Original Article

Long-Term Oral Administration of Dipyridamole Improves Both Cardiac and Physical Status in Patients with Mild to Moderate Chronic Heart Failure: A Prospective Open-Randomized Study

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Adenosine is known as an endogenous cardioprotectant. We previously reported that plasma adenosine levels increase in patients with chronic heart failure (CHF), and that a treatment that further elevates plasma adenosine levels may improve the pathophysiology of CHF. Therefore, we performed a prospective, open-randomized clinical trial to determine whether or not exposure to dipyridamole for 1 year improves CHF pathophysiology compared with conventional treatments. The study enrolled 28 patients (mean±SEM: 66±4 years of age) attending specialized CHF outpatient clinics with New York Heart Association (NYHA) class II or III, no major complications, and stable CHF status during the most recent 6 months under fixed medications. They were randomized into three groups with or without dipyridamole (Control: $n=9$; 75 mg/day: $n=9$; 300 mg/day: $n=10$) in addition to their original medications and were followed up for 1 year. The other drugs were not altered. Among the enrolled patients, 100%, 4%, 100%, and 79% received angiotensin-converting enzyme inhibitors, aldosterone analogue, loop diuretics, and β-adrenoceptor blocker, respectively. Fifteen patients suffered from dilated cardiomyopathy, and 7/3/3 patients suffered from ischemic/valvular/hypertensive heart diseases, respectively. Mean blood pressure was comparable among the groups. While the baseline conditions were comparable, we found that echocardiographic ejection fraction ($p<0.01$ *vs.* baseline, $p<0.01$ *vs.* Control), left ventricular systolic diameter ($p<0.05$, $p<0.05$), Specific Activity Scale (SAS) score ($p<0.05$, $p<0.01$), maximal oxygen consumption ($p<0.05$, $p<0.05$) and plasma B-type natriuretic peptide level ($p<0.01$, $p<0.01$) were significantly improved in patients with dipyridamole after 1 year, generally in a dose-dependent manner. Therefore, we suggest that an additional administration of dipyridamole further improves CHF pathophysiology. (*Hypertens Res* 2007; 30: 913–919)

***Key Words*: dipyridamole, heart failure, exercise, natriuretic peptide, adenosine**

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Introduction

Chronic heart failure (CHF) is primarily characterized by a reduction of cardiac performance, but several neurohormonal factors (*1*), such as catecholamines, cytokines, growth factors, renin and angiotensin are reported (*2–5*) to be involved in the pathophysiology of CHF through a variety of cellular signal transduction pathways. Indeed, recent reports revealed that CHF is effectively treated by β-adrenoceptor blockers, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), or aldosterone analogs (*6*, *7*), and these drugs have been proven effective for the treatment of CHF in large-scale clinical trials (*6*, *7*). However, these strategies are not sufficient to conquer CHF because mortality due to chronic heart failure remains high.

Interestingly, we have reported that plasma adenosine levels are elevated in patients with CHF (*8*). Adenosine, produced not only in cardiomyocytes but also in endothelial cells, is known to be cardioprotective by its stimulation of adenosine receptors (*9*): briefly, adenosine attenuates the release of catecholamine, β-adrenoceptor–mediated myocardial hypercontraction and calcium overload *via* A1 receptors. It also increases coronary blood flow and inhibits platelet and leukocyte activation *via* A2 receptors. Furthermore, adenosine inhibits renin release and tumor necrosis factor-α production in experimental models (*10*, *11*). These rationales lead us to hypothesize that increased adenosine levels in CHF may compensate for the worsening of CHF, suggesting that further elevation of adenosine levels may be beneficial to CHF pathophysiology. Accordingly, we performed a pilot study on 22 patients with stable CHF (New York Heart Association [NYHA] class II or III) to evaluate whether or not treatment with dipyridamole (300 mg/day, $n=17$) or dilazep (300 mg/day, $n=5$) for 6 months would modulate the pathophysiology of CHF; we found that dipyridamole increased the echocardiographic ejection fraction and the maximal oxygen consumption while ameliorating the severity of CHF (NYHA: 2.1±0.5 to 1.7±0.2) after 6 months, accompanied by an increase in plasma adenosine levels (202±34 to 372±74 nmol/L, $p<0.005$) (*12*).

