Original Article

The Effects of Nicorandil and Nifekalant, Which Were Injected into the Pericardial Space, for Transmural Dispersion of Repolarization in the Pig

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Introduction: Some studies have reported that transmural dispersion of repolarization (TDR) is involved in the onset of ventricular arrhythmia. We investigated the effects of nicorandil (NIC) and nifekalant (NIF) injected into the pericardial space, on TDR and T waves in the pig. Methods and Results: We injected NIC 4 or 8 mg and NIF 50 or 100 mg at intervals into the pericardial space for eleven pigs. The effects of these drugs were investigated on the effective refractory period (ERP) between the endocardial and epicardial myocardial cells, as well as on QT time, QT peak-end (QTcpe) as an index of TDR, and T waveforms, respectively. QTcpe increased from 91 ± 21 to 116 ± 19 msec, 2.8 min after injection of NIC ($p < 0.01$), although corrected QT (QTc) interval did not changed. But 5.5 min after injection, QTc decreased while QTcpe recovered. T wave amplitude significantly increased, and epicardium ERP decreased. When NIF was injected, TDR decreased from 55 ± 10 msec to 44 ± 8 msec ($p < 0.01$) although QTc did not change. In a later phase, QTc increased ($p < 0.01$) and QTcpe recovered. T wave amplitude rapidly decreased and became negative. Conclusion: Injected into the pericardial space, NIC and NIF brought about certain changes in ERP, QT and T waveform. Furthermore, NIC increased TDR while NIF decreased TDR.
(J Arrhythmia 2007; 23: 46–57)

Key words: Transmural dispersion of repolarization, Electrophysiolosical study, Injection into pericardial space

Introduction

In recent years, some studies have reported that dispersion of repolarization time from epicardial cells to endocardial cells (transmural dispersion of repolarization; TDR) is involved in ECG changes associated with Brugada syndrome and in the onset of ventricular arrhythmia.[1–3] Short QT syndrome (SQTS) is a novel genic disorder that occurs in individuals with a structurally intact heart and

Received 9, January, 2007: accepted in final form 9, February, 2007.
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an increased susceptibility to ventricular arrhythmia and sudden death.[17] Priori et al. reported SQT3, which has a unique ECG phenotype characterized by asymmetrical T waves, and a defect in the gene coding for the inwardly rectifying Kir2.1 (I_{K1}) channel.[4,5]

Nicorandil (NIC) has been shown to open IK-ATP channels and shorten QT and effective refractory period (ERP).[6–8] Nifekalant (NIF) blocks IKr channels to extend action potential duration (APD) in a frequency-dependent manner, and this increases QT time and ERP. Recently, it has been used as a first-line drug in cardiopulmonary resuscitation.[9,10] When administered intravenously, NIF increases TDR, induces phase 2 re-entry, and causes Torsade de Pointes,[6,7] possibly because of increasing ERP in the endocardial myocardium. So, if NIF is administrated into the pericardial space, theoretically TDR may become shortened. However, to the best of our knowledge, there have been no studies into administering these drugs into the pericardial space.[11]

The purpose of this study was to investigate the effects of NIC and NIF, which were injected into the pericardial space of pigs, on the ERP of the endocardial and epicardial myocardial cells, as well as on QT time, TDR and waveforms, as measured by surface ECG. Furthermore, prevention of phase 2 re-entry by pericardial injection and reproducibility of Brugada-like and short QT syndrome-like ECG waveforms were investigated.

Subjects and Methods

Subjects were eleven female pigs aged 3–4 months and weighing 31 ± 2 kg. The following three drugs were prepared: an injection containing 50 mg or 100 mg of NIF, an injection containing 4 mg or 8 mg of NIC, and physiological saline at 37°C as control. Each drug preparation was dissolved in physiological saline at 37°C (total 5 ml) immediately before injection.

Pigs were placed in the supine position and arterial oxygen saturation was monitored. Anesthesia was induced with 5 mg/kg of xylazine and 5 mg/kg of ketamine intravenously, and maintained with inhaled 1.1%～2.7% isoflurane. Pigs were intubated and ventilated with N_2O and O_2 (1:1). The Seldinger method was employed to puncture the right internal carotid vein and both femoral veins and arteries, and a 7 or 8 French sheath was inserted into each artery and vein. Through the sheath placed in the right internal carotid vein and the left and right femoral veins, multiple electrode catheters (Boston Scientific-EP Technologies) were placed: an 8-electrode catheter in the high right atrium, an 8-electrode catheter in the right cardiac apex, and a 10-electrode catheter in the coronary sinus. In addition, from the left margin of the sternum in the fourth intercostal space, pericardiocentesis was performed using an epidural needle (17G). Small amounts of contrast media were injected through the needle as it was advanced into the pericardial space under fluoroscopic guidance. When the pericardial space was thought to be reached, a small bolus of contrast media was injected, and this was confirmed by diffusion of contrast media throughout the pericardial space. A guide wire was then passed through the needle, over which the 8F sheath was advanced. Through the sheath placed in the epicardial space, a 7 Fr electrode catheter was inserted and placed on the anterior wall side of the left ventricular epicardium under fluoroscopic guidance in order to perform the electrophysiological study (**Figure 1**).

1. Methods for drug injection

Drug injection followed the schedule shown in **Figure 1**. As a control, 10 ml of physiological saline (37°C) was injected into the pericardial space over a 30-s period, and EPS was performed starting at 1 min after the injection. The pig was monitored for 5 min after the injection, and the drug solution was eliminated. Next, after a break of about 10 min, either 4 or 8 mg of NIC was dissolved in 37°C physiological saline to bring the volume to 10 ml, and this was then injected into the epicardial space over a 30-s period. At 1 min after the end of injection, EPS was started. The pig was monitored for 10 min after the end of injection, and the drug solution was eliminated. Next, 10 ml of 37°C physiological saline was injected to wash out the epicardial cavity and was then drained. Because the half-life of NIC is short, drug effects disappeared within 10 min of draining the drug solution. Either 50 or 100 mg of NIF was then dissolved in 37°C physiological saline to bring the volume to 10 ml, and this was then injected into the epicardial space over a 30-s period. ERP measurement was initiated at 1 min after the injection. ERP was measured from both epicardial and endocardial sides at the same tame. The pig was monitored for 30 min after the end of injection, and the drug solution was then drained. During this period, surface ECG was continuously monitored. The same procedures were performed on each of the eleven pigs.

