Cilostazol, which has potent cyclic nucleotide phosphodiesterase type-3 inhibitory activity, was approved for marketing in Japan in 1988 as an antiplatelet agent to improve ischemic symptoms, such as pain and cold sensation, that were caused by chronic arterial occlusive diseases. In 1999, this agent was approved by the US Food and Drug Administration for the treatment of intermittent claudication. Cilostazol inhibits human platelet aggregation by potent cyclic nucleotide phosphodiesterase type-3 inhibitory activity.
does not interrupt the adhesion of platelets to the vascular wall at the initial step in thrombus formation. Thus, it has been thought that cilostazol is less likely to cause a tendency for bleeding. After treatment with cilostazol, bleeding time is not noticeably prolonged.

It has been demonstrated that cilostazol has positive chronotropic and dromotropic effects in patients with supraventricular bradycardia, such as those with sick sinus syndrome, and in those patients with Wenckebach-type atrioventricular block. However, there have been no reports on the effects of cilostazol on atrioventricular conduction or on the QRS rate of the escape pacemaker in patients with third-degree atrioventricular block. This prospective, but nonrandomized, study was designed to assess whether the administration of oral cilostazol can affect the ventricular escape rate and neurohumoral factors in patients with third-degree atrioventricular block.

**Materials and Methods**

**Patient Population**

Twenty-two consecutive patients with idiopathic third-degree atrioventricular block who were admitted to our hospital between April 1998 and March 2001 were screened for enrollment in this study. Atrioventricular block was labeled as idiopathic when there were no diseases that could precipitate atrioventricular block, such as inflammatory or infiltrative disease, cardiac tumors, toxicity of drugs (particularly His-Purkinje system depressant drugs, such as those for arrhythmia) or electrolyte (particularly potassium) disturbances. The following studies were performed as a baseline: (1) physical examination, including measurement of the BP at rest with the patient in a supine position; (2) standard 12-lead ECG and continuous 24-h ECG monitoring; (3) chest radiograph; (4) blood tests; (5) echocardiography; and (6) His bundle recording.

Patients were selected for this study if they had experienced subjective symptoms that were attributable to third-degree atrioventricular block at the intra-His or infra-His levels. However, patients with dyspnea, which is indicative of functional class IV of the New York Heart Association (NYHA) classification, and syncope were not included. Patients with prior myocardial infarction, atrial fibrillation/flutter, other significant heart diseases (eg, valvular or congenital heart disease), or renal dysfunction with serum creatinine levels of >1.5 mg/dL, also were excluded.

In 7 of 22 patients, it was necessary to insert a temporary transvenous right ventricular pacemaker just after hospital admission because of recurrent Adams-Stokes attacks or severe dyspnea that was indicative of functional class IV of the NYHA classification. These seven patients were excluded from this study. Similarly, oral or IV administration of β-adrenergic receptor agonists (eg, isoproterenol), adenosine-receptor antagonists (eg, theophylline), and vagolytic agents (eg, atropine) were given to three other patients who had near-syncope or pulmonary congestion with pleural effusion that was attributable to third-degree atrioventricular block. These three patients also were excluded from the study. Five of the remaining 12 patients, who had already been treated with these drugs for >1 week at the time of hospital admission, were included in this study. The remaining seven patients had received no drugs that had chronotropic effects. Ultimately, 12 patients (five men and seven women; mean [± SD] age, 79 ± 3 years; range, 58 to 92 years) formed the study group. Eligible patients provided written informed consent.

**Study Protocol**

Cilostazol, 100 mg twice daily, was given orally to all patients for a minimum of 1 week (mean duration, 2.9 ± 1.0 weeks; range, 1 to 12 weeks). Data for the following variables that were obtained at the initial examination were used as follow-up variables after treatment with cilostazol: chest radiograph cardiothoracic ratio; standard 12-lead ECG and 24-h ECG findings; concentrations of plasma natriuretic peptides; and the percentage of fractional shortening (FS) assessed by echocardiography.

