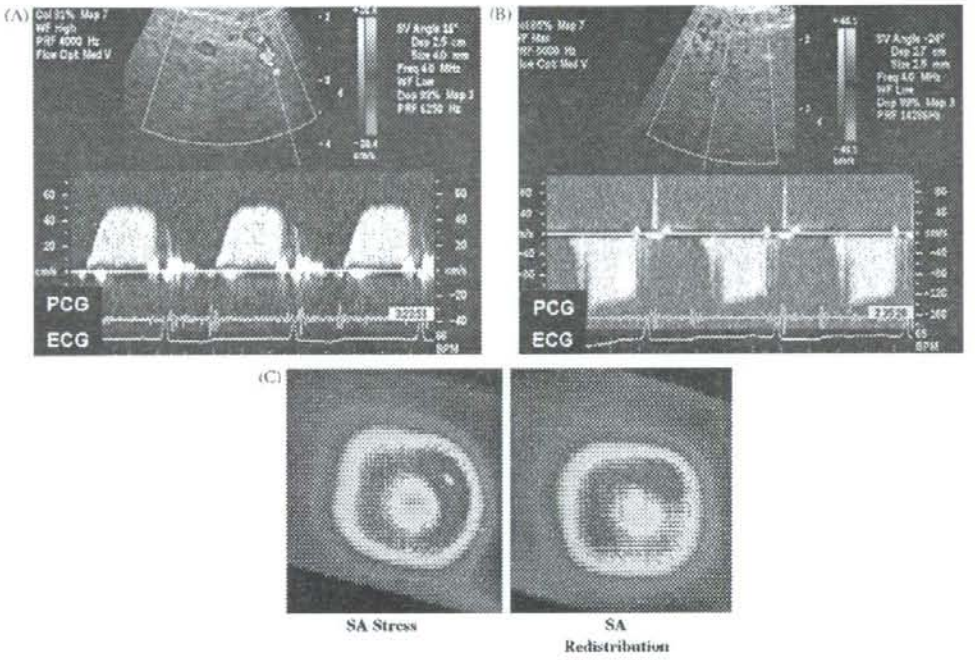

Figure 1 Fifty-two-year-old female without symptoms. Transthoracic Doppler echocardiographic measurement of left anterior descending coronary artery (A) and intramyocardial coronary artery (B). Diastolic peak velocity of intramyocardial coronary flow decreases gradually, so we classified this patient into group A. (C) Thallium-201 scintigraphy showing stress and redistribution images in the short-axis (SA) views. It demonstrates no ischemia.

the two groups (Table 2). Syncope was observed in 1 patient (4%) in Group A and 8 patients (36%) in Group B, and chest pain was observed in 6 patients (22%) in Group A and 10 patients (48%) in Group B. Thus, the incidence of cardiovascular symptoms (chest pain or syncope) was significantly higher in group B than in group A ($p=0.008$) (Table 2).

Comparison of thallium-201 scintigraphy between two groups in HCM patients

Exercise thallium-201 scintigraphy was performed in 18 of the 48 patients with HCM. Exercise-induced myocardial ischemia at the anteroseptal or apical segment was found in 6 of the 9 patients (67%) in group B, while none of the 9 patients (0%) in group A showed ischemia, a statistically significant difference in incidence ($p=0.009$) (Table 2). Figures show representative images of coronary flow velocity patterns in the LAD and IMCA as seen by transthoracic Doppler echocardiography, both without and with exercise-induced apical ischemia as detected by thallium-201 scintigraphy.

Observer variability

Interobserver variabilities for peak diastolic velocity, time velocity integral and deceleration time of diastolic flow were 4.2%, 4.9%, and 3.9%, respectively. Interobserver variabilities for peak diastolic velocity, time velocity integral and deceleration time of diastolic flow were 3.8%, 4.1%, and 3.9%, respectively.

Discussion

In the present study, we evaluated the value of intramyocardial coronary flow velocity measurements using transthoracic Doppler echocardiography in patients with HCM. We have found that there were two different IMCA flow patterns in patients with HCM, despite no difference of LAD flow velocity pattern between these patients. One flow pattern obtained from IMCA showed anterograde diastolic flow velocity, reaching peak velocity in early diastole with subsequent gradual deceleration. The other flow pattern showed no reflow-like pattern (sharp acceleration of coro-

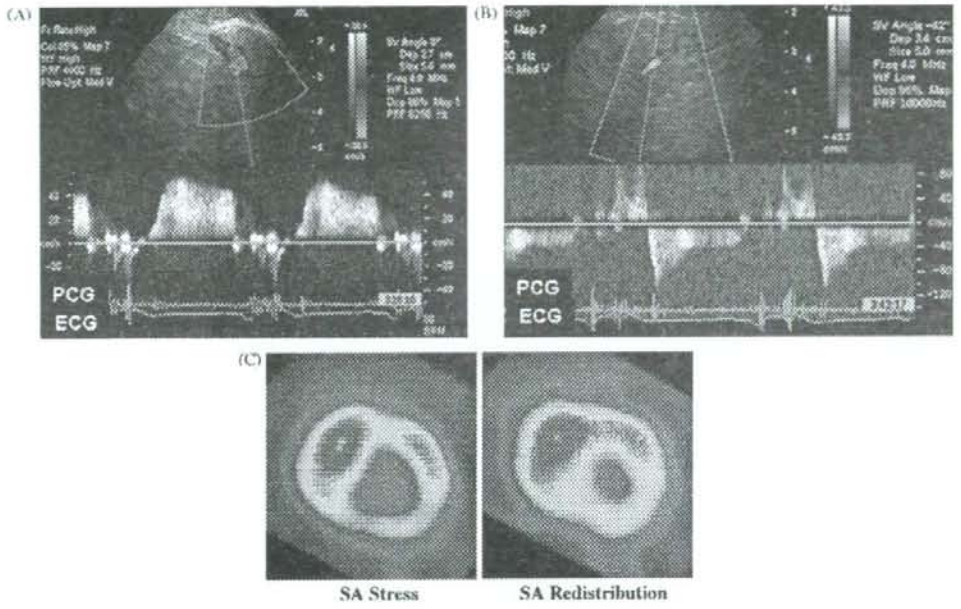

Figure 2 Fifty-three-year-old female with a history of syncope. Transthoracic Doppler echocardiographic measurement of left anterior descending coronary artery (A) and intramyocardial coronary artery (B). The pulsed Doppler echocardiography in the intramyocardial coronary artery demonstrating characteristic no reflow-like pattern, so we classified this patient into group B. (C) Thallium-201 scintigraphy showing abnormal perfusion with reversible ischemia in the anteroseptal segments.

nary flow velocity at early diastole followed by a subsequent steep deceleration). The latter characteristic flow pattern in the IMCA was associated with clinical symptoms (chest pain or syncope) and exercise-induced myocardial ischemia detected by thallium-201 scintigraphy, while the former flow pattern was not associated with clinical symptoms or myocardial ischemia. Our new findings in this study suggest that the no reflow-like pattern in the IMCA could be related to myocardial ischemia

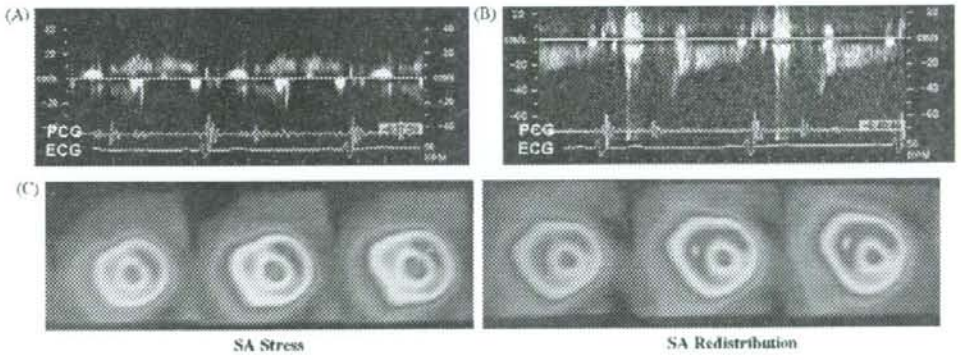

Figure 3 Thirty-year-old male with a history of syncope and chest discomfort. Transthoracic Doppler echocardiographic measurement of left anterior descending coronary artery (A) and intramyocardial coronary artery (B). The pulsed Doppler echocardiography in the intramyocardial coronary artery demonstrating characteristic no reflow-like pattern, so we classified this patient into group B. (C) Thallium-201 scintigraphy showing abnormal perfusion with reversible ischemia in the anteroseptal segments.