2. Observation items and test methods

1) Electrophysiological test

From each electrode catheter placed in the left

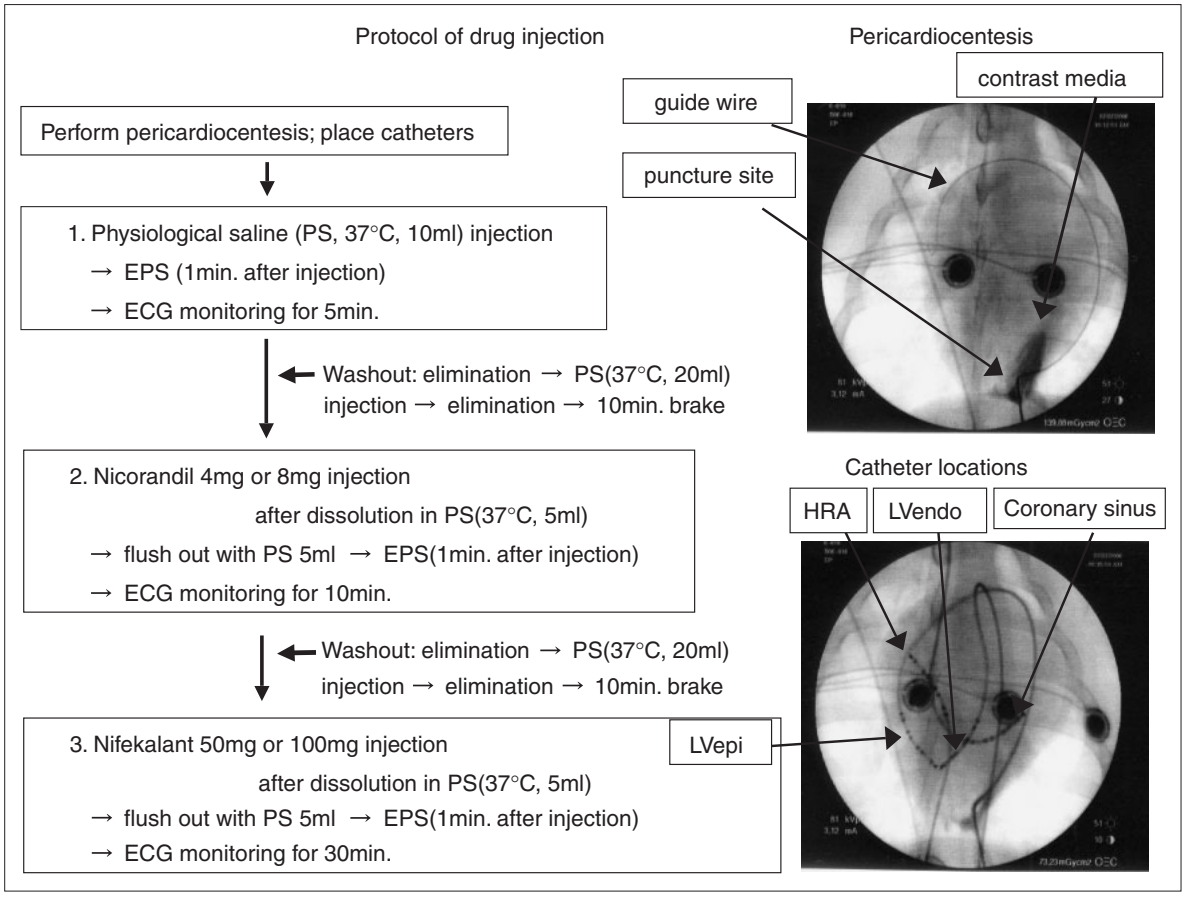

Figure 1 Drug injection protocol and catheter location.
After pericardiocentesis, catheters were located at the position of the photo.
EPS: electrophysiological study, ECG: electrocardiogram, LV (endo, epi): left ventricular (endocardium, epicardium), HRA: high right atrium

ventricular apical endocardium and epicardium, continuous stimulation with a basic cycle length (BCL) of either 400 or 500 ms was applied, and the minimal output with which the left ventricle responded was measured as the threshold value. The intensity of ventricular stimulation was twice the threshold value, and further experiments were conducted.

After delivering stimulation seven times at 400 or 500 ms BCL by the early stimulation method, the shortest interval for QRS waves in relation to single early simulation with a shortened interval was measured as ERP. Measurement was started 1 min after the injection and required about 5 min to complete. In three pigs, ERP was also measured at 8 min and 18–20 min after the injection.

2) ECG

Using Cardio Lab (GE Medical), surface 12-lead and intracardiac ECG was digitally recorded continuously. Paper speed was set at 50 mm/s with a gain of 20 mm/mV. RR interval (msec), QT time (msec) and T wave height (mV) in V1 lead were measured on the Cardio Lab screen every 30 sec from immediately before drug injection to 5 min after injection, every 1 min from 5 to 10 min after injection, every 2 min from 10 to 20 min after injection, and every 3 min from 20 to 30 min after injection. As shown in **Figure 2**, QT peak (QTp) was defined as the distance from the starting point of the QRS complex to the peak of the T wave, serving as an indicator for APD of myocardium of epicardial side. QTend (QTe) was defined as the distance from the starting point of the QRS complex to the end point of the T wave, and was measured by the tangential method, serving as an indicator for the APD of M cells distributed in the middle myocardial layer. QTpeak-end (QTpe) was defined as the distance from the peak of the T wave to the end point of the T wave, serving as an indicator for TDR.[1)]