It has been reported that an increase in plasma natriuretic peptide concentrations may represent a compensatory mechanism to the hemodynamic disadvantage of atrioventricular asynchrony, such as ventricular pacing in patients with third-degree atrioventricular block. Therefore, we selected plasma natriuretic peptide concentrations as follow-up variables in this study. Blood samples were collected after the patients had rested in a supine position for at least 15 min, and concentrations of plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were measured with a commercial kit (Sumitomo Laboratory: Tokyo, Japan). In addition, plasma renin activity (PRA) and concentrations of plasma aldosterone, epinephrine, and norepinephrine were measured with the same commercial kit. The laboratory reference ranges for these concentrations are as follows: plasma ANP, <430 pg/mL; plasma BNP, <18.4 pg/mL; PRA, 0.3 to 2.9 ng/mL/L; plasma aldosterone, 30 to 159 pg/mL; plasma epinephrine, <80 pg/mL; and plasma norepinephrine, 90 to 420 pg/mL.

We obtained continuous 24-h ECG recordings using modified V1 and V5 leads. Because bipolar leads were used, the output was the potential difference between positive and negative inputs. The positive electrodes were placed in the conventional positions of V1 and V5 for modified V1 and V5 leads, respectively. The negative electrode was placed on the upper end of the sternum. Maximum heart rate, mean heart rate, minimum heart rate, maximum R-R interval over a period of 24 h, 24-h total QRS counts, and 24-h total counts of premature ventricular complexes were assessed.

Two-dimensionally targeted, M-mode echocardiographic studies were carried out with the subjects in the left lateral decubitus position. To measure the left ventricular cavity and wall thickness, an M-mode scan of the left ventricle with the ultrasound beam aimed just below the tips of the mitral valve leaflets was recorded on strip chart paper. The following variables were measured according to the American Society of Echocardiography and Penn conventions: left ventricular end-diastolic volume, left ventricular end-systolic volume, left ventricular ejection fraction, left ventricular fractional area change, left ventricular mass, and left ventricular mass index. The output was the potential difference between positive and negative inputs. The positive electrodes were placed in the conventional positions of V1 and V5 for modified V1 and V5 leads, respectively. The negative electrode was placed on the upper end of the sternum. Maximum heart rate, mean heart rate, minimum heart rate, maximum R-R interval over a period of 24 h, 24-h total QRS counts, and 24-h total counts of premature ventricular complexes were assessed.

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% FS (%) = 100 × (LVEDD − LVESD) / LVEDD,

where LVEDD is the left ventricular end-diastolic dimension, and LVESD is the left ventricular end-systolic dimension. His bundle recordings were performed to delineate the site of atrioventricular block. The multipolar electrode catheter was inserted into the right femoral vein and was advanced fluoroscop-
ically across the tricuspid valve into the right ventricle. Then, the catheter was slowly pulled back until potentials of right atrium, His bundle, and right ventricle appeared. When the His deflection did not follow the atrial deflection, but preceded the ventricular deflection, a block site was defined as the supra-His level. When the His deflection followed the atrial deflection, but did not precede the ventricular deflection, a block site was defined as the infra-His level. When His deflections were split into two parts, that is, when the first His deflection followed the atrial deflection, and the second one preceded the ventricular deflection, a block site was defined as the intra-His level.