Table 2 Baseline characteristics and echocardiographic measurements of HCM patients

	Group A ($n=27$)	Group B ($n=21$)	p value
Age (years)	55 ± 13	51 ± 19	NS
Men/women (n)	20/7	13/8	NS
Heart rate (beats/min)	62 ± 11	60 ± 10	NS
Type of HCM			
ASH	17 (63%)	15 (71%)	NS
Apical	10 (37%)	6 (29%)	NS
Symptom			0.008
No symptoms	20 (74%)	7 (33%)	
Chest pain or syncope	7 (26%)	14 (67%)	
Echocardiographic measurements			
Maximal wall thickness (mm)	23 ± 5	25 ± 6	NS
IVS thickness (mm)	19 ± 6	23 ± 8	NS
PW thickness (mm)	12 ± 3	12 ± 3	NS
LV end-diastolic dimension (mm)	45 ± 6	44 ± 7	NS
LV end-systolic dimension (mm)	27 ± 5	26 ± 6	NS
Fractional shortening (%)	40 ± 5	44 ± 10	NS
LA dimension (mm)	38 ± 5	40 ± 6	NS
Gradient ≥ 30 mmHg	4 (15%)	5 (24%)	NS
LAD flow			
Peak diastolic velocity (cm/s)	52 ± 28	45 ± 14	NS
Mean diastolic velocity (cm/s)	34 ± 18	29 ± 9	NS
Diastolic velocity time integral (cm)	24 ± 14	21 ± 7	NS
Diastolic deceleration time (ms)	975 ± 349	1045 ± 362	NS
IMCA flow			
Peak diastolic velocity (cm/s)	90 ± 44	101 ± 43	NS
Mean diastolic velocity (cm/s)	70 ± 35	51 ± 22	0.036
Diastolic velocity time integral (cm)	38 ± 19	29 ± 11	0.042
Diastolic deceleration time (ms)	989 ± 338	166 ± 67	< 0.001
201-thallium scintigraphy ($n=18$)			
Ischemia	0 (0%)	6 (67%)	0.009

ASH = asymmetric septal hypertrophy. Abbreviations as in Table 1.

in patients with HCM in the absence of epicardial coronary stenosis.

Clinical findings suggestive of myocardial ischemia in patients with HCM are found to have normal coronary arteries at angiography despite having objective evidence of reversible exercise induced defects in myocardial perfusion by thallium-201 imaging [15]. Abnormalities in coronary flow dynamics have been considered as a possible mechanism for myocardial ischemia in HCM patients with normal coronary arteries [2–4]. Previously, alterations of the phasic coronary flow velocity profile in the LAD in patients with HCM characterized by flow reversal in early systole, a reduced systolic component, and preserved or even increased diastolic flow velocity have been demonstrated in several studies using invasive or noninvasive Doppler methods. However, these studies demonstrated no relationship between LAD flow velocity profiles and those with symptoms and myocardial ischemia [5–7].

In this study, we have demonstrated that no reflow-like pattern in the IMCA was related to clinical symptoms in addition to exercise-induced ischemia by thallium-201 scintigraphy. The normal value of the diastolic deceleration time is a matter of dispute, but it has been reported that the decay in the diastolic deceleration slope correlated with the severity of microvascular dysfunction [16,17]. The mechanism of this diastolic change is speculative, but rapid deceleration of diastolic flow would be expected in patients with increased microvascular resistance and impedance [18–21]. Morphologic studies have revealed that HCM is characterized by many abnormal intramural coronary arteries and subendocardial arterioles characterized by thickened walls and narrowed lumens [4,22–24]. This may result in an increase in minimal coronary resistance

and might be a cause of no reflow-like pattern in the IMCA.

Thallium scintigraphy could potentially provide a means of obtaining the cause of myocardial ischemia, which is reported in 50–80% of patients with HCM in the absence of epicardial coronary disease [25]. Previously, thallium perfusion defects during exercise have been attributed to exercise-induced ischemia due to microcirculation abnormalities [26,27]. Using transthoracic Doppler echocardiography in the present study, the presence of myocardial ischemia was found to be closely related to the flow velocity pattern in the IMCA. Thus, the characteristic intramyocardial coronary flow velocity pattern demonstrated in the present study might be related to exercise-induced ischemia due to microcirculation abnormalities.

Angina and myocardial ischemia are predominant features of HCM and ischemia may contribute to the development of syncope and sudden cardiac arrest in such patients [26]. Previous reports indicate that abnormalities of intramural coronary artery may be the cause of myocardial ischemia. It is thus possible that ischemia caused by these vascular abnormalities may eventually result in myocardial scarring and diminished left ventricular function [28]. In the present study, basal left ventricular thickness and coronary velocity profiles in the LAD were similar in the two groups, but cardiac events were frequently developed in patients with no reflow-like pattern in the IMCA, reflecting disturbed coronary microcirculations in such patients.

In this study, the characteristic pattern observed in the IMCA had no relationship to the pattern seen in the epicardial LAD flow. This discrepancy between IMCA and LAD flow suggests that the intramyocardial coronary flow pattern may express abnormalities of the microcirculation in relatively small areas. Thus, the intramyocardial coronary flow velocity measurement appears to be more sensitive than epicardial coronary flow analysis for detecting abnormal coronary microcirculation in patients with HCM.

Clinical implications

Visualization of small arteries by coronary arteriography is limited by the physical properties of radiographic systems. Although other imaging modalities (such as magnetic resonance imaging and positron emission tomography) may provide significant information regarding the functional and metabolic consequences of small coronary artery disease [29,30], transthoracic Doppler echocardiography is the most inexpensive and probably the simplest to apply. Moreover, transthoracic Doppler echocardiography is the only available method for directly detecting the flow velocity of the IMCA (500–1000 μm). Thus, this noninvasive technique has clinical merit for investigating and understanding of the role of IMCA physiology in coronary circulation, hemodynamics, and natural history of disease with left ventricular hypertrophy. Additionally, early detection of no reflow-like pattern in the IMCA by transthoracic Doppler echocardiography may provide a useful prediction of cardiac events in patients with HCM.

Limitations

There are several limitations in this study. The echocardiographic technique described here allows noninvasive assessment of phasic coronary flow velocity profiles in the LAD as well as IMCA. The methods have satisfactory interobserver and intraobserver variability. However, assessment of coronary flow velocity profiles in the IMCA using transthoracic Doppler echocardiography is restricted to the hypertrophic septal wall. Therefore, information about the rest of the wall cannot be used for comparison. We analyzed IMCA flow velocity from diastolic flow velocities alone and not from velocities throughout the entire cardiac cycle, because cyclic cardiac motion makes it difficult to obtain complete Doppler spectral envelopes especially in systoles. We did not measure coronary flow velocity reserve with intravenous infusion of adenosine, although we believe this measurement might be useful to find out the effect of microvessel mechanism on myocardial ischemia. However, the purpose of the present study was to define the relationship between IMCA flow velocity patterns and clinical manifestations, and we found a characteristic flow velocity pattern specific to microvascular damage even without intravenous infusion of adenosine. The thallium-201 scintigraphic evaluations could not be performed entirely at our institution. Although there were no clinical differences in the patients who underwent thallium-201 scintigraphy compared with those who did not undergo 201-thallium scintigraphy, the number of study patients was limited in the present study.

Conclusion

We evaluated coronary flow velocity profiles in the LAD and IMCA by transthoracic Doppler echocardiography in patients with HCM. Two different intramyocardial flow velocity patterns are noted.