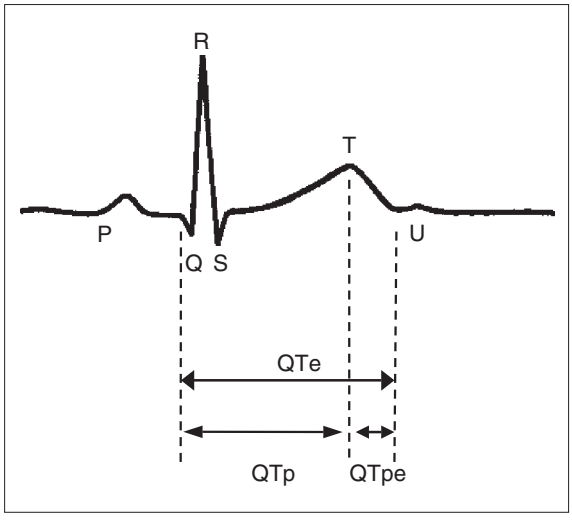

Figure 2 QRS measurement methods in V1.
QT peak (QTp) was defined as the distance from the starting point of the QRS complex to the peak of the T wave. QTend (QTe) was defined as the distance from the starting point of the QRS complex to the end point of the T wave, and was measured by the tangential method, serving as an indicator for the APD of M cells distributed in the middle myocardial layer. QTpeak-end (QTpe) was defined as the distance from the peak of the T wave to the end point of the T wave, serving as an indicator for TDR.

After correcting using Budget's formula ($QTc = QT/RR^{1/2}$), each parameter (QTcp, QTce and QTcpe) was expressed as mean ± standard deviation (SD) and was then plotted. The heart rate was close to 100 bpm while calculating. Comparison was made among four time points: (1) before injection, (2) maximum change in QTcpe after injection, (3) maximum change in QTce, and (4) end of observation.

3) Plasma concentration

Blood samples were collected at 1, 5, 10, 15, 20 and 30 min after injecting NIF, and plasma concentration was measured by HPLC (Mitsubishi BCL).

4) Ethics

The current study was performed according to the Guidelines for the Care and Use of Laboratory Animals published by the US National Institutes of Health. The study protocol was reviewed by the Committee of the Ethics on Animal Experiments of Showa University.

3. Analysis methods

Chronological changes in ERP and ECG parameters (repeated comparison to before drug injection) were analyzed, and stratified comparison (low-dose group, high-dose group, epicardium group and endocardium group) was carried out using 2-sample t-test or paired t-test. These analyses were performed with the Stat View 5J program (SAS Institute, Cary, NC). Significant differences were defined as $p < 0.05$, while $p < 0.1$ was considered to indicate a trend.

Results

1. QT time, QTc peak-end (QTcpe) in V1

When physiological saline was injected, no clear changes were seen in QTce, QTcp or QTcpe before and after injection ($p = NS$) (**Figure 3a**).

After 8 mg of NIC was injected, no significant changes were seen in either QTcp or QTce in the early phase (2.8 ± 0.7 min after injection), but QTcpe significantly increased from 91 ± 21 ms to 116 ± 19 ms ($p < 0.01$). In the later phase (5.5 ± 3.3 min after injection), QTce changed from 486 ± 34 ms (before injection) to 459 ± 23 ms ($p < 0.1$), while QTcpe recovered. 10 min after injection, QTce also recovered to 474 ± 46 ms ($p < 0.05$). When 4 mg of NIC was injected, the results were nearly the same as for an 8 mg injection (**Figure 3b**).

After 100 mg of NIF was injected, no significant changes were seen in either QTcp or QTce in the early phase (5.1 ± 2.3 min), but QTcpe significantly decreased from 56 ± 10 ms to 44 ± 8 ms ($p < 0.01$). Then, in the later phase (9.7 ± 3.0 min after injection), both QTce and QTcp significantly changed from 457 ± 44 ms and 401 ± 42 ms (before injection) to 540 ± 49 ms and 485 ± 40 ms, respectively ($p < 0.01$), but neither of the values recovered, even at 30 min after injection, while QTcpe simultaneously recovered to the control levels. When 50 mg of NIF was injected, the results were nearly the same as for a 100 mg injection (**Figure 3c**).

2. Amplitude and morphology of T wave in V1

When physiological saline was injected, T wave amplitude showed no clear changes ($p = NS$) (**Figure 4a**). When 8 mg of NIC was injected, T wave amplitude increased from 0.543 ± 0.179 mV to 0.897 ± 0.335 mV (3.5 min after injection) ($p < 0.05$), which was higher than 4 mg-injection in a dose-dependent manner (**Figures 4b and 5a**). In addition, these changes gradually recovered to pre-drug levels as measured by the changes in QTcpe. On the other hand, when 50 mg of NIF was injected, T wave amplitude decreased from 0.433 ± 0.301 mV before injection to 0.107 ± 0.192 mV at 10 min after injection ($p < 0.01$). When 100 mg of NIF was injected, T wave amplitude rapidly decreased from 0.25 ± 0.10 mV before injection to -0.01 ± 0.11 mV at 3.5 min after injection ($p < 0.01$). T wave amplitude tended to have a negative value at 4.5 min