However, that study enrolled patients who underwent either dilazep or dipyridamole in the same group, and consisted of a single group without a control against which to compare directly. Therefore, we sought to further confirm the effect of a single drug in a prospective randomized case-control study. In addition, recent studies evidenced that plasma B-type natriuretic peptide (BNP) level is a good marker of the status of heart failure (*13*) and can even predict prognosis (*14–17*). Therefore, we designed a prospective, open randomized clinical trial, including a control group, to evaluate the dose-dependent effects of dipyridamole as well as BNP status in order to determine whether treatment with either a large or a small dose of dipyridamole for 1 year modulates the pathophysiology of CHF patients with conventional broadly accepted treatments.

Methods

Patients and Protocol

The primary candidates for this study were patients diagnosed with CHF on the basis of medical history, echocardiography, catheterization and myocardial biopsy, and who attended a specialized CHF clinic and had been categorized as NYHA class II or III. Among these candidates, those who were finally eligible for the study met all of the following criteria: unchanged stable status under fixed medications; no past or present smoking habit, no specific medical histories (acute myocardial infarction, symptomatic angina, active myocarditis, cerebrovascular diseases, primary respiratory disorders, hypotension <90 mmHg, bradycardia <50 bpm, pregnancy, or severe liver/kidney functional disorder >3 times the upper limit of normal blood test values) for more than the adjacent 6 months, as confirmed by monthly outpatient follow-up; and finally an echocardiographic ejection fraction under 45% within the previous month.

Among 33 patients who were finally asked to participate in this study, 28 patients (mean±SEM: 66±4 years old; 21 males, range 43–79 years old) were enrolled between April and December 2003. Among them, 100%, 4%, 100% and 79% received ACE-Is, aldosterone analogue, loop diuretics and β-adrenoceptor blocker, respectively. The causes of CHF were dilated cardiomyopathy ($n=15$, 12 males), ischemic heart diseases ($n=7$, 6 males), valvular heart diseases ($n=3$, 2 males) and hypertensive heart ($n=3$, 1 male). The subjects were assigned into three groups by an open-randomized method: a Control group ($n=9$, 8 males) with no additional medication; a dipyridamole 75 mg/day group ($n=9$, 6 males); and a 300 mg/day group ($n=10$, 7 males) in addition to original medication regimens. They were followed up monthly at the original clinic for an additional year. Due to the expected limitations resulting from the strict criteria for enrollment and the fixed follow-up period, the primary endpoint was set to evaluate improvement in CHF status, such as cardiac function or physical activity, whereas the cardiovascular events for rehospitalization or death were observed as secondary endpoints.

NYHA and Specific Activity Scale (SAS) evaluation, ECG, chest X-ray, echocardiogram, exercise ECG/maximal oxygen consumption test with an ergometer and blood sampling were performed at the beginning of the study and 1 year after the study began, as well as at proper periods during the study as needed for each individual. Well-trained medical technicians and research nurses performed all physiological examinations and completed SAS evaluation sheets, without knowing the assignment of each patient. All values measured by echocardiogram were obtained from transthoracic standard long-axis view (B and M modes) followed by short-axis view (B and M modes) for verification, with the Teichholz