Statistical Analysis

All data were tested for normality with the Shapiro-Wilks statistic. The distribution of the maximum R-R interval over a 24-h period, the 24-h total count of premature ventricular beats, and the plasma concentrations of neurohumoral factors was skewed but approximated well to a normal distribution following logarithmic transformation. The data are expressed as the mean ± SEM, unless otherwise specified. For logarithmically transformed variables, geometric means (95% confidence intervals [CIs]) were used. Data comparisons were made with paired or nonpaired Student t tests when appropriate. In addition, simple linear regression analysis was performed to describe the relationship between the change in the P (atrial) rate and the change in the QRS (ventricular) rate in response to the administration of oral cilostazol. All tests were two-tailed, and a p value of < 0.05 was assumed to represent statistical significance. The maximum R-R intervals over a 24-h period before the administration of cilostazol for patients 2 and 10 were 15,600 ms and 10,500 ms, respectively. These data were well outside the range of the distribution for the other 10 patients, when outlying observations were tested with the Smirnov-Grubbs statistic. We therefore excluded these data from the analysis.

RESULTS

Baseline Characteristics

Of 12 patients, 6 had cardiovascular diseases that required drug therapy (hypertension, 4 patients; hypertension and vasospastic angina pectoris, 1 patient; and stroke, 1 patient). The period between the onset of third-degree atrioventricular block and treatment with oral cilostazol ranged from 1 to 208 weeks. Before treatment with cilostazol, oral β-adrenergic receptor agonists were administered to five patients. Three of these patients received adenosine-receptor antagonists orally. These drugs were administered before hospital admission. Eight patients were in functional NYHA class II, and four patients were in functional NYHA class III. Six patients had block sites at intra-His levels, whereas the other six had block sites at infra-His levels. The details of the baseline clinical characteristics are shown in Table 1.

The Effects of Cilostazol on Standard 12-Lead ECG and Holter Monitoring Data

During the administration of cilostazol, none of the patients required the insertion of a temporary transvenous right ventricular pacemaker or the new administration of β-adrenergic receptor agonists, phosphodiesterase inhibitors other than cilostazol, or vagolytic agents because of uncontrollable heart failure or Adams-Stokes attacks.

There was a significant positive linear correlation between the change in P rate and the change in QRS rate on the standard 12-lead ECG in response to oral cilostazol (r = 0.59; p = 0.04) [Fig 1]. Patients 2 and 10, in whom long ventricular standstill (ie, a maximum R-R interval of > 10 s before treatment with cilostazol) had been seen, were not excluded from the study because the long ventricular standstill had developed during sleep and, therefore, did not produce an Adams-Stokes attack. In 5 of 12 study patients, atrioventricular synchrony, which was dis-

<table>
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<th>Patient/Age, y/Sex</th>
<th>Block Site</th>
<th>NYHA Functional Class</th>
<th>Period Between Onset and Treatment, wk</th>
<th>β-Adrenergic Receptor Agonists</th>
<th>Adenosine-receptor Antagonists</th>
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* = male; F = female.
cerned by baseline Holter monitoring data analysis, was seen transiently before treatment with cilostazol. On follow-up Holter monitoring, the duration of the synchrony was prolonged in three of the patients and remained unchanged in one of the patients after treatment with cilostazol. In the fifth patient, atrioventricular synchrony disappeared after treatment with cilostazol. Of the seven patients with no atrioventricular synchrony documented on baseline Holter monitoring before treatment with cilostazol, synchrony was transiently obtained after treatment with cilostazol in only one patient and was not obtained at all in the remaining six patients. None of the patients showed abolishment of the atrioventricular conduction abnormality.

Overall, cilostazol significantly increased the mean total 24-h QRS count from 57,300 ± 2,800 to 74,400 ± 3,200 beats (p = 0.001), as is shown in Figure 2. The mean heart rate (before treatment, 41 ± 2 beats/min; after treatment, 50 ± 2 beats/min; p = 0.0005) and minimum heart rate (before treatment, 30 ± 3 beats/min; after treatment, 40 ± 2 beats/min; p = 0.0006) significantly increased after treatment with oral cilostazol, whereas maximum heart rate did not change (before treatment, 61 ± 4 beats/min; after treatment, 75 ± 7 beats/min; p = 0.09). On the other hand, the maximum R-R interval over a 24-h period decreased significantly from 1,900 ms (95% CI, 1,700 to 2,100 ms) to 1,600 ms (95% CI, 1,400 to 1,900 ms; p = 0.02) [Fig 3]. The total 24-h count of premature ventricular beats did not change (before treatment, 15 beats [95% CI, 5 to 44 beats]; after treatment, 12 beats [95% CI, 5 to 30 beats]; p = 0.57). Representative 24-h heart-rate trendgrams are shown in Figures 4 and 5.