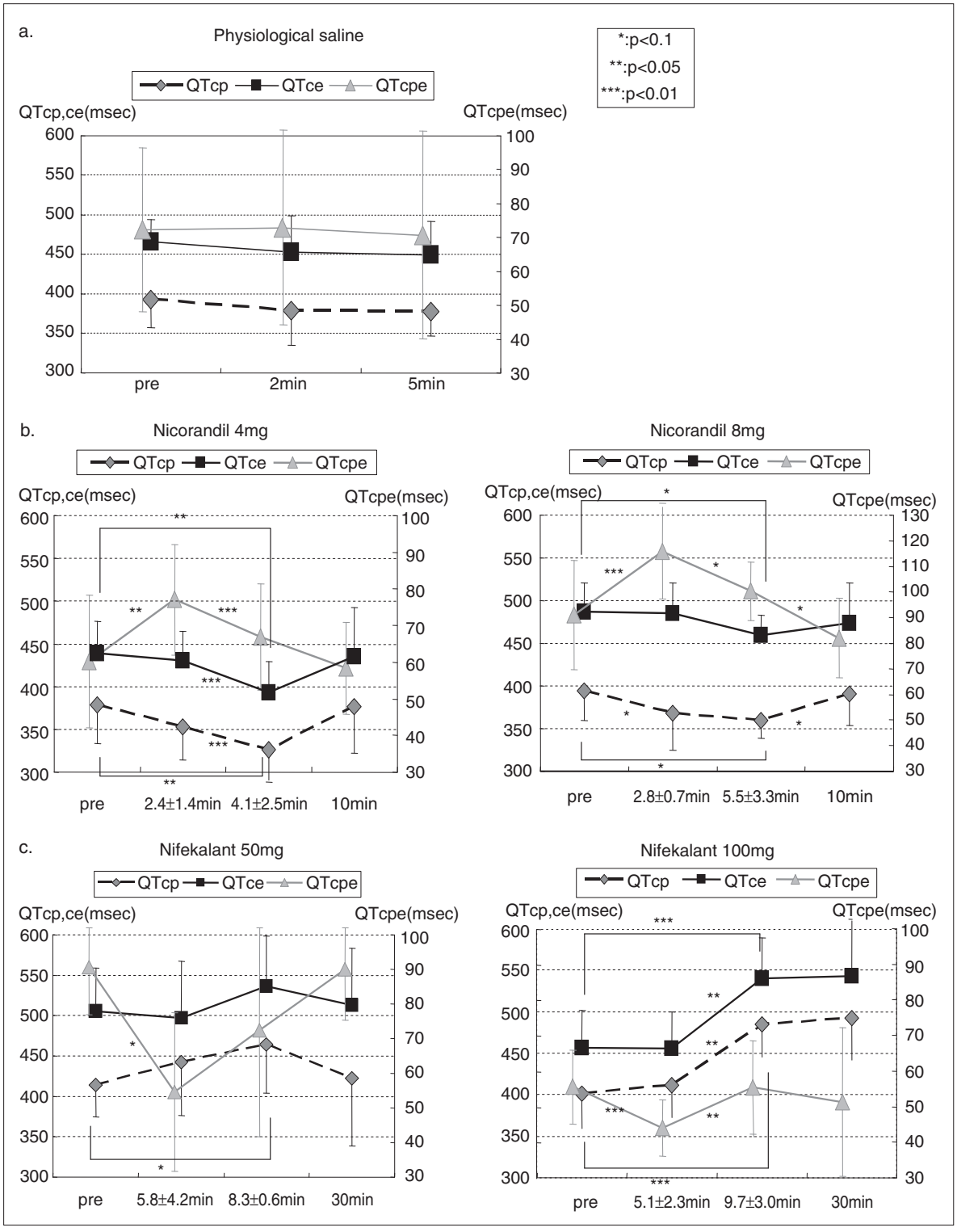

Figure 3 QTc (physiological saline, NIC and NIF).
QTcp: Corrected QT peak, QTce: Corrected QT end, and QTcpe: Corrected QT peak-end. No clear changes were seen in QTce or QTcpe before and after injection of physiological saline (p = NS). At 4.1 ± 2.5 min after injection, NIC 4 mg significantly decreased QTce and QTcp. At 9.7 ± 3.0 after NIF 100 mg injection, both QTcp and QTce increased significantly and remained high at 30 min after injection.