Table 1. The Baseline Characteristics and Conditions of Each Group in This Study

Groups	Control	75 mg/day	300 mg/day	*p*
Age (mean±SEM)	66±2.9	66±4.1	66±3.7	n.s.
Sex (male/female)	8/1	6/3	7/3	n.s.
NYHA classifications (I/II/III/IV)	0/5/4/0	0/1/8/0	0/4/6/0	n.s.
Mean blood pressure (mean±SEM)	86±2.9	88±2.5	90±4.4	n.s.
Original diseases				
Dilated cardiomyopathy (male/female)	6/1	4/0	2/2	n.s.
Ischemic heart diseases (male/female)	1/0	1/1	4/0	n.s.
Valvular heart diseases (male/female)	1/0	1/1	0/0	n.s.
Hypertensive heart (male/female)	0/0	0/1	0/2	n.s.
Complications				
Hypertension (male/female)	0/0	2/0	1/1	n.s.
Hyperlipidemia (male/female)	1/0	1/0	2/0	n.s.
Diabetes (male/female)	0/0	0/0	1/0	n.s.
Original medications (*n* (%))				
ACE-Is	9 (100)	9 (100)	10 (100)	n.s.
ARBs	0 (0)	0 (0)	0 (0)	n.s.
Aldosterone analogues	1 (11)	0 (0)	0 (0)	n.s.
Loop diuretics	9 (100)	9 (100)	10 (100)	n.s.
β-Adrenoceptor blockers	7 (78)	6 (67)	8 (80)	n.s.
Statins	1 (11)	1 (11)	2 (20)	n.s.

Values are either numbers of patients or percentile of the patients. NYHA, New York Heart Association; ACE-Is, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

formula used to measure the ejection fraction. Blood was sampled at least 15 min after the bedrest condition and tested together with safety laboratory parameters (hemoglobin, hematocrit, white blood cell count, platelet count, total cholesterol, low- and high-density lipoprotein (LDL and HDL, respectively) cholesterols, creatinine, liver enzymes, and bilirubin), 7 days before the study and after completion of the study in all patients. The administration of other drugs the patients were already taking for CHF was not altered during the study.

When a patient experienced death or hospitalization due to any cardiovascular diseases, it was recognized as an endpoint and the protocol was discontinued. When any other reason emerged to discontinue medications, including the patient's choice, it was counted as a dropout.

This study was approved by the ethics committees of all participating hospitals, including that of Osaka University Medical School, Suita, Japan. Written informed consent was obtained from all subjects prior to participation.

Statistical Analysis

Data were presented as the mean±SEM. The *t*-test was used to compare each value in the same group at different periods. To compare among the three groups, ANOVA with modified Bonferroni's post hoc test was employed. $p<0.05$ was considered significant.

Results

General Status

As shown in the Table 1 indicating the patients' characteristics in each group, the baseline conditions were comparable among the groups.

All patients completed the protocol without death, hospitalization, or dropout throughout the 1-year study period. Although a few patients temporarily complained of a mild skin rash at the very beginning, dipyridamole was well tolerated in all patients in this study, causing neither unexpected hypotension <90 mmHg nor new anginal attack. Mean blood pressure before and after the study in each group was as follows: 86±2.9 to 84±2.8 mmHg in the control group, 88±2.5 to 86±2.2 mmHg in the 75 mg/day group, and 90±4.4 to 86±3.4 mmHg in the 300 mg/day group. No group showed significant changes in mean blood pressure (n.s. in each).

Echocardiographic Data

Figure 1 indicates all measurements in this section. In the control group, the left ventricular ejection fraction was unchanged throughout the study (33.3±2.9 to 32.2±3.1%, n.s.). However, in the 75 mg/day group, the ejection fraction shifted from 32.4±2.7 to 43.9±3.9% during the study ($p<0.01$) and that in the 300 mg/day group also increased,