No reflow-like pattern in the IMCA was related to cardiovascular symptoms and exercised-induced myocardial ischemia. Thus, measurements of IMCA flow using transthoracic Doppler echocardiography are useful for evaluating intramyocardial perfusion abnormality and prediction of cardiac events in patients with HCM.

Acknowledgment

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A Technique for Diagnosis of Accessory Pathway Using the H-H and A-A Intervals of the First Entrained Cycle During Ventricular Overdrive Pacing

Takehiko Matsushita, MD, PhD*, Sanemasa Ishida, MD, Naoya Oketani, MD, Hitoshi Ichiki, MD, Yuichi Ninomiya, MD, Shuichi Hamasaki, MD, and Chuwa Tei, MD

Although advancement of succeeding atrial activation by a ventricular extrastimulus (VES) on His refractoriness during supraventricular tachycardia (SVT) has been used as evidence of an accessory pathway (AP), the sensitivity of this methodis suboptimal. This study was designed to compare the His-His (H-H) and atrial-atrial (A-A) intervals of the first entrained cycle during ventricular overdrive pacing (VOD) for the diagnosis of AP, in comparison to the conventional VES method. In 55 patients with SVT, a VES was elicited on His refractoriness during SVT. VOD was subsequently performed at cycle lengths 30 to 40 ms shorter than SVT cycle lengths. When the A-A interval became equal to the pacing cycle length after some beats of VOD, the cycle was considered the first entrained cycle and the H-H interval preceding the A-A interval was measured. VES advanced the next atrial activation in 16 patients (52%) with an AP, but in no patient without an AP. The H-H interval of the first entrained cycle was longer than the pacing cycle length by ≥15 ms in all patients with an AP, but was equal to the pacing cycle length in all patients without an AP. The criterion of H-H greater than A-A by ≥15 ms for the first entrained cycle provided higher diagnostic yield for AP compared with the VES method(100% vs 52%, p <0.001). In conclusion, this new criterion reliably diagnoses the presence of an AP in patients with SVT, with higher sensitivity compared with the VES method. (Am J Cardiol 2008;102:197–202)

Determination of the tachycardia mechanism is critical in catheter ablation therapy in patients with supraventricular tachycardia (SVT). However, when atrial activation during SVT is concentric, proper differentiation of the various forms of atrioventricular nodal reentrant tachycardia (AVNRT) or atrial tachycardia from orthodromic reciprocating tachycardia using a septal accessory pathway (AP) is a challenging clinical problem. Advancement of succeeding atrial activation by a ventricular extrastimulus (VES) applied at the time of His refractoriness during SVT confirms the presence of an AP.[1,2] However, the diagnostic yield of this VES method for the presence of an AP was reported to be approximately 50% to 80%, depending on the proximity of the stimulation site to the tachycardia circuit.[3–5] In this study, we postulated that the response of His-His (H-H) and atrial-atrial (A-A) intervals to ventricular overdrive pacing (VOD) during SVT might help establish the presence of an AP. Thus, the purpose of this study was to test the utility of comparing the H-H and A-A intervals of the first entrained cycle during VOD for the diagnosis of AP, in comparison to the conventional VES method.

Methods

A total of 55 consecutive patients (22 men, age 46 ± 16 years, range 15 to 75) with clinically documented SVT who underwent electrophysiologic study and subsequent radiofrequency catheter ablation were enrolled in this study. Informed consent was obtained from all patients before enrollment, and all study protocols were approved by the local institutional review board.

Figure 1 shows a schematic illustration of the activation sequence during AVNRT with no AP and that during orthodromic reciprocating tachycardia using an AP. In the absence of an AP (Figure 1), ventricular activation by VOD conducts to the atrium solely by penetrating the His bundle when the atrium is entrained by VOD (i.e., A-A interval = pacing cycle length). In this situation, the His bundle electrogram is produced by the retrograde conduction through the His bundle. Hence, the H-H interval has to be equal to the subsequent A-A interval. Conversely, in the presence of an AP, the His bundle is not mandatory for atrial activation during VOD. Atrial activation can be generated by the retrograde impulse through the AP. The atrial activation then conducts through the atrioventricular node and the His bundle and collides with the impulse produced by the next ventricular stimulation at the infra-Hisian region. Thus, the His bundle electrogram is produced by the anterograde

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*Corresponding author: Tel: +81-99-275-5318; Fax: +81-99-265-8447.
E-mail address: t-matsu@m2.kufm.kagoshima-u.ac.jp (T. Matsushita).

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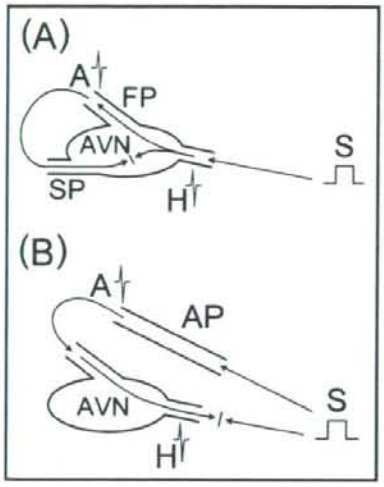

Figure 1. *(A)* Schematic illustration of activation during AVNRT with no AP. The His bundle electrogram is produced by retrograde conduction when the atrium is entrained (i.e., A-A interval = pacing cycle length) by VOD. *(B)* Schematic illustration of activation during orthodromic reciprocating tachycardia using an AP. In the presence of an AP, atrial activation can be generated by the retrograde impulse through the AP and then penetrates the AVN and the His bundle anterogradely. Therefore, the H-H interval during VOD can be longer than the subsequent A-A interval for several beats when atrial entrainment is being achieved (for details, see text). A = atrial electrogram recording site; AVN = atrioventricular node; FP = fast pathway; H = His electrogram recording site; S = stimulation site; SP = slow pathway.

conduction (Figure 1). In this situation, the H-H interval during VOD can be longer than the subsequent A-A interval for several beats when atrial entrainment is being achieved because the H-H interval is dependent on the preceding A-A interval, not the subsequent A-A interval.

Electrophysiologic study was performed with patients in a fasting unsedated state. All antiarrhythmic drugs were discontinued for ≥5 half-lives before the electrophysiologic study. Four multipolar electrode catheters were introduced using standard percutaneous techniques and advanced to the high right atrium, coronary sinus, His bundle region, and right ventricular apex, respectively. Intracardiac electrograms from these catheters, along with surface electrocardiogram leads I, II, and V_1, were displayed on a monitor and simultaneously recorded on an optical disk (CardioLab System; Prucka Engineering Inc., Houston, Texas).

Bipolar pacing was performed at twice the diastolic threshold from the distal electrode pair using a programmable stimulator (SEC-3102; Nihon Kohden, Tokyo, Japan). The pacing protocol consisted of atrial and ventricular incremental overdrive pacing and programmed single and double extrastimuli after 8-beat drive trains at cycle lengths of 600 and 400 ms, respectively. If SVT was not induced in the baseline state, isoproterenol (1.0 to 2.0 μg/min) was administered and the same pacing protocol was repeated. When SVT was induced, a VES was delivered exactly at the time of His deflection from the right ventricular apex when the tachycardia cycle length was constant. The A-A interval encompassing the VES was measured and compared with the tachycardia cycle length. VOD was subsequently performed from the right ventricular apex during SVT at a cycle length that was 30 to 40 ms shorter than the SVT cycle length. With the initiation of VOD, the A-A interval shortened from SVT cycle length to pacing cycle length within a few beats (Figure 2). When the A-A interval became equal to the pacing cycle length, the cycle was considered the first entrained cycle, and the H-H interval preceding the A-A interval was measured. In all patients, SVT continued after termination of VOD with the same cycle length and the same activation sequence as that before performing VOD.

Diagnoses of tachycardia mechanism were made on the basis of established criteria.[6–9] After electrophysiologic study, radiofrequency catheter ablation was performed using standard techniques. In all patients, diagnosis of the presence of an AP was confirmed by changes in retrograde atrial activation sequence after successful ablation and/or response to adenosine triphosphate.