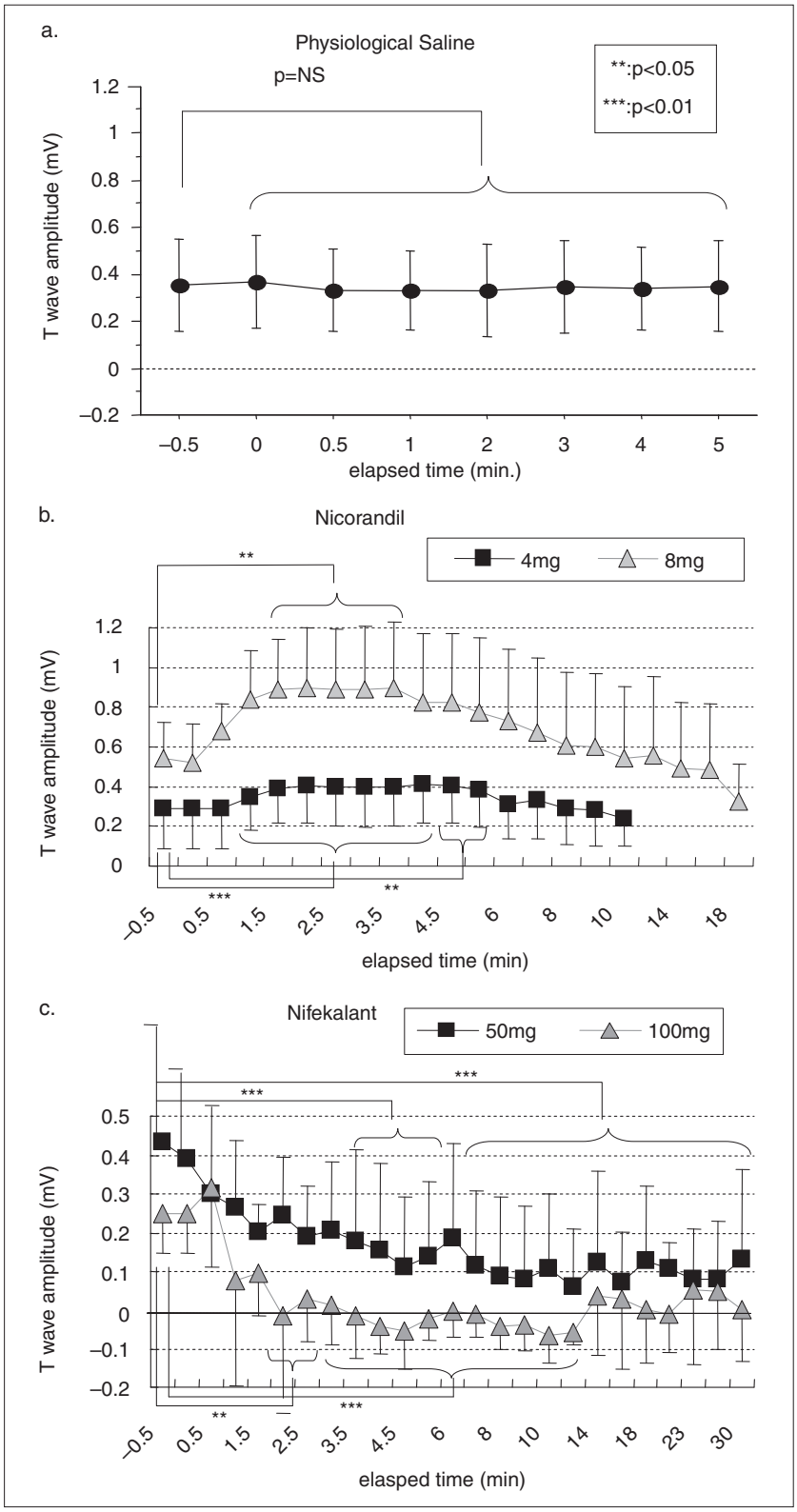

Figure 4 Time course of T wave amplitude in V1 lead (physiological saline and NIC, NIF).
Physiological saline did not cause any significant change in T wave amplitude. Starting at 30 s after NIC injection, T wave amplitude increased rapidly ($p < 0.05$) for about 3 min, after which it gradually recovered. At twice the dose, T wave amplitude increased even further. After NIF injection, T wave amplitude decreased gradually, and at 100 mg, T wave height had a negative value in some cases.

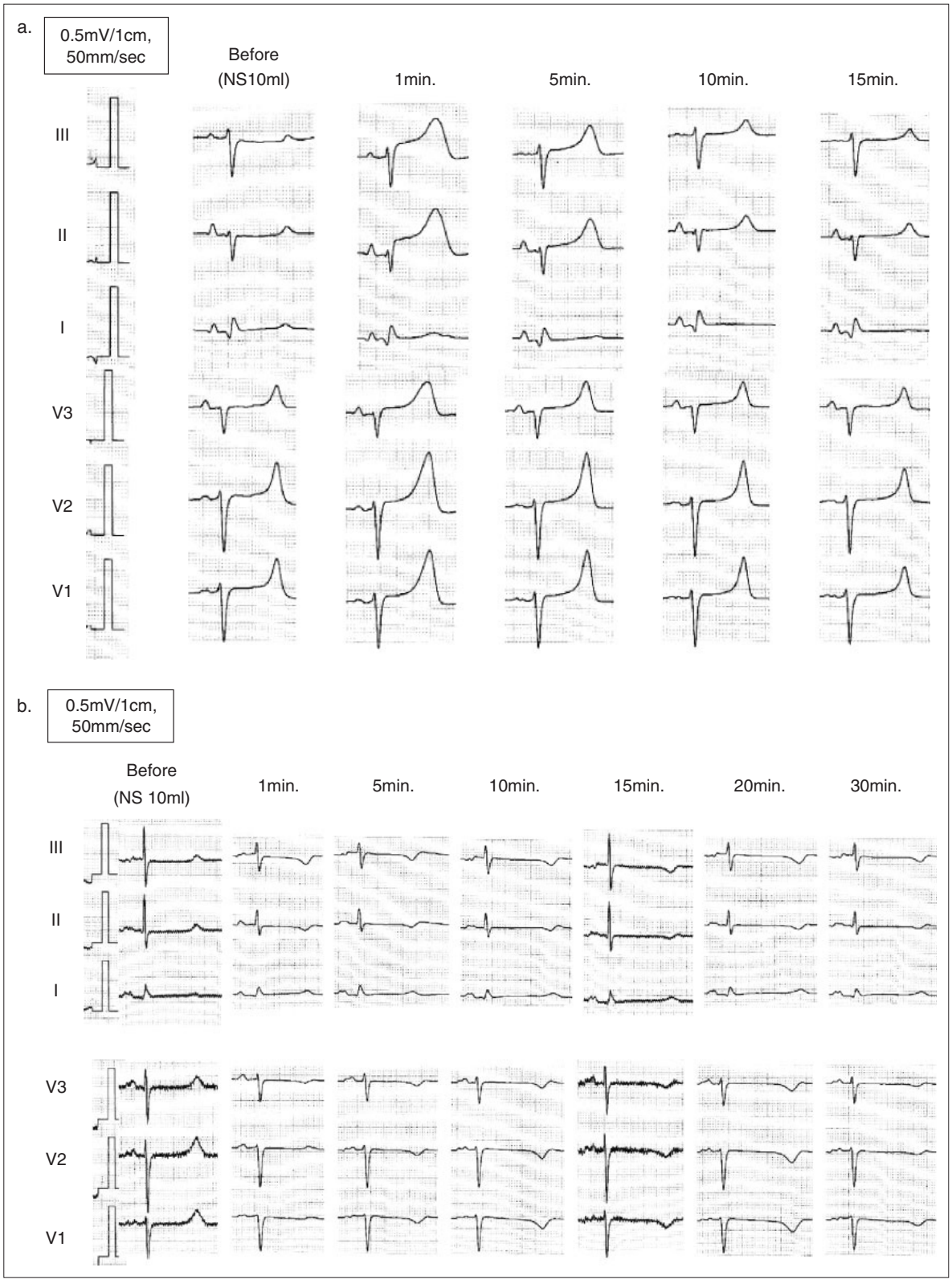

Figure 5 Time course of T wave morphology (NIC 8 mg).
a: When 4 mg of NIC was injected, T wave amplitude significantly increased (2 min after injection) ($p < 0.01$), while 8 mg of NIC increased (3.5 min after injection) ($p < 0.05$) in a dose-dependent manner.
b: T wave height amplitude rapidly decreased after injection. T wave amplitude tended to have a negative value at 4.5 min after injection.