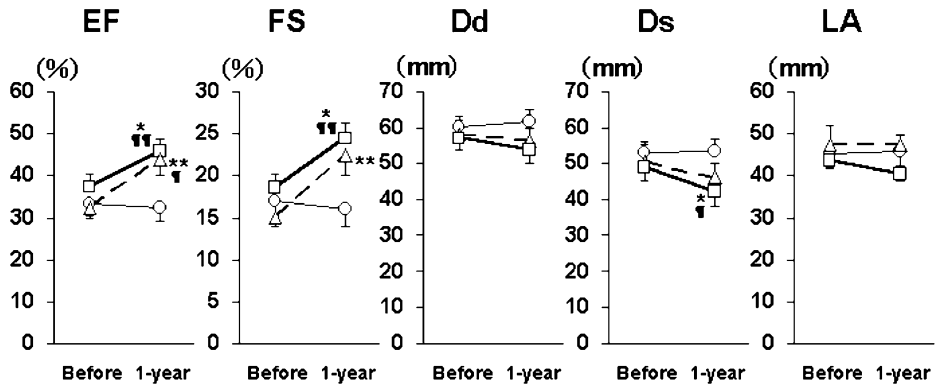

Fig. 1. *Echocardiographic measurements before and after the study in each group. Circles and solid lines: Control; triangles and broken lines: 75 mg/day; squares and bold solid lines: 300 mg/day. *$p<0.05$ vs. baseline, **$p<0.01$ vs. baseline, ¶$p<0.05$ vs. Control, ¶¶$p<0.01$ vs. Control. D_d, left ventricular diastolic diameter; D_s, left ventricular systolic diameter; EF, left ventricular ejection fraction; FS, fractional shortening; LA, left artrial diameter.*

from 36.2±3.2 to 46.7±2.5% ($p<0.05$). Both of these were significantly different from the control group ($p<0.05$ and $p<0.01$, respectively) at the end of the 1-year period.

Accordingly, while left ventricular fractional shortening was unchanged in the control group throughout the study (16.9±2.9 to 16.0±2.1%, n.s.), it significantly increased in the 300 mg/day group, from 18.5±1.7 to 24.4±1.8% during the study ($p<0.05$), which was also significantly different from the control group at the end of the 1-year period ($p<0.01$). Although the fractional shortening in the 75 mg/day group also significantly increased, from 14.9±1.3 to 22.4±2.4% ($p<0.05$), it did not differ significantly compared with the control group at the end of the 1-year period.

In the control group, left ventricular systolic diameter was almost the same from the beginning to the end of the study period (52.8±3.3 and 53.3±3.4 mm, respectively), but significantly decreased in the 300 mg/day group (from 48.8±3.6 to 42.1±3.8 mm) ($p<0.05$), and differed significantly from the control group ($p<0.05$). However, the change in the 75 mg/day group, from 49.3±4.9 to 46.2±2.4 mm, did not differ significantly from the control group.

On the other hand, the changes were not significant in either left ventricular diastolic diameter (60.3±2.8 to 61.7±3.2 mm in the control, 58.1±3.9 to 56.2±3.6 mm in the 75 mg/day group and 57.4±3.7 to 53.3±3.4 mm in the 300 mg/day group, n.s. or left atrial diameter (45.1±3.6 to 45.6±3.4 mm in the control, 47.1±4.9 to 47.1±2.5 mm in the 75 mg/day group, and 43.5±1.6 to 40.5±1.9 mm in the 300 mg/day group, n.s.).

Physical Activities

The left panels in Fig. 2 show the measurements in this section. In the control group, the distribution of NYHA classifications I, II, III, and IV was 0, 5, 4, and 0 subjects, respectively, before the study and never shifted throughout the study. However, in the 75 mg/day group, the distribution shifted from 0, 1, 8, and 0 to 1, 6, 2, and 0. The 300 mg/day group showed a similar shift, from 0, 4, 6, and 0 to 3, 5, 2, and 0.

In the control groups, SAS scores were 4.8±0.36 and 4.9±0.35 before and after the study, respectively (n.s.). However, the score in the 75 mg/day group increased from 5.1±0.72 to 6.2±0.44 ($p<0.05$) and that in the 300 mg/day group increased from 5.1±0.48 to 6.5±0.43 ($p<0.05$). Both increases were significantly different from the control group ($p<0.05$ and $p<0.01$, respectively) at the end of the 1-year period.