In seven patients who did not receive any drugs before cilostazol administration, cilostazol significantly increased the mean total 24-h QRS count from 59,400 ± 3,700 to 76,600 ± 3,600 beats (p = 0.03). The mean heart rate (before treatment, 41 ± 3 beats/min; after treatment, 49 ± 3 beats/min; p = 0.02) and the minimum heart rate (before treatment, 30 ± 3 beats/min; after treatment, 37 ± 2 beats/min; p = 0.003) also significantly increased after treatment with oral cilostazol, whereas the maximum heart rate did not change (before treatment, 65 ± 6 beats/min; after treatment, 85 ± 10 beats/min; p = 0.17). The maximum R-R interval over a 24-h period decreased from 2,000 ms (95% CI, 1,700 to 2,500 ms) to 1,800 ms (95% CI, 1,400 to 2,200 ms), but this difference was not statistically significant (p = 0.12). Also, the total 24-h count of premature ventricular beats was not different (before treatment, 14 beats [95% CI, 2 to 96 beats]; after treatment, 8 beats [95% CI, 2 to 30 beats]; p = 0.30). In the remaining five patients, who had received drugs > 1 week before the administration of cilostazol, cilostazol significantly increased the mean total 24-h QRS count from 55,800 ± 4,900 to 71,300 ± 5,900 beats (p = 0.01). The mean heart rate (before treatment, 41 ± 3 beats/min; after treatment, 51 ± 5 beats/min; p = 0.04) and minimum heart rate (before treatment, 29 ± 7 beats/min; after treatment, 43 ± 5 beats/min; p = 0.02) also signifi-
Significantly increased after treatment with oral cilostazol, whereas the maximum heart rate did not change (before treatment, 54 ± 2 beats/min; after treatment, 62 ± 6 beats/min; p = 0.31). The maximum R-R interval over a 24-h period decreased from 1,800 ms (95% CI, 1,300 to 2,500 ms) to 1,400 ms (95% CI, 1,000 to 1,900 ms), but the difference just failed to reach statistical significance (p = 0.06). The total 24-h count of premature ventricular beats did not change (before treatment, 18 beats [95% CI, 7 to 49 beats]; after treatment, 23 beats [95% CI, 5 to 106 beats]; p = 0.75).

The Effects of Cilostazol on the Concentrations of Plasma Natriuretic Peptides

As shown in Figures 6 and 7, the oral administration of cilostazol significantly decreased the concentration of plasma ANP from 88 pg/mL (95% CI, 49 to 160 pg/mL) to 51 pg/mL (95% CI, 32 to 80 pg/mL; p = 0.007) and decreased the concentration of BNP from 166 pg/mL (95% CI, 71 to 389 pg/mL) to 77 pg/mL (95% CI, 30 to 178 pg/mL; p = 0.02).