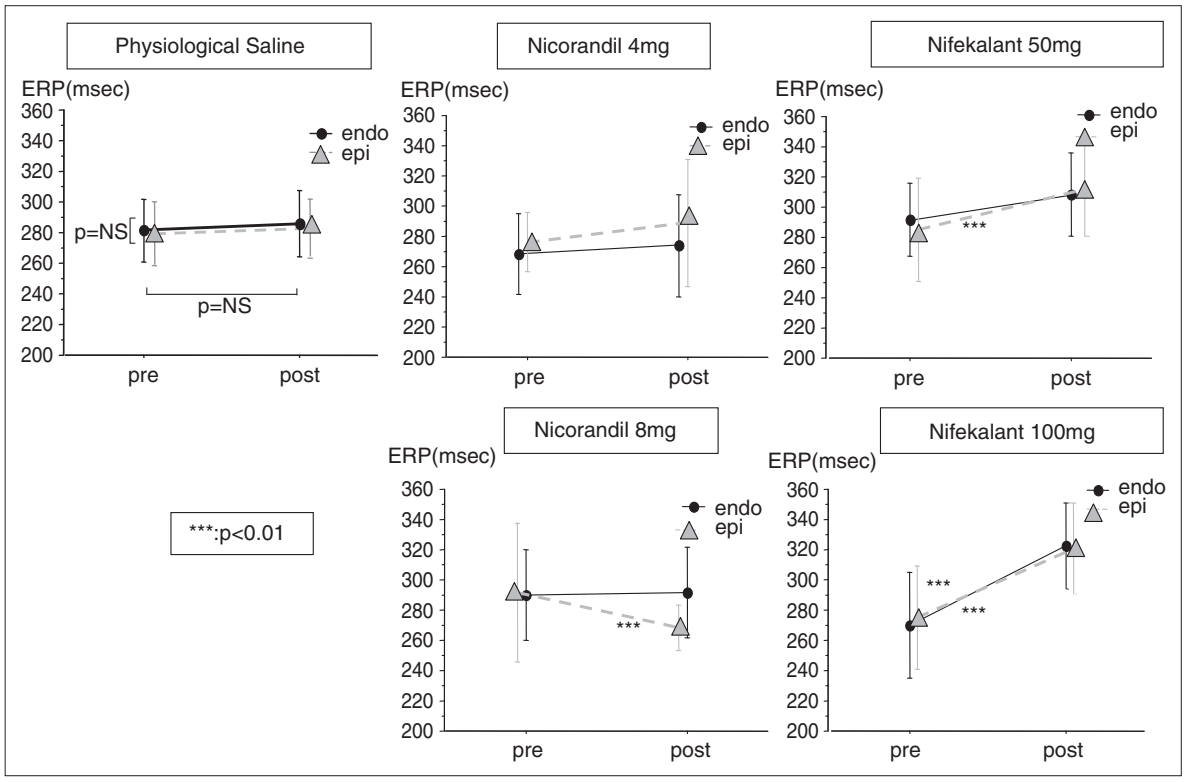

Figure 6 ERP.
ERP (physiological saline); Following physiological saline injection, no significant differences were seen in epicardial and endocardial ERP.
ERP (NIC and NIF); Following 8 mg NIC injection, ERP decreased only on the epicardial side. Following 50 mg NIF injection, ERP significantly increased only on the epicardial side. Therefore it was thought that at 1–5 min after injection, the pharmacological effects of NIC and NIF were only apparent on the epicardial side. But with a dose of 100 mg, infiltration to the endocardial side was faster, thus negating the difference between the epicardial and endocardial sides.

after injection, decreasing from 0.25 ± 0.10 mV before injection to -0.051 ± 0.10 mV (**Figures 4c and 5b**).

3. ERP

After physiological saline was injected, ERP showed no clear changes ($p = NS$) (**Figure 6**). When 8 mg of NIC was injected, ERP on the epicardial side significantly decreased from 292 ± 46 ms to 268 ± 15 ms ($p < 0.01$), although 4 mg of NIC made no significant difference. However, ERP on the endocardial side showed no clear changes ($p = NS$). After 50 mg of NIF was injected, ERP on the epicardial side increased significantly from 285 ± 34 ms to 312 ± 31 ms ($p < 0.01$). However, ERP on the endocardial side showed no clear changes, increasing slightly from 292 ± 24 ms to 308 ± 28 ms ($p = NS$).

When 100 mg of NIF was injected, ERP on both the endocardial and epicardial sides increased significantly from 270 ± 35 ms to 322 ± 28 ms and from 275 ± 34 ms to 321 ± 30 ms, respectively ($p < 0.01$).

Figure 7 shows chronological changes in ERP. When 8 mg of NIC was injected, ERP on the epicardial side decreased from 292 ± 46 ms before injection to 268 ± 15 ms at 1 min after injection ($p < 0.01$) and recovered to 290 ± 24 ms at 8 min after injection. With some delay when compared to the epicardial side, ERP on the endocardial side decreased slightly from 307 ± 25 at 1 min after injection to 293 ± 31 ms at 8 min after injection ($p < 0.1$), and then recovered to 303 ± 25 ms. When NIF was injected, ERP on the epicardial side before injection was 285 ± 34 ms, increased to 312 ± 31 ms at 1 min after injection ($p < 0.01$), and remained high for 20 min. On the endocardial side, ERP before injection was 293 ± 25 ms, and this increased to 333 ± 33 ms at 8 min after injection, which was 1 min later than the increase on the epicardial side ($p < 0.01$).