All data were expressed as mean ± SD. Unpaired *t* test was used for comparison of continuous variables. Frequency analysis for categorical variables was performed using chi-square analysis. A p value <0.05 was considered statistically significant.

Results

Electrophysiologic study showed a tachycardia mechanism of orthodromic reciprocating tachycardia using a septal AP in 13 patients, orthodromic reciprocating tachycardia using a freewall AP in 18 patients, and AVNRT without an AP in the remaining 24 patients. In the 24 patients with AVNRT, typical (slow-fast) form was induced in 21 patients, whereas fast-slow form was observed in 2 patients, 1 of whom had both forms. In the remaining 2 patients, the earliest atrial activation site during AVNRT was at the middle or distal coronary sinus. In this series of patients, there was no patient with multiple APs or AVNRT with a bystander AP.

During VOD, the H-H interval of the first entrained cycle was measurable in all patients with an AP. However, in patients without an AP, the H-H interval of the first entrained cycle could not be measured in 6 of 24 patients (25%) because of the difficulty identifying the retrograde His deflection.

VES advanced the next atrial activation in 8 of 13 patients (62%) with a septal AP and 8 of 18 patients (44%) with a freewall AP (Tables 1 and 2). During VOD, the H-H interval was longer than the A-A interval by ≥15 ms for the first entrained cycle in all patients with an AP. In those without an AP, VES did not advance the next atrial activation in any patient. During VOD, the H-H interval was equal to the A-A interval for the first entrained cycle in all patients without an AP in whom the H-H interval of the first entrained cycle could be measured.

Comparisons between the VES and VOD methods are listed in Table 3. As listed, when H-H interval longer than the A-A interval by ≥15 ms for the first entrained cycle was

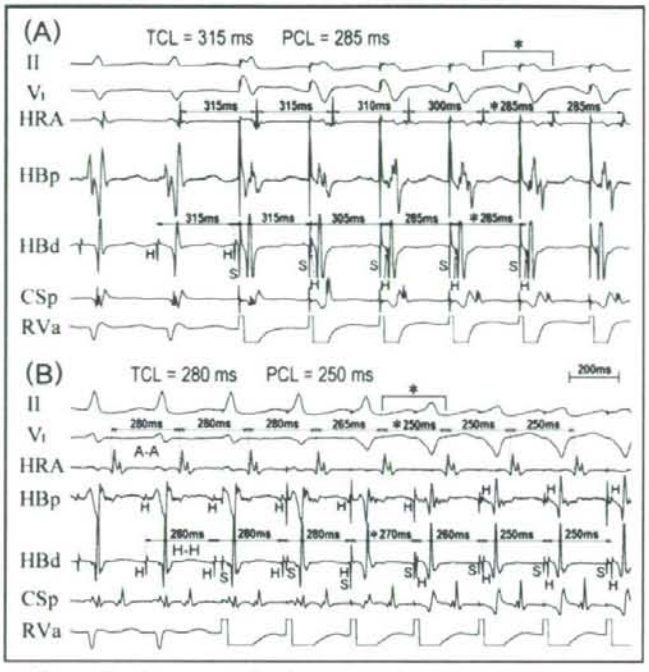

Figure 2. Simultaneous recordings of intracardiac electrograms and surface electrocardiogram leads II and V_1. *(A)* An example of atrial entrainment in a patient with AVNRT without an AP. With the initiation of VOD pacing, the A-A interval shortens from the tachycardia cycle length (315 ms) to the pacing cycle length (285 ms). When the A-A interval becomes equal to the pacing cycle length (*), the H-H interval preceding this A-A interval equals the A-A interval. *(B)* An example of atrial entrainment in a patient with orthodromic reciprocating tachycardia using an anteroseptal AP. With the initiation of VOD during tachycardia, the A-A interval shortens from the tachycardia cycle length (280 ms) to the pacing cycle length (250 ms) within a few beats. When the A-A interval becomes equal to the pacing cycle length (*), the H-H interval preceding this A-A interval is still longer than the A-A interval. The difference is 20 ms in this particular case (270 vs 250 ms). CSp = proximal coronary sinus; H = His bundle electrogram; HBd = distal His recording site; HBp = proximal His recording site; HRA = high right atrium; PCL = pacing cycle length; RVa = right ventricular apex; S = stimulus artifact; TCL = tachycardia cycle length.

defined as the diagnostic criterion for the presence of an AP, this diagnosis was established in all patients with a septal AP and those with a freewall AP. For the overall population with an AP, the criterion provided significantly greater diagnostic yield for the presence of an AP compared with the VES method.

Discussion

It has been well appreciated that advancement of succeeding atrial activation by a VES applied at the time of His refractoriness during SVT suggested the existence of an AP. However, the sensitivity of this VES method was not extremely high, ranging from 50% to 80%, largely dependent on the proximity of the stimulation site to the tachycardia circuit. Therefore, a more sensitive diagnostic maneuver would be of benefit in a clinical electrophysiology laboratory. The present study showed that the criterion H-H greater than A-A interval by ≥15 ms for the first entrained cycle during VOD was met in all patients with an AP. The diagnostic utility of this criterion for the presence of an AP was significantly higher compared with the VES method.

Proper differentiation of the various forms of AVNRT from orthodromic reciprocating tachycardia using a septal AP is a challenging clinical problem. Procedures used to distinguish the 2 include comparison of the ventricular-atrial (VA) or His-atrial (HA) interval during SVT compared with that during ventricular pacing,[10,11] resetting or entrainment of SVT with ventricular fusion,[12] para-Hisian pacing,[13] or analyses of the postpacing interval in response to the entrainment ventricular pacing during SVT.[14,15] Comparison of the HA interval during SVT versus ventricular pacing at a similar pacing cycle length may be difficult in terms of recording the His deflection during stable VOD. The retrograde His deflection during VOD has been notoriously difficult to discern because of fusion with the ventricular electrogram. The H-H interval could not be measured during VOD in 25% of patients without an AP because of difficulty identifying the retrograde His deflection in this study. However, identification of retrograde His deflection during VOD was possible in all patients with an AP until the first atrial entrainment was achieved. The advantage of the VOD method is that identification of His deflection during stable SVT is not necessary because this method requires identification of His deflection for only the initial several

Table 1
Measurements in patients with a septal accessory pathway (n = 13)

Patient No.	AP Location	TCL (ms)	Adv. of A by VES	(H-H)-(A-A) (ms)
1	R-AS	280	+	20
2	R-PS	300	+	30
3	R-PS	290	+	20
4	R-PS	330	+	25
5	R-PS	410	+	30
6	L-PS	340	+	20
7	L-PS	300	+	20
8	L-PS	330	+	25
9	R-AS	350	–	25
10	R-PS	315	–	20
11	L-PS	360	–	20
12	L-PS	300	–	20
13	L-PS	380	–	20

Adv. of A by VES = the atrial activation succeeding the VES advanced; (H-H)-(A-A) = the difference between the H-H and A-A intervals for the first entrained cycle during VOD pacing; TCL = tachycardia cycle length; R-AS = right anteroseptal; R-PS = right posteroseptal; L-PS = left posteroseptal.

Table 2
Measurements in patients with a freewall accessory pathway (n = 18)

Patient No.	AP Location	TCL (ms)	Adv. of A by VES	(H-H)-(A-A) (ms)
1	R-L	350	+	35
2	R-L	350	+	25
3	L-PL	380	+	30
4	L-PL	400	+	15
5	L-L	400	+	15
6	L-L	390	+	15
7	L-L	400	+	15
8	L-L	365	+	25
9	L-AL	355	–	15
10	L-AL	350	–	20
11	L-AL	370	–	20
12	L-L	325	–	15
13	L-L	335	–	15
14	L-L	310	–	30
15	L-L	420	–	15
16	L-PL	370	–	15
17	L-PL	460	–	25
18	L-P	370	–	25

R-L = right lateral; L-PL = left posterolateral; L-L = left lateral; L-AL = left anterolateral; L-P = left posterior; other abbreviations as in Table 1.

beats until atrial entrainment is achieved. Para-Hisian pacing is a useful technique to diagnose the presence of an AP. Unlike many other pacing maneuvers, this method does not necessitate induction of stable SVT. However, proper para-Hisian pacing may be technically challenging, and although this procedure may help diagnose the presence of an AP, it does not serve to prove that the AP is part of the tachycardia circuit. Analyses of the postpacing interval after entrainment ventricular pacing during SVT cannot be performed when SVT does not continue after VOD is terminated. Conversely, the present VOD method uses the H-H and A-A intervals for only the first few beats after VOD is initiated and hence does not require persistence of SVT after termination of VOD.