Four patients were classified into a good-response group according to Holter monitoring data, as mentioned above. Three of the patients were those who had experienced transient atrioventricular synchrony before treatment with cilostazol, which improved after treatment. One of the patients experienced atrioventricular asynchrony before treatment with cilostazol and experienced a transient synchrony after treatment with cilostazol. The eight remaining patients were classified as the poor-response group. In the good-response group, oral cilostazol administration decreased the concentration of plasma ANP from 80 pg/mL (95% CI, 9 to 728 pg/mL) to 34 pg/mL (95% CI, 11 to 99 pg/mL) and the concentration of BNP from 127 pg/mL (95% CI, 6 to 2,980 pg/mL) to 33 pg/mL (95% CI, 3 to 402 pg/mL). However, these differences were not significant (p = 0.17 and p = 0.16, respectively). On the other hand, in the poor-response group, oral cilostazol administration significantly decreased the concentration of plasma ANP from 93 pg/mL (95% CI, 51 to 171 pg/mL) to 62 pg/mL (95% CI, 39 to 97 pg/mL; p = 0.003), and the concentration of BNP from 189 pg/mL (95% CI, 79 to 451 pg/mL) to 110 pg/mL (95% CI, 34 to 301 pg/mL; p = 0.03).

The differences in the concentrations of plasma ANP and BNP before and after the administration of cilostazol were greater in the good-response group than in the poor-response group, but these differences were not statistically significant (p = 0.15 and p = 0.22, respectively).
Other Follow-up Variables

The mean systemic systolic BP tended to decrease after treatment with oral cilostazol (before treatment, 152 ± 6 mm Hg; after treatment, 146 ± 7 mm Hg), but this difference was not statistically significant (p = 0.13). Oral cilostazol did not change the chest radiograph cardiothoracic ratio (before treatment, 53 ± 2%; after treatment, 54 ± 2%; p = 0.55), or the percentage of FS assessed by echocardiography (before treatment, 44 ± 1%; after treatment, 43 ± 1%; p = 0.27). In addition, PRA and concentrations of plasma aldosterone, epinephrine, and norepinephrine did not change after the administration of cilostazol. PRA was 0.7 ng/mL/h (95% CI, 0.3 to 1.7 ng/mL/h) before treatment vs 1.4 ng/mL/h (95% CI, 0.8 to 2.5 ng/mL/h) after treatment (p = 0.07). The aldosterone concentration was 36.3 pg/mL (95% CI, 30.0 to 43.9 pg/mL) before treatment vs 37.4 pg/mL (95% CI, 22.0 to 63.4 pg/mL) after treatment (p = 0.93). The epinephrine concentration was 38.0 pg/mL (95% CI, 22.4 to 64.4 pg/mL) before treatment vs 33.6 pg/mL (95% CI, 23.5 to 48.1 pg/mL) after treatment (p = 0.68).

Figure 4. Twenty-four-hour heart rate trendgrams obtained from patient 5 before treatment (top) and after treatment (bottom) with cilostazol. The heart rate was almost constant throughout the day both before and after treatment, although cilostazol administration increased the heart rate by about 10 beats/min. The constant heart rate was due to third-degree atrioventricular block with neither the abrupt cessation of escape beats nor atrioventricular synchrony.

Figure 5. Twenty-four-hour heart-rate trendgrams before treatment (top) and after treatment (bottom) with cilostazol that were obtained from patient 7. The heart rate was constant and was around 30 beats/min at baseline. After treatment, atrioventricular synchrony was seen between 4:00 PM (hour 16) and 4:00 AM (hour 4), and between 1:00 PM (hour 13) and 4:00 PM (hour 16). During these periods, the heart rate increased.
Finally, the norepinephrine concentration was 429.4 pg/mL (95% CI, 295.2 to 624.6 pg/mL) before treatment vs 484.8 pg/mL (95% CI, 349.2 to 673.0 pg/mL) after treatment (p = 0.57).

Permanent Pacemaker Implantation

Ultimately, 9 of the 12 patients underwent permanent pacemaker implantation without discontinuing cilostazol therapy, just after post-cilostazol administration tests were performed. No bleeding complications were seen during surgery. The remaining three patients did not undergo pacing therapy because of dementia (two patients) or poor general condition (one patient). They continued receiving cilostazol in addition to β-adrenergic receptor agonists and adenosine-receptor antagonists. Patient 1 died of aspiration pneumonia 4 months after receiving treatment with oral cilostazol. Patient 8 died suddenly 9 months after receiving treatment with oral cilostazol. The remaining patient (patient 5) was alive and had been receiving cilostazol therapy for 12 months at the time of the last follow-up. No exacerbation of heart failure or occurrence of Adams-Stokes attacks was seen in the three patients who did not undergo pacing therapy. The third patient was in functional NYHA class I, although he was not very active.