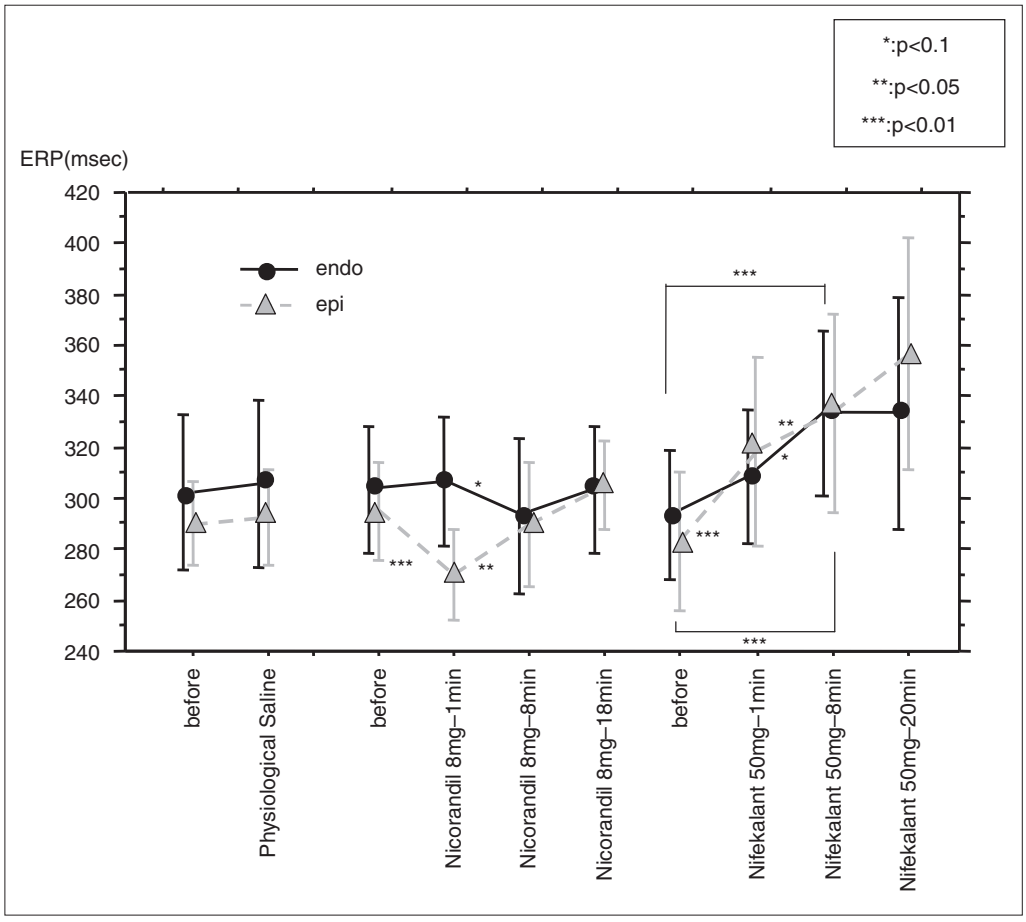

Figure 7 Time course of ERP.
With NIC, ERP decreased on the epicardial side at 1 min after injection and recovered at 8 min after injection. With some delay, a mild decrease was seen on the endocardial side at 8 min after injection, and ERP recovered at 18 min after injection. With NIF, ERP increased significantly on the epicardial side at 1 min after injection, and it remained high for 20 min after injection. On the endocardial side, a clear increase was seen at 8 min after injection.

5. Plasma concentration

Figure 8 shows shifts in the plasma concentration of NIF following intravenous administration into humans[12] and pericardial injection to pigs. When 50 mg of NIF was injected into the pericardial space of a pig, the plasma concentration of NIF at 5 min after injection was 225 ± 107 ng/ml, which was comparable to that at 5 min after intravenous injection (0.2 mg/kg) to a human. When 100 mg of NIF was injected, the plasma concentration of NIF at 5 min after injection was 419 ± 273 ng/ml, which was comparable to that at 5 min after intravenous injection (0.3 mg/kg) to a human. At these plasma concentrations, there was no significant arrhythmogenecity.

Discussion

The main findings of this study are as follows. When NIC or NIF was injected into the pericardial space, QTcpe (TDR indicator) increased or decreased in the early phase, and recovered in the later phase. This shows that both drugs were effective only on the epicardial side in the early phase, which is from 1 min to 4 min after injection for NIC and from 1 min to 8 min after injection for NIF.

When NIC was injected into the epicardium, the shape of T waves became acute in all cases, and T wave amplitude exhibited dose dependency. On the other hand, when NIF was injected, the shape of T waves edged down in a dose-dependent manner.

1. QT time and TDR

In a study using sections of arterially perfused left ventricular myocardium, Shimizu et al. reported that QTpeak, as assessed by surface ECG, represents the APD of epicardial myocardium, while QTend represents the APD of M cells (mid-myocardial cells in

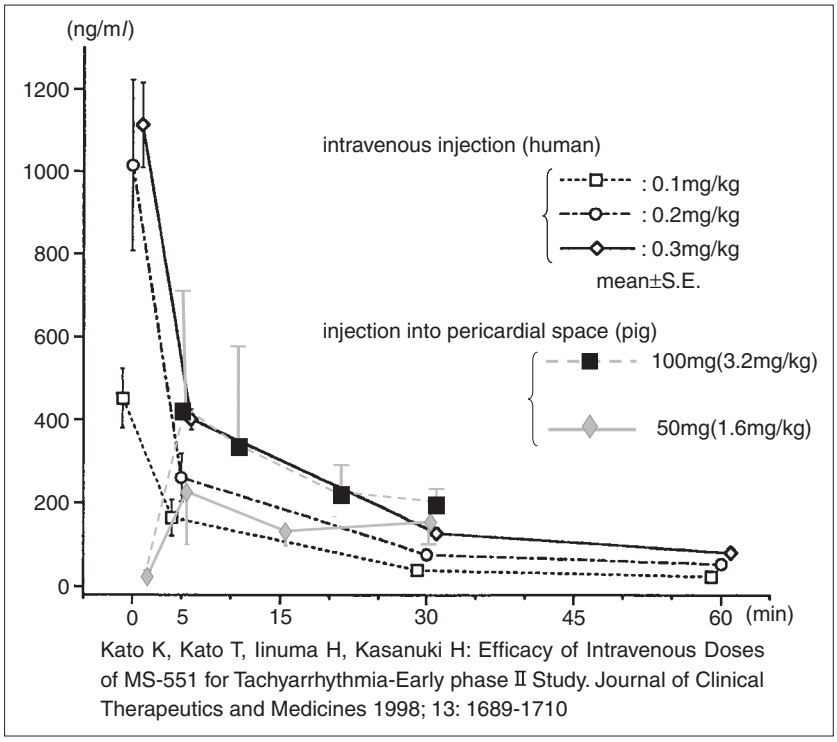

Figure 8 Plasma concentration of NIF following intravenous administration (humans) or pericardial injection (pigs).
Even when large doses of NIF are injected into the epicardium, large amounts of the drug are not transferred to the circulating blood. Furthermore, at these plasma concentrations there was no significant arrhythmogenecity.

