. S.E.M. values are included in each symbol since they are smaller than the size of the symbol.
in Fig. 3. The concentration-response curves for R were shifted to the right by propranolol (10^{-8} M and 10^{-7} M) and atenolol (10^{-7} M and 10^{-6} M) in both control and diabetic groups, and pA_{2} values of propranolol and atenolol were not different between the two groups (Table 3). Propranolol and atenolol shifted similarly the concentration-response curves of F and ±dF/dt for isoproterenol to the right (Figs. 4, 5 and 6), and pA_{2} values for each parameter were not different between these two groups (Table 3).

Discussion

It has been well-documented that streptozotocin selectively destroys the beta cells of the pancreas (17), causing a reduction of insulin levels, and this results in pathological conditions characteristic of diabetes mellitus such as hyperglycemia, hypoinsulinemia, hyper-glycosylated hemoglobinemia, low body weight and low heart wet weight (8, 9, 18–20). Thus streptozotocin has generally been used as a drug to induce an experimentally diabetic state. Similarly in our experimentally diabetic model, streptozotocin induced a diabetic state: body weight and wet weights of the heart and right atrium in the diabetic rats were lower than those of the control rats, and the glycosylated hemoglobin level which reflects the mean plasma glucose level during the past 4 to 8 weeks (21) and the plasma glucose level were higher in the diabetic group than in the control group.

The present results in experimentally diabetic rats at 6 weeks after streptozotocin injection showed that the basal value of R in the right atrium was lower than that in the control rats, but basal F and basal ±dF/dt in the right ventricular papillary muscle were not different between the two groups. This lower R in the atrium coincided with other results that the basal value of R in the right atrium decreased in the isolated myocardium of experimentally diabetic animals (7, 9, 18, 22). On the other hand, in contrast to the present
result, Fein et al. (19) reported that the basal value of $-dF/dt$ decreased more markedly than that of $+dF/dt$ in the left ventricular papillary muscle of diabetic rats. The discrepancy between the results of Fein et al. and ours might be related to differences in experimental methods, for example, type of rat, period from streptozotocin injection to the start of experiment, temperature, glucose and calcium concentration in the medium, resting tension and/or stimulating frequency. The respective conditions employed by Fein et al. were as follows: female Wistar rats, 5–30 weeks after injection, 30°C, 5.5 mM, 0.6–2.4 mM, 1.0 g and 0.1–0.8 Hz, while we employed the following conditions: male Sprague-Dawley rats, 6 weeks after injection, 37°C, 11.0 mM, 1.25 mM, 0.3 g and 3.3 Hz.

In the present study, increases in $R$ by isoproterenol were concentration-dependent in both the control and diabetic groups, but the maximum response of $R$ was smaller in the diabetic group than in the control group. ED50 values of $R$ were not significantly different between the two groups of this study. These were in accordance with the results reported by Ramanadham and Tenner (9) and Ojewole (18) that the maximal responses of $R$ to isoproterenol or norepinephrine were smaller in diabetic animals than in control ones, but the chronotropic sensitivity of the right atrium for isoproterenol mediated by beta-receptors was not different between the control and diabetic animals. Thus, the present results concerning $R$ in the atrium of diabetic rats were almost similar to those observed in the previous studies. However, the reason for the decreased $R$ in diabetic rats was not clarified in this study.

In right ventricular papillary muscles, increases in $F$ by isoproterenol (10$^{-8}$ M–10$^{-5}$ M) tended to be smaller in the diabetic group than in the control group and increases in $+dF/dt$ and $-dF/dt$ by isoproterenol (10$^{-7}$ M–10$^{-6}$ M) were significantly less in the diabetic group than in the control group, but
ED50 values for isoproterenol were not different between the two groups in F and +dF/dt except for -dF/dt: ED50 value of -dF/dt was higher in the diabetic group than in the control group. These results show that the affinity of beta-receptors on papillary muscle for isoproterenol may not be altered between the control and diabetic states, but the relaxant velocity (-dF/dt) decreases in the diabetic state. In isolated and perfused rat hearts in our previous study (20), it was observed that the responsiveness of F to isoproterenol and norepinephrine was lower in the diabetic group than in the control group, and -dF/dt was more easily influenced by the diabetic condition, being similar to the present results. This is concomitant with the reports of Heyliger et al. (8) and Ramanadham and Tenner (9). For example, Heyliger et al. (8) have reported no alteration of affinity to beta-receptors and depression of responsiveness to beta-agonists in isolated ventricular papillary muscle from diabetic heart when compared with the results in control heart. The possibility that the lower body weight in the diabetic group may influence the depressed F and ±dF/dt is not completely denied in this study, although it has been shown that malnutrition is not the primary factor responsible for the changes in cardiac performance observed after the streptozotocin treatment in pair-fed animals (19, 23).

Thus, the present results suggest that the depressed responsiveness of diabetic hearts such as less increases in F and ±dF/dt by isoproterenol may be due to the decrease in the number of beta-adrenoceptors, while the function of receptors, at least affinity, would be intact even under the present diabetic state, judging from no change in ED50 and pA2 values of R, F and +dF/dt for isoproterenol or beta-blockers, except for the ED50 value of -dF/dt for isoproterenol. Since pA2 values in R, F and ±dF/dt were not different between the two groups, it is considered that propranolol and atenolol exert the same beta-adrenoceptor blocking potency in both diabetic and non-diabetic rat hearts.

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