Table 3
Comparison between the ventricular extrastimulus and overdrive pacing methods

Variable	Patients With Septal AP (n = 13)	Patients With Freewall AP (n = 18)	Overall Patients With an AP (n = 31)
Age (yrs)	45 ± 15	44 ± 18	44 ± 17
Men/women	8/5	10/8	18/13
SVT cycle length (ms)	330 ± 38	373 ± 35	355 ± 42
Advancement of next A wave by VES	8 (62%)	8 (44%)	16 (52%)
H-H > A-A by ≥15 ms for the first entrained cycle during VOD	13 (100%)	18 (100%)	31 (100%)
p Value	<0.05	<0.005	<0.001

P value for comparison between the VES and VOD methods in each group.

The diagnostic utility of the VES method is determined by several factors, including proximity of the stimulation site to the tachycardia circuit, tachycardia cycle length, and local refractory period of the myocardial tissue in the reentrant circuit. It is well known that the VES method is less sensitive in diagnosing orthodromic reciprocating tachycardia using a freewall AP compared with that using a septal AP.[2,4] In this study, the VES method was diagnostic in only 44% of patients with a freewall AP, whereas the VOD method was able to diagnose the presence of an AP in all patients (Figure 3). This indicated that the VOD method was more useful for the diagnosis of an AP than the VES method, particularly in patients with SVT with eccentric atrial activation. Recent reports described that some unusual variants of AVNRT present with eccentric retrograde atrial activation sequences. Although a left-sided atrioventricular nodal extension and/or the ligament of Marshall have been proposed as potential mechanisms,[16–18] the precise mechanisms by which eccentric retrograde activation occurs during AVNRT are unclear. The VOD method may help discriminate orthodromic reciprocating tachycardias using a freewall AP from such unusual AVNRTs.

In one fourth of the patients without an AP, the H-H interval could not be measured during VOD because of difficulty identifying the retrograde His deflection. However, the H-H interval of the first entrained cycle was measurable in all patients with an AP, and the presence of an AP was correctly diagnosed.

In this study, no patient had an AP with decremental properties, multiple APs, or AVNRT with a bystander AP. The relative infrequency of such types of SVT did not allow for inclusion of these patients. Hence, our findings must be viewed as preliminary pending studies with such various types of SVT. Finally, the protocol of this study did not include assessment of effects of VES introduced earlier than the His deflection or VES delivered at the His recording region or the left ventricle with regard to enhancement of the diagnostic yield.

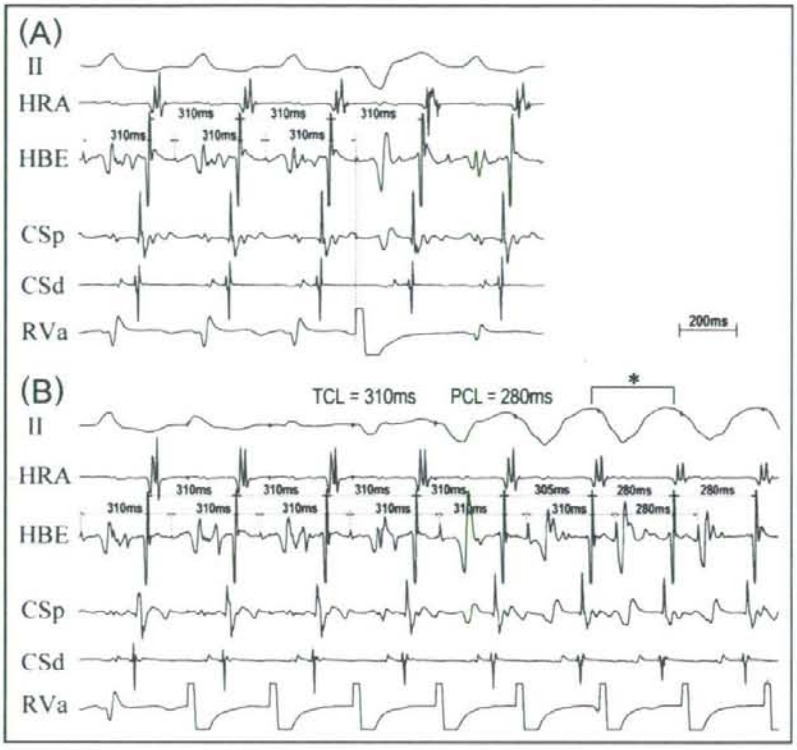

Figure 3. Simultaneous recordings of intracardiac electrograms and surface electrocardiogram lead II obtained from a 49-year-old man with a left lateral AP. *(A)* A VES elicited from the right ventricular apex at the time of His deflection did not affect the A-A interval encompassing the extrastimulus. *(B)* In the same patient, the H-H interval preceding the first atrial entrained cycle (*) during VOD pacing from the right ventricular apex (same stimulation site as in Figure 3A) was longer than the A-A interval by as much as 30 ms, which is diagnostic for the presence of an AP. CSd = distal coronary sinus; HBE = His recording site; other abbreviations as in Figure 2.

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ORIGINAL ARTICLE

**Yuichi Ninomiya · Shuichi Hamasaki · Keishi Saihara
Sanemasa Ishida · Tetsuro Kataoka · Masakazu Ogawa
Koji Orihara · Naoya Oketani · Tsuyoshi Fukudome
Hideki Okui · Tomoko Ichiki · Takuro Shinsato
Takuro Kubozono · Etsuko Mizoguchi · Hitoshi Ichiki
Chuwa Tei**

Comparison of effect between nitrates and calcium channel antagonist on vascular function in patients with normal or mildly diseased coronary arteries

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Abstract The comparative long-term antianginal efficacy of long-acting nitrates versus calcium channel antagonists remains unclear. The goal of the present study was to compare the coronary endothelial cell function and coronary artery vasoconstriction between patients with normal or mildly diseased coronary arteries treated with long-acting nitrates or calcium channel antagonists. Forty-two patients suspected to have angina pectoris and with normal or mildly diseased coronary arteries underwent Doppler flow study of the left anterior descending coronary artery. All patients were suspected to have angina pectoris and were receiving either long-acting nitrates ($n = 18$; Nitrates group) or calcium channel antagonists ($n = 24$; Ca-antagonists group) for at least 1 year. Vascular reactivity was assessed by intracoronary administration of papaverine, acetylcholine (Ach), and nitroglycerin using a Doppler guidewire. Segments that showed the greatest constrictive response to Ach were used for assessment of vasoconstriction. The percent increase in coronary blood flow (CBF) and coronary artery diameter (CAD) induced by Ach was significantly smaller in the Nitrates group than in the Ca-antagonists group (33% ± 74% vs 83% ± 77%, $P < 0.05$; −3% ± 16% vs 11% ± 12%, $P < 0.01$, respectively). The percent diameter reduction in the region of greatest constrictive response to Ach was significantly greater in the Nitrates group than in the Ca-antagonists group (44% ± 39% vs 15% ± 32%, $P < 0.02$). Long-term treatment with long-acting nitrates may produce less favorable effects on coronary endothelial function and the constrictive response to Ach when compared with long-acting calcium channel antagonists in patients with normal or mildly diseased coronary arteries.