the middle myocardial layer).[1)] They also proposed QTcpe (peak-end) as a TDR indicator, which is involved in the ECG changes associated with Brugada syndrome and in the onset of ventricular arrhythmia.[1)] In the present study, NIC increased QTcpe without changing QTce in a early phase, thus suggesting that NIC only shortened the APD of the epicardial side and quickly increased TDR. Furthermore, in a later phase, QTce also shortened, while TDR tended to recover.

On the other hand, NIF shortened QTcpe without changing QTce in an early phase, thus suggesting that NIF only increased epicardial APD and decreased TDR. Furthermore, in a later phase, QTce also increased and TDR tended to recover. These results show that injection of NIC or NIF into the pericardial space expresses their pharmacological effects over time from the epicardial myocardium to the endocardial myocardium, and the QT-decreasing or increasing effects of the present study do not contradict the results of those injected intravenously. A clinical implication which may be inferred is that an NIF injection into the epicardial side may be useful for preventing phase 2 reentry. In the future, administration of these drugs to the epicardial side during open-heart surgery or in epicardial ablation for intractable arrhythmia[13)] is also expected.

2. Amplitude and morphology of T wave

Many cases of idiopathic ventricular fibrillation (VF) in younger individuals with structurally normal hearts have been documented.[14)] Some of what was thought to be idiopathic is now better defined as specific clinical entities, such as long QT syndrome, Brugada syndrome, catecholaminergic ventricular tachycardia (VT) and short QT syndrome (SQTS).[15)] SQTS is characterized by a high incidence of syncope, sudden cardiac death and supraventricular arrhythmias, short refractory period and inducibility of VF during programmed electrical stimulation.[16)] Among the subtypes of SQTS, SQT3 (KCNSJ2) is particularly characterized by an asymmetrically shaped T wave with a rapidly descending limb, and a peculiarly tall and narrow T-wave shape.[17)] In this study, when NIC was injected into the epicardium, the shape of T waves assumed unusually tall and narrow shapes in all cases, and T wave amplitude exhibited dose dependency. As a result, short QT syndrome-3 like waveforms[17)] were seen. Furthermore the ST-segment was also elevated after injection. When NIF was injected, the shape of T waves edged down in a dose-dependent manner. Brugada syndrome is characterized by ST-segment elevation in the right precordial leads (V1–3) and an episode of VF in the absence of structural heart disease.[18)] In an experimental Brugada syndrome

model using arterially perfused right ventricular myocardial sections, pinacidil, a K^+ channel opener, enhanced ST-segment elevation.[19] It is also reported that late r′ waves and ST elevation become prominent just before VF episode in Brugada syndrome.[20] However, the mechanism responsible for ST elevation in Brugada syndrome remains unclear. Following epicardial injection of NIC, an IK-ATP channel opener, outward K^+ current in the epicardial myocardium increased, thus making ST-segment elevation more notable, in addition to the T wave changes.

3. ERP

When NIC was injected into the pericardial space, ERP decreased. This does not contradict the ERP-decreasing action of intravenous NIC. When NIF was injected into the pericardial space, ERP increased. This does not contradict the ERP-increasing action of intravenous NIF either. ERP was also measured in time intervals after NIC and NIF injection into the pericardial space, and pharmaceutical effects were seen earlier in the epicardium than in the endocardium. The results show that the pharmacological effects of NIC and NIF are only apparent on the epicardial side shortly after injection. Thus a drug injection into the pericardial space seems more effective, especially on the epicardial side, than an intravenous injection.

After 8 mg of NIC was injected, ERP significantly decreased only on the epicardial side, although 4 mg of NIC resulted in no significant changes. On the other hand, at a dose of 50 mg, NIF markedly increased ERP on the epicardial side alone, but at a dose of 100 mg, NIF increased ERP both on the epicardial and endocardial side. Above results suggested that 4 mg of NIC was too small an amount to change the ERP of both the epicardial and endocardial side, and that 100 mg of NIF was too large an amount making the infiltration from the epicardial side into the endocardial side too fast, thus no difference was seen between the epicardial and endocardial sides (**Figure 6**). It was thought that about 8 mg of NIC and about 50 mg (1.6 mg/kg) of NIF was the optimal dose.

4. Plasma concentration

At 5 min after injecting 100 mg of NIF into the pericardial space of pigs or intravenously administering 0.3 mg/kg NIF to humans, both plasma concentrations of NIF were about 400 ng/ml. The results show that NIF injected into the pericardial space moved quickly from the epicardial side to the endocardial side, and affected electrophysiological activity in the same way as did intravenous injection. In addition, it also showed that even when large doses of NIF are injected into the epicardium, large amounts of the drug are not necessarily transferred to the circulating blood.

Conclusions

When injected into the pericardial space, NIC and NIF brought about specific changes in ERP, QT and T waveform. Furthermore, NIC increased TDR, while NIF decreased TDR.

Limitations

Although the result of this study suggested the usefulness of epicardial administration of NIC and NIF for ventricular arrhythmia, certain study limitations must be noted. First, the number of subjects was limited. Second, it has not been confirmed that the clinical effects of NIC and NIF to pigs can be applied to human beings. We are planning to continue to evaluate the significance of this finding by increasing the number of subjects.

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