Maximal oxygen consumption was 16.9±1.3 and 17.0±1.2 mL/kg/min before and after the study, respectively, in the control group (n.s.). The score in the 75 mg/day group increased from 17.0±1.1 to 20.9±0.7 mL/kg/min ($p<0.05$), which was significantly different from the control group ($p<0.05$) at the end of the 1-year period. Although that in the 300 mg/day group increased similarly, from 16.4±1.4 to 20.0±1.3 mL/kg/min (n.s.), it was not significantly different from the control group at the end of the 1-year period.

Blood Tests

There were no significant changes in the safety parameters assessed by blood analysis of hemoglobin, hematocrit, white blood cell count, platelet count, total cholesterol, LDL or HDL cholesterol, creatinine, liver enzymes, and bilirubin (data not shown). The right panel of Fig. 2 shows the measurements in this section. In the control group, plasma BNP level was unchanged during the study (270±61 to 273±55 pg/mL, n.s.). However, in the 75 mg/day group it shifted from 282±60 to 121±35 pg/mL ($p<0.01$), and in the 300 mg/day group it increased from 238±56 to 100±24 pg/mL ($p<0.05$). Both of these were significantly different from the control group ($p<0.01$ and $p<0.05$, respectively).

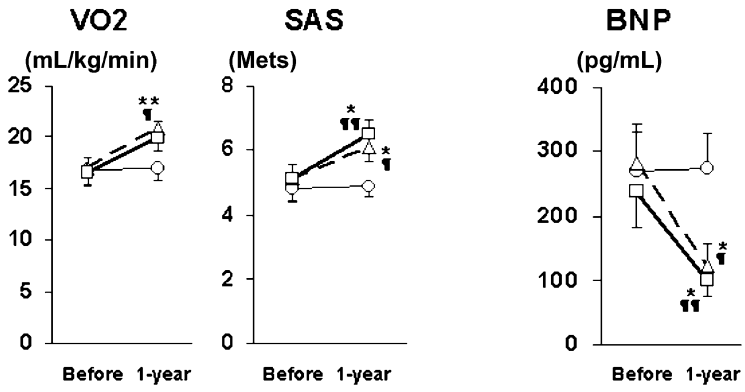

Fig. 2. *Measurements before exercise tolerance and plasma BNP level before and after the study in each group. Circles and solid lines: Control; triangles and broken lines: 75 mg/day; squares and bold solid lines: 300 mg/day. *$p < 0.05$ vs. baseline, **$p < 0.01$ vs. baseline, ¶$p < 0.05$ vs. Control, ¶¶$p < 0.01$ vs. Control. V_{O_2}, maximal oxygen consumption; SAS, specific activity scale; BNP, B-type (brain) natriuretic peptide.*

Discussion

Although many reports revealed that both β-adrenoceptor blockers and the inhibitors or antagonists of the renin-angiotensin-aldosterone system (ACE-Is, ARBs, or aldosterone analogs) significantly attenuated the severity of CHF and improved prognosis in large-scale clinical trials (*6*, *7*), these strategies were not fully sufficient to treat CHF completely because mortality due to CHF remains high. Here, we found a novel therapeutic strategy using dipyridamole, which can dramatically improve the status of patients with CHF in combination with established medications as indicated above.

Dipyridamole and Adenosine in CHF

In fact, some previous reports have pointed out the close relationship between common adenosine monophosphate deaminase-1 variant and the better outcomes, including improved long-term event-free ratios, in patients with left ventricular dysfunction (*18*, *19*) *via* the increase in cardiac local adenosine level (*19*, *20*). On the other hand, we found that either a long-acting adenosine analogue or an adenosine A1–receptor agonist attenuates cardiac hypertrophy and failure in a mouse experimental CHF model (*21*). Since the oral administration of dipyridamole elevated plasma adenosine levels of patients with CHF in our previous study (*12*), this beneficial effect might be expected by increased plasma adenosine level, especially through adenosine A1–receptor activation.