**Discussion**

This study demonstrated that the short-term administration of cilostazol accelerated the rate of escape rhythms in patients with third-degree atrioventricular block, although none of the patients showed abolishment of the atrioventricular conduction abnormality. In addition, it was shown that the drug decreased the concentrations of plasma natriuretic peptides.

**Therapy for Third-Degree Atrioventricular Block**

With advances in cardiac pacemaker technology and the establishment of the therapeutic benefits of cardiac pacing, permanent pacemaker implantation has become the first-line treatment for patients with symptomatic third-degree atrioventricular block. However, careful consideration should be given to performing this operation in patients with coexisting dementia or poor general condition, such as the three patients who did not undergo permanent pacing.

In patients with idiopathic third-degree atrioventricular block at intra-His or infra-His levels, drug therapy is not expected to improve atrioventricular conduction sufficiently. Oral, or preferably IV, cate-
cholamine agents, such as isoproterenol, may be used to accelerate the impulse of the escape pacemaker in these patients, but it cannot be relied on for more than a few hours or days without producing significant side effects. Generally, these drugs are used for short-term therapy until adequate pacing therapy can be established. The insertion of a temporary transvenous pacemaker as a bridge to permanent pacing is the most effective strategy. However, such intervention is invasive. Moreover, the insertion of a temporary transvenous pacemaker often requires patients to stay in bed until the implantation of a permanent pacemaker. Bed rest should be avoided, particularly in the elderly, as it can lead to complications like disuse muscle atrophy, pulmonary thromboembolism, and delirium.

**Effects of Cilostazol on Atrioventricular Conduction and the Escape Pacemaker**

In anesthetized dogs, cilostazol increases heart rate and decreases BP dose-dependently. In humans, cilostazol produces a significant increase in heart rate. It has been demonstrated that cilostazol has positive chronotropic effects in patients with sick sinus syndrome and has positive dromotropic effects in those with Wenckebach second degree atrioventricular block.

In this study, cilostazol administration accelerated the rate of the escape rhythm, although the atrioventricular conduction abnormality was not abolished in any of the patients. By contrast, cilostazol administration significantly decreased the maximum R-R interval over a 24-h period, even in two patients with a maximum R-R intervals of > 10 s. The total 24-h count of premature ventricular beats did not change after treatment with oral cilostazol. Furthermore, no bleeding complications were seen during surgery in patients who underwent permanent pacemaker implantation without discontinuing cilostazol. The incidence of adverse events requiring the discontinuation of cilostazol is very low in general. Thus, cilostazol could be safely given to selected patients with third-degree atrioventricular block over the short term.

In patients with symptomatic third-degree atrioventricular block at intra-His or infra-His levels, a rapid increase in QRS rate often is needed. Niki and Mori demonstrated that the rapid onset of action of oral cilostazol is advantageous. In humans, cilostazol is promptly absorbed, with a maximum plasma concentration observed 3 to 4 h after oral administration. The heart rate increases within 6 h of the administration of oral cilostazol, although this is too long a delay for patients with symptomatic third-degree atrioventricular block. None of the patients included in this study required chronotropic support, even during this period. Therefore, there may have been a bias due to flaws in the study design or patient selection. However, cilostazol might make invasive and risky procedures, such as temporary pacing, unnecessary until permanent pacemaker implantation in some patients with symptomatic third-degree atrioventricular block at intra-His or infra-His levels. In addition, the usefulness of cilostazol in accelerating the rate of the escape rhythm may allow more time to evaluate the need for permanent pacing, although resolution of the symptoms caused by atrioventricular block must be observed.