Key words Nitrates · Endothelial function · Shear stress · Vasoconstriction

Y. Ninomiya[1] · S. Hamasaki[1] (✉) · K. Saihara[1] · S. Ishida · T. Kataoka · M. Ogawa · K. Orihara · N. Oketani · T. Fukudome · H. Okui · T. Ichiki · T. Shinsato · T. Kubozono · E. Mizoguchi · H. Ichiki · C. Tei
Department of Cardiovascular, Respiratory and Metabolic Medicine, Graduate School of Medicine, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan
Tel. +81-99-275-5318; Fax +81-99-265-8447
e-mail: hamasksh@m.kufm.kagoshima-u.ac.jp

[1]These authors contributed equally to this study.

Introduction

Nitrates are widely used for the treatment of angina pectoris, and their ability to reduce left ventricular remodeling and cardiac mortality during acute myocardial infarction has been well described.[1,2] Recent large mega-trials (GISSI-3 and ISIS-4) failed to demonstrate any benefit for nitroglycerin on mortality in patients with acute myocardial infarction. Since these studies utilized populations that received nitrates for 5–6 weeks, the effect of long-term administration of nitrates remains unclear.[3,4] However, Ishikawa et al.[5] suggested that long-term use of nitrates increased cardiac events in patients with previous myocardial infarction. The pharmacologic and physiologic mechanisms of this unfavorable result remain unknown, but may involve neurohormonal counter-regulatory mechanisms, impaired nitrates biotransformation, or intrinsic changes in the vasculature.[6–8]

Calcium (Ca) channel antagonists have also been used for the treatment of angina pectoris. The negative cardiovascular impact of some short-acting formulations of Ca channel antagonists was described in the 1990s and has led to the reduced use of Ca channel antagonists.[9–11] However, several recent randomized studies have suggested that long-acting Ca channel antagonists are safe and beneficial for the treatment of coronary artery disease.[12–14]

Many patients were suspected to have angina pectoris based on clinical history of chest pain symptoms elicited by their physicians rather than by objective findings on cardiac catheterization, and these patients were treated with either nitrates or calcium channel antagonists. Many studies have demonstrated that endothelial dysfunction is one of the earliest markers in patients with atherogenic risk factors

(e.g., male gender, aging, hypertension, diabetes mellitus, smoking, family history) in the absence of angiographic evidence of atherosclerosis.[15-17] Further, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and long-acting Ca-antagonists have been reported to alleviate endothelial dysfunction.[18,19] Therefore, patients with normal or mildly diseased coronary arteries were selected as the study population with the goal of comparing coronary endothelial cell function and coronary artery vasoconstriction between the patients treated with long-acting nitrates and those treated with calcium channel antagonists. Moreover, to explore the hypothesis that shear stress may be associated with impairments in coronary endothelial function, this study investigated shear stress and endothelial function in patients undergoing treatment with long-acting nitrates or calcium channel antagonists.

Subjects and methods

Study population

Forty-two patients with suspected angina pectoris (15 women, 27 men; 63 ± 12 years) and normal coronary caliber or mildly stenotic coronary lesions (% diameter stenosis <30%) were enrolled in this study. All participants were receiving long-acting nitrates (Nitrates groups) or calcium channel antagonists (Ca-antagonists group) and underwent Doppler flow study of the left anterior descending coronary artery. The Nitrates group consisted of 18 patients undergoing nitrate therapy for at least 1 year (average of 2.5 years), and the Ca-antagonists group consisted of 24 patients undergoing treatment with Ca channel antagonists for at least 1 year (average of 2.3 years). Inclusion criteria were: (1) angiographically smooth arteries; (2) mild irregularities with no coronary artery lesion >30% lumen diameter stenosis by visual assessment in major epicardial vessel; and (3) proximal coronary arteries >2.0 mm. Patients with previous myocardial infarction, previous coronary revascularization, valvular heart disease, vasospastic angina, cardiomyopathy, or myocarditis were excluded from study. Nitrates or Ca channel antagonists were administered orally during the study, in continuous dosing; patients in the Nitrates group received long-acting isosorbide dinitrate (40 mg/day) or long-acting isosorbide mononitrate (40 mg/day), while patients in Ca-antagonists group received long-acting amlodipine besylate (5 mg/day), or long-acting nifedipine (20 mg/day). Written informed consent was obtained from all patients before catheterization in accordance with guidelines established by the Committee for the Protection of Human Subjects in our institution.

Study protocol

Diagnostic coronary angiography was performed using a 6-F Judkins catheter with a standard femoral percutaneous approach. Five thousand units of heparin were administered at the beginning of the procedure. Nonionic contrast material was used for all patients. No nitroglycerin was given prior to the diagnostic procedure.

Coronary blood flow response to papaverine, acetylcholine (Ach), and nitroglycerin was studied according to previous reports.[20-22] After completion of the diagnostic catheterization, interventions were performed as follows: (1) a 0.014-inch Doppler guidewire (Cardiometrics, Santa Anna, CA, USA) was introduced into the left anterior descending coronary artery; (2) after obtaining a stable Doppler signal, a bolus of papaverine (an endothelium-independent vasodilator in resistance coronary arteries) (12.5 mg/5 ml) was injected through a catheter; (3) infusion of Ach (an endothelium-dependent vasodilator in resistance and epicardial coronary arteries) (0.5 ml/min) at dosages of either 3 or 30 μg/min for 2 min was performed via the catheter;[23,24] and (4) a bolus of nitroglycerin (an endothelium-independent vasodilator in epicardial coronary arteries) (200 μg/5 ml) was administered. Drugs were infused at least 5 min apart. Coronary angiography was performed before and 2 min after each dose of Ach and after administration of nitroglycerin. The infusion of Ach was terminated either when a significant vessel constriction occurred or when the dose of 30 μg/min was reached. Phasic coronary blood flow velocities, arterial blood pressure, and heart rate were monitored continuously and recorded. Measurements obtained during steady state conditions were used as control values for later analysis.

Quantitative coronary angiographic images

Technically suitable single-plane angiograms were selected for computer analysis. Quantitative coronary angiographic images (DBAC-1000; MID, Fukuoka, Japan) were recorded using validated densitometric analysis, as previously reported.[25] Endothelium-dependent and -independent vasodilation of the epicardial coronary artery was estimated by measuring the coronary artery luminal diameter at the tip of the Doppler guidewire. Segments showing the greatest constrictive response to Ach in the left anterior descending coronary artery were used for analysis of vasoconstriction. The degree of vasoconstriction induced by Ach was normalized by the diameter obtained at baseline and is presented as the percent diameter reduction.

Assessment of coronary blood flow

Doppler flow velocity spectra were analyzed on-line to determine time-averaged peak velocity. Volumetric coronary blood flow (CBF) was determined using the formula: CBF = cross-sectional area × average peak velocity × 0.5.[26] Coronary flow reserve (CFR) to papaverine was calculated as the ratio of maximal CBF induced by papaverine to basal CBF, which reflects the endothelium-independent function of the resistance coronary artery. Endothelium-dependent function was calculated as the percent increase of CBF or coronary artery diameter (CAD) in response to Ach. Endothelium-independent vasodilation of the epicardial

coronary artery was assessed by the percent increase of CAD in response to nitroglycerin.[20,22]

Coronary wall shear stress

The Doppler guidewire tip was placed at the target lesion to record average peak velocity at baseline. All parameters were calculated on a beat-to-beat basis for 30s and averaged. Aortic blood was then collected to measure blood viscosity. Coronary wall shear stress (in dynes per centimeter squared) was estimated by the Hägen–Poiseuille formula $(4\mu Q)/(\pi r^3)$, where Q is coronary blood flow, μ is the blood viscosity, and r is the radius of the lumen. Dynamic viscosity, μ, was calculated from the shear rate, hematocrit, and total protein, according to the regression equations described by de Simone et al.[27]

Statistical analysis

Values are expressed as the mean ± SD. Statistical significance was accepted when the P value was less than 0.05. The relationship between two parameters was evaluated with a linear regression analysis. Comparison of the baseline cardiovascular risk variables between the two groups was performed using Pearson's chi-square test, and comparisons of hemodynamic and echocardiographic data between the study groups were performed using one-way analysis of variance.