Cardiac Function

Similar to a finding in our previous study (*12*), the left ventricular ejection fraction increased significantly in both the 75 mg/day and 300 mg/day groups during the 1-year period, accompanied by a dose-dependent increase in left ventricular fractional shortening and a decrease in left ventricular systolic diameter that became significant at the 300 mg/day dose, suggesting that the improvement of contractile function occurred on the left ventricular myocardium treated with dipyridamole. However, since the reduction of neither left ventricular diastolic diameter nor left atrial diameter became significant, it is not likely that the reverse remodeling of the left ventricle or the reduction in heart preload significantly contributed to improve contractile function in this study. Furthermore, blood pressure was not significantly affected by dipyridamole after 1 year, suggesting that the reduction of afterload is also not the major cause of this contractile improvement.

Taken together, the elevated plasma adenosine level by dipyridamole after a long period might primarily induce left ventricular myocardial contractility. However, this effect, like that of inotropic agents (*e.g.*, catecholamines or phosphodiesterase inhibitors) might not be a direct pharmacological effect of adenosine, because adenosine is a well-known cardiodepressant that acts by attenuating the release of catecholamine, β-adrenoceptor–mediated myocardial contraction and calcium overload *via* A1 receptors (*9*).

Physical Activities

In the control group, the distribution of NYHA classes was unchanged during the study. However, the 75 mg/day and the 300 mg/day groups showed similar improvements. Furthermore, the identical pattern was observed in the SAS score evaluation by semi-quantitative analysis. These results clearly show that the 1-year treatment with dipyridamole, whether at low or high doses, improved the tolerance to exercise over conventional medications. Quantitative analysis confirmed that maximal oxygen consumption in the 75 mg/day group differed significantly from both the baseline value ($p < 0.05$) and the 1-year control value ($p < 0.05$).

Although the similar increase in the 300 mg/day group did

not differ significantly from that of the control group at 1 year, we strongly expect that an analysis of a larger number of patients might make the difference obviously significant, for at least two reasons: first, the data from both before and after the study are in quite close range compared with those of the 75 mg/day group, and second, this result resembles our previous observation (*12*) that 300 mg/day administration of dipyridamole in 17 patients with mild to moderate (NYHA class II or III) CHF for 6 months prominently improved maximal oxygen consumption, from 17.1±1.1 to 20.0±1.4 mL/kg/min ($p<0.001$).

Blood Tests

There were no significant changes during the study period in the safety parameters assessed by the blood analysis in each patient, suggesting that dipyridamole was well tolerated by patients with mild to moderate CHF.

One of the most interesting findings of this study is that dipyridamole dramatically decreased the plasma BNP level. Some previous reports have nicely revealed that plasma BNP level is a good independent predictor of event-free ratio in patients with symptomatic left ventricular dysfunction (*14*) as well as in patients with acute myocardial infarction (AMI) (*15*). The best cutoff value of BNP for predicting the event-free ratio for 36 months or the survival ratio was estimated to be 125 or 130 pg/mL, respectively (*16*, *17*). We could not evaluate the mortality or event-free ratio in the present population because no such event occurred during the study period and, among even up to the present, there has been only one event among all subjects (a sudden death in the control group). However, the sharp decrease in plasma BNP level beyond the cutoff values in the dipyridamole-treated groups (121±35 pg/mL in the 75 mg/day group and 100±24 pg/mL in the 300 mg/day group) strongly indicate the potential to improve the prognosis of patients with CHF by the addition of dipyridamole.

Since BNP is reported to be not only a good biomarker (*14*–*17*) but also a biologically negative inotropic substance through the cyclic-GMP pathway (*22*), the decrease in BNP production may be a primary effect of dipyridamole (or adenosine) to increase the contraction of the left ventricle in this study. Further study is needed to confirm this.