Cilostazol augments the increased beating rate of isoproterenol-treated isolated guinea pig atria. In this study, five patients had received β-adrenergic receptor agonists before the administration of cilostazol. In these five patients, cilostazol increased the total 24-h QRS count. Thus, cilostazol may be considered as an alternative or a supplement when front-line drug therapy for chronotropic support, such as the administration of β-adrenergic receptor agonists, is insufficient.

The long-term effects of cilostazol on the escape pacemaker in patients with third-degree atrioventricular block were not investigated in this study, although 3 of the 12 patients took the drug for at least 4 months. If cilostazol effectively resolved the symptoms caused by third-degree atrioventricular block for a long period of time, as was the case in patient 5, cilostazol administration would obviate the need for permanent pacemaker implantation, particularly in patients with coexistent dementia or those in poor general condition. The long-term chronotropic or dromotropic effects of cilostazol in patients with third-degree atrioventricular block must be clarified.

**Effects of Cilostazol on Plasma Levels of Natriuretic Peptides**

In patients with third-degree atrioventricular block, an increase in plasma ANP concentrations is mainly caused by the increased atrial wall stretch that results from the occurrence of atrial systole during ventricular systole and from the increased cardiac preload due to marked bradycardia. It is thought that ANP release provides a mechanism for compensating for the hemodynamic disadvantage of atrioventricular asynchrony through its ability to promote sodium and water excretion, to reduce systemic and pulmonary vascular resistance, and to modulate volume-regulating hormones. On the other hand, it has been shown that atrial contraction against closed mitral valves leads to left atrial distension and increased pulmonary vascular pressure, which affects the right ventricle and results in the release of BNP. In addition, BNP might be cosecreted with ANP in response to the same stimuli.
In this study, the short-term administration of cilostazol significantly decreased the concentrations of plasma ANP and BNP, although Vardas et al. have reported that short-term ventricular demand pacing, which increases the QRS rate but leaves atrioventricular asynchrony, does not change the concentration of ANP. In 4 of 12 patients whose atrioventricular synchrony improved transiently in response to oral cilostazol administration, the transient atrioventricular synchrony might have slightly decreased the atrial wall stretch and might have led to a decrease in the plasma levels of natriuretic peptides. On the other hand, even in the remaining eight patients in whom atrioventricular synchrony was not attained, was worsened, or remained unchanged, oral cilostazol significantly decreased the concentration of plasma natriuretic peptides. In these patients, volume expansion as a hemodynamic disadvantage of both atrioventricular asynchrony and slow escape rhythms might have been partially improved by an increased escape rhythm in response to the administration of oral cilostazol. This might have resulted in decreased plasma levels of natriuretic peptides. Further studies using a larger number of patients are needed to clarify the physiologic role of natriuretic peptides under these circumstances.

Study Limitations

This study has some limitations. First, the sample size was very small. Second, improvements in subjective symptoms were not followed, because the observation period was short in most patients studied. In addition, exercise-tolerance testing was not performed, because exercise worsens intra-His or infra-His atrioventricular block. Third, 3 of the 12 study patients did not undergo permanent pacemaker implantation. Fourth, neither patients who were in functional NYHA class IV nor those who had experienced Adams-Stokes attacks were included. Fifth, coronary angiography was performed only in two study patients, who had no atherosclerotic luminal narrowing in the epicardial coronary arteries. Another limitation of this study was that bleeding time was not investigated.

Conclusions

In patients with third-degree intra-His or infra-His atrioventricular block who were in functional NYHA class II or III and had not experienced Adams-Stokes attacks, the impulse of the escape pacemaker was increased and was made stable after treatment with oral cilostazol. Together with these findings, cilostazol significantly decreased the level of circulating natriuretic peptides. Thus, cilostazol could be safely given to selected patients with third-degree atrioventricular block over the short term.

References