Results

A total of 42 patients were evaluated. Patient characteristics of both groups are summarized in Table 1. Gender distribution, age, body mass index (BMI), New York Heart Association (NYHA) classification, and additional cardiovascular drugs were similar when comparing the two groups. The prevalence of hypertension and smoking were significantly higher in the Ca-antagonists group than in the Nitrates group, whereas the prevalence of hyperlipidemia and diabetes were similar when comparing the two groups. Total-cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, fasting plasma sugar, left ventricular dimension at diastole and systole, intraventricular septum thickness, left ventricular (LV) posterior wall thickness, LV mass, and systolic, diastolic, and mean arterial pressure were also similar when comparing the two groups (Table 2).

Coronary wall shear stress

Comparisons of coronary wall shear stress are shown in Fig. 1. Coronary wall shear stress at baseline was significantly greater in the Nitrates group than in the Ca-antagonists group (109 ± 54 vs 76 ± 30 dynes/cm^2, $P < 0.02$). Both coronary artery diameter (CAD) and coronary blood flow (CBF) at baseline were similar when comparing the Nitrates group and the Ca-antagonists group (2.9 ± 0.4 vs 3.2 ± 0.6 mm; 88 ± 46 vs 83 ± 58 ml/min, respectively).

Changes in coronary blood flow

The percent change in CBF induced by papaverine and Ach is shown in Fig. 2. The percent increase in CBF induced by Ach was significantly smaller in the Nitrates group than in the Ca-antagonists group (33% ± 74% vs 83% ± 77%, $P < 0.05$). The percent change in CBF induced by papaverine tended to be smaller in the Nitrates group than in the Ca-antagonists group (195% ± 93% vs 230% ± 94%), but this difference did not reach the level of statistical significance.

Table 1. Patient characteristics

	Nitrates group ($n = 18$)	Ca-antagonists group ($n = 24$)	
Men	10/18 (56%)	17/24 (71%)	NS
Age (years)	63 ± 17	63 ± 8	NS
BMI (kg/m^2)	24.0 ± 4.1	24.0 ± 3.5	NS
Hyperlipidemia	7/18 (39%)	8/24 (33%)	NS
Diabetes	4/18 (22%)	5/24 (21%)	NS
Hypertension	7/18 (39%)	19/24 (79%)	$P < 0.01$
Smoking	3/18 (17%)	11/24 (46%)	$P < 0.05$
NYHA classification			
Class I	7/18 (39%)	14/24 (58%)	NS
Class II	11/18 (61%)	10/24 (42%)	NS
Medication			
ACE inhibitor	4/18 (22%)	8/24 (33%)	NS
AT-II antagonist	7/18 (39%)	7/24 (29%)	NS
β-blocker	3/18 (17%)	3/24 (13%)	NS
Nicorandil	1/18 (6%)	3/24 (13%)	NS
Statin	2/18 (11%)	3/24 (13%)	NS
Aspirin	8/18 (44%)	9/24 (38%)	NS

Values are mean ± SD
BMI, body mass index; ACE, angiotensin converting enzyme; AT-II, angiotensin II; NS, not significant

Table 2. Patient characteristics

	Nitrates group ($n = 18$)	Ca-antagonists group ($n = 24$)	
Laboratory data			
Total cholesterol (mg/dl)	187 ± 32	186 ± 32	NS
Triglyceride (mg/dl)	119 ± 45	108 ± 39	NS
HDL-cholesterol (mg/dl)	48 ± 14	53 ± 12	NS
LDL-cholesterol (mg/dl)	116 ± 26	115 ± 24	NS
Fast plasma sugar (mg/dl)	99 ± 23	105 ± 18	NS
Echocardiographic data			
LVDd (mm)	52 ± 9	52 ± 9	NS
LVDs (nm)	37 ± 13	34 ± 10	NS
IVS (mm)	14 ± 7	14 ± 6	NS
LVPW (mm)	11 ± 2	11 ± 4	NS
LVMI (g)	265 ± 92	260 ± 109	NS
Hemodynamics data			
Systolic BP (mmHg)	122 ± 20	132 ± 17	NS
Diastolic BP (mmHg)	73 ± 14	80 ± 12	NS
Mean BP (mmHg)	89 ± 16	98 ± 12	NS

Values are mean ± SD

HDL and LDL, high- and low-density lipoprotein cholesterol; LVDd, left ventricular dimension at diastole; LVDs, left ventricular dimension at systole; IVS, interventricular septum thickness; LVPW, left ventricular post wall thickness; LVMI, left ventricular mass index; BP, blood pressure; NS, not significant

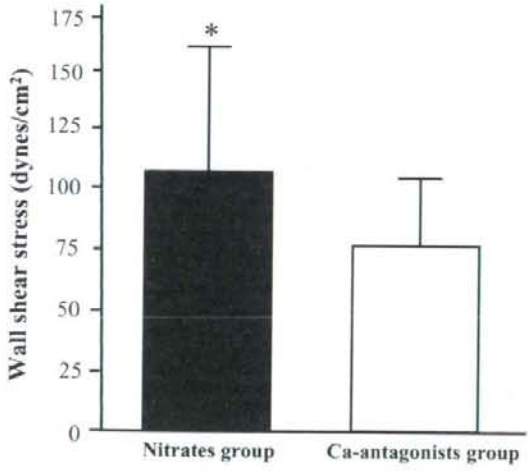

Fig. 1. Wall shear stress in the two study groups. Mean ± SD. *$P < 0.05$ vs Ca-antagonists group

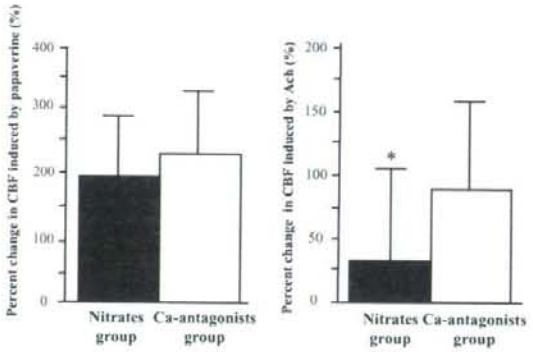

Fig. 2. Percent change in coronary blood flow (*CBF*) induced by papaverine and the percent change in CBF induced by acetylcholine (*Ach*) in the two study groups. Mean ± SD. *$P < 0.05$ vs Ca-antagonists group

Changes in coronary artery diameter

The percent change of CAD induced by Ach and nitroglycerin is shown in Fig. 3. Baseline CAD did not differ when comparing the two groups. The percent change in CAD induced by Ach was significantly smaller in the Nitrates group than in the Ca-antagonists group (−3% ± 16% vs 11% ± 12%, $P < 0.01$). The percent change in CAD induced by nitroglycerin tended to be smaller in the Nitrates group than in the Ca-antagonists group (15% ± 13% vs 21% ± 22%), but this difference did not reach the level of statistical significance.

Coronary vasoconstriction induced by Ach

Constrictor responses to Ach were quantified as percent reduction in luminal diameter relative to the luminal diameter obtained at baseline (Fig. 4). The percent reduction in luminal diameter was significantly greater in the Nitrates group than in the Ca-antagonists group (44% ± 39% vs 15% ± 32%, $P < 0.05$).