Clinical Impact, Dose-Dependency, and Limitations of the Study

By showing significant changes within as few as 28 samples, this study suggested that an exogenous increase in plasma adenosine levels can improve cardiac function and tolerance of exercise in patients with mild to moderate CHF. Although a large-scale clinical trial can evaluate the difference more precisely in many cases, this study has at least three merits that help validate its results.

First, the study was designed as a prospective study, and independent well-trained health care professionals who were completely blinded to the assignments performed all semi-quantitative and quantitative examinations.

Second, we were fortunately able to replicate the observation in our previous report showing significant increases in ejection fraction and exercise capacity (*12*) in a different population with the same category of patients.

Furthermore, majority of patients in this study were already treated with ACE-Is (100%) and β-adrenoceptor blockers (79%), which have both been found to improve heart function, morbidity and mortality (*6*, *7*), as well as diuretics (100%) so that they show the stable chronic status of heart failure, but still remained symptomatic (NYHA class II or III). However, the addition of dipyridamole treatment in this population could overridingly improve cardiac function, tolerance of exercise and particularly neurohormonal status to shift these patients under the safety cutoff points.

Indeed, we agree that such a small study population is one of the limitations of this study, because the eligible patients were primarily limited to those who were symptomatic but stable and not severe, who had no complications, and who were under frequent outpatient care. As mentioned above, this issue is preventing us from evaluating the difference in event-free ratio, since even up to the present there has been only one event (a sudden death in the control group) out of all enrolled patients. However, as also mentioned above, we strongly believe this limitation does not preclude the possibility that dipyridamole could significantly improve the long-term event-free ratio.

Next, an enhanced overriding effect of dipyridamole might be highly expected in some specific diseases related to ischemia, since adenosine is well known as a vasodilator (*9*). However, we did not see any difference in the effectiveness of dipyridamole among primary diseases that led to CHF. Indeed, the major reason for this might derive from the limited number of enrolled patients, but another reason might be that ACE-Is and β-blockers, which were highly included in the original medications, also help to decrease ischemic damage to cardiac muscle (*6*, *23*), which might have masked the overriding ischemia-reducing effect of dipyridamole. As for the dose-dependent effect, different doses of dipyridamole did not cause significant differences in plasma adenosine level after 6 months of treatment (323±69 ng/mL in 75 mg/day and 364±78 ng/mL in 300 mg/day, respectively, $n=6$ each, n.s.), and neither ejection fraction, V_{O_2}, nor plasma BNP level was significantly correlated with plasma adenosine level within these 12 patients. Increasing the number of samples might cause a dose-dependent difference, but a 75 mg/day dose of dipyridamole exerted similar effects as the 300 mg/day dose in every examination in the present study, while the tendency toward stronger effects was generally seen in the higher dose. Also, Laghi-Pasini *et al*. (*24*) reported that patients with dilated cardiomyopathy exhibit higher basal plasma adenosine level but exhibited a reduced response to intravenous dipyridamole administration that finally resulted

in a lower plasma adenosine level than control by the end of the study. According to these arguments, we can only say that the lower dose of dipyridamole might be sufficient to exert beneficial effects.

In addition, we have to consider whether the doses of the original medications in each patient are appropriate or not for exerting the maximal impacts as evidenced in previous trials (*6*, *7*) in order to determine whether the effect of dipyridamole or adenosine is completely additional to those of both ACE-Is and β-adrenoceptor blockers. However, it might be difficult in each case to evaluate this issue, as described above.

Furthermore, even though this study is not double-blinded, we made sufficient efforts to perform all data collection blindly.

Finally, although a prospective, large-scale and double-blinded trial is apparently needed to confirm the present results, we strongly suggest that dipyridamole administration, apparently by increasing plasma adenosine level, provides a novel, safe, and economic therapy that enhances the effectiveness of established beneficial medications in patients with mild to moderate CHF.

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