Discussion

This study may show that endothelium-dependent vasodilation of the resistance and epicardial coronary arteries are more impaired and that epicardial coronary arteries are

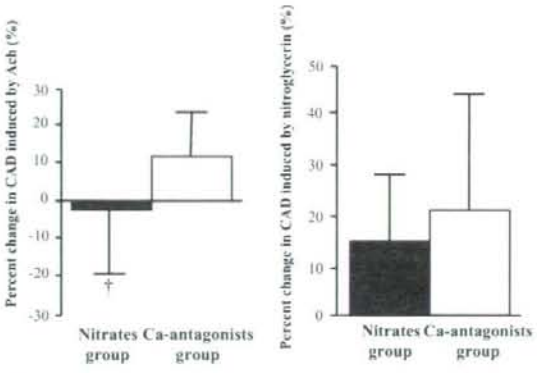

Fig. 3. Percent change in coronary artery diameter (*CAD*) induced by Ach and the percent change in CAD induced by nitroglycerin in the two study groups. Mean ± SD. †$P < 0.01$ vs Ca-antagonists group

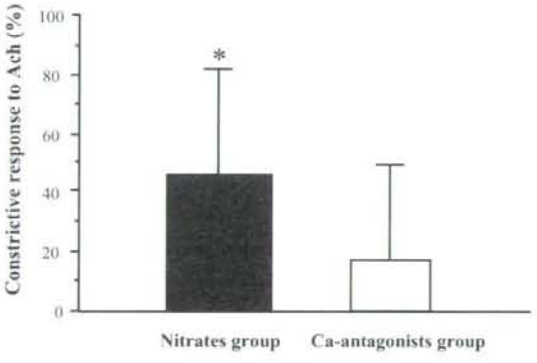

Fig. 4. Constrictive response to Ach in the two study groups. Mean ± SD. *$P < 0.05$ vs Ca-antagonists group

more vulnerable to Ach-induced coronary spasm in patients undergoing long-term treatment with nitrates when compared with those undergoing long-term treatment with Ca channel antagonists. This study may also demonstrate that long-term treatment with nitrates result in impaired endothelium-dependent coronary artery vasodilation, possibly via increases in wall shear stress.

Effect of long-term nitrate therapy

Recently, the GISSI-3 study failed to demonstrate any beneficial effect of 6 weeks of transdermal nitroglycerin therapy on mortality rate following acute myocardial infarction, and the ISIS-4 study failed to demonstrate any survival benefit in the first 5 weeks following a 1-month course of nitrate treatment.[3,4] Further, Ishikawa et al.[5] suggested that long-term treatment with nitrates increased cardiac events in patients with previous myocardial infarction. Nakamura et al.[28] performed prospective analysis of data acquired in a large, observational study involving 1042 patients enrolled in the MSMI study and 1779 patients enrolled in the MDPIT, and demonstrated that nitrate therapy was associated with a significantly increased risk of mortality in patients that had recovered from an acute coronary event.[29,30] However, these reports were different from our study because most of their subjects were patients with previous myocardial infarction who received short-term nitrates treatment. Caramori et al.[31] demonstrated exaggerated coronary vasomotor response after nitrate treatment and also described in detail impaired endothelial dysfunction elicited by long-term nitrate therapy. However, the period of nitrate therapy in that study was only 5 days, and nitrates were administered continuously via transdermal patch. In our study, patients with suspected angina pectoris received oral nitrate treatment for at least 1 year (average of 2.3 years). Furthermore, Parker and Gori[32] described in detail impaired endothelial dysfunction elicited by long-term nitrates treatment and suggested caution with this regimen.

Potential mechanisms underlying nitrate therapy and poor outcomes

Mechanisms that may account for the unfavorable effect of nitrate therapy on long-term outcomes in patients with coronary artery disease include nitrate tolerance and activation of the neurohumoral system.[33–35] Endothelial nitric oxide synthase (eNOS) is constitutively expressed and activated by cell surface receptors or mechanical forces such as shear stress and stretch.[36] Nitric oxide released by vascular endothelial cells mediates relaxation of vascular smooth muscle, inhibition of platelet activation, and modulation of migration and growth of vascular smooth muscle. Several reports suggest that alterations in the NO pathway might be involved in endothelial dysfunction and atherosclerosis.[37–40]

Shear stress is the principal fluid-mechanical signal that regulates flow-mediated remodeling and therefore provides functional assessment of the adequacy of flow-mediated remodeling.[41,42] Shear stress-mediated signal transduction is endothelium-dependent, and, in the present study, wall shear stress at baseline was greater in the Nitrates group than in the Ca-antagonists group.[43,44] Further, intracoronary Ach-induced endothelium-dependent vasodilation in conduit and resistance coronary arteries was lower in the Nitrates group than in the Ca-antagonists group.

Nitric oxide production can be stimulated by mechanical forces, such as shear stress, or by signal transduction pathways activated by Ach.[45] In the present study, the Nitrates group demonstrated impaired response to Ach and a greater response to shear stress when compared with the Ca-antagonists group. Thus, it is possible that NO overproduction in response to shear stress results in downregulation of Ach-activated signal transduction elements. Indeed, Griscavage et al.[46] reported that NO inhibits the activity of nitric oxide synthase. Therefore, NO generated from exogenous nitrate therapy may also suppress Ach-induced synthesis of NO. In the present study, shear stress was greater in the Nitrates

group than in the Ca-antagonists group. Thus, suppression of Ach-induced NO synthesis may result in less Ach-induced vasodilation in the Nitrates group than in the Ca-antagonists group.

Association between coronary endothelial function and coronary events

In this study, the prevalence of atherogenic risk factors (e.g., hypertension and smoking) were significantly higher in the Ca-antagonists group than in the Nitrates group. However, long-term treatment with long-acting nitrates was more closely associated with impaired endothelium-dependent vasodilation. Thus, the higher prevalence of hypertension and smoking in the Ca-antagonists group did not affect the results in this study.

Since the endothelium is regarded as an atheroprotective cell line, loss of endothelial cell function would logically be associated with progression of atherosclerotic disease. Indeed, Suwaidi et al.[47] reported that patients with mild coronary artery disease and severe endothelial dysfunction are at increased risk for cardiac events, and Schachinger et al.[48] demonstrated that coronary endothelial dysfunction predicted long-term atherosclerotic disease progression and cardiovascular events. These patient population of this study comprised patients without coronary artery disease. Therefore, our study suggests that treatment of patients with normal or mildly diseased coronary arteries with long-acting nitrates may be associated with cardiovascular events due to coronary endothelial dysfunction.

Abnormal vascular responses to acetylcholine, as demonstrated in the present study, may represent a reduction in NO bioavailability.[49] A decrease in NO bioavailability is associated with accelerated atherogenesis and increased monocyte–endothelial cell adhesion, which may result in local inflammation of the vascular wall and promote plaque rupture.[50,51] Further, absence of an appropriate increase in blood flow secondary to endothelial cell dysfunction may lead to relative myocardial ischemia even in the absence of coronary artery disease.[22,52]

Limitations

This study possesses several limitations. First, the calculations used for shear stress assumed a steady laminar flow in a circular, rigid, nontapering tube. Therefore, the current study investigated hemodynamic in circular, discrete, and mildly stenotic target lesions while excluding marked curvatures and bifurcations of the coronary arteries when measuring coronary blood flow and wall shear stress. Second, this study was not performed in a prospective and randomized fashion. A randomized, placebo-controlled trial would be of benefit in confirming the unfavorable effects of long-term nitrate therapy on coronary endothelial function and coronary vasoconstriction. Third, only patients with normal or mildly diseased coronaries were studied. Thus, the findings of this study cannot be applicable to the patients with significant coronary artery disease. Finally, the response to papaverine, acetylcholine, and nitroglycerin was tested without withdrawal of nitrates or calcium antagonists. However, we performed coronary catheterization in combination with a Doppler flow study without stopping these medications for the following reasons. First, the prevalence of coronary spastic angina is apparently higher in Japanese patients with coronary heart disease than in their Caucasian counterparts.[53] Thus, we were afraid that if we stopped these medications, a coronary spasm would occur during control coronary angiography and disturb the exact estimation of coronary function. Second, we were interested in the direct effect of nitrates and calcium channel antagonists on coronary endothelial function and coronary artery vasoconstriction at the time when the patients were under the effect of these medications.

Conclusions

When compared with long-term treatment with long-acting Ca channel antagonists, long-term treatment with long-acting nitrates may be more closely associated with impaired endothelium-dependent vasodilation in conduit and resistance coronary arteries and with an exaggerated vasoconstrictive response in conduit coronary arteries in patients with normal or mildly diseased coronary arteries, potentially via increases in wall shear stress.

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