Tight Heart Rate Control Reduces Secondary Adverse Events in Patients With Type B Acute Aortic Dissection

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***Background*—**Although type B aortic dissection has been treated with β blockers to lower the arterial blood pressure (BP), there has been little evidences about reduction in heart rate (HR). We assessed whether tight HR control improved the outcome of medical treatment in patients with aortic dissection.

***Methods and Results*—**From 1997 to 2005, 171 patients with acute aortic dissection medically treated and controlled to lower BP under 120 mm Hg were enrolled. Based on the average HR at 3, 5, and 7 days after the onset, patients were divided into tight HR (<60 beat per minute) control group (32 patients; mean HR of 56.6±3.1 beat per minute) and conventional HR (≥60 beat per minute) control group (139 patients; mean HR of 71.7±8.2 beat per minute). We compared the frequency of aortic events including late organ or limb ischemia, aortic rupture, recurrent dissection, and aortic expansion of >5 mm, and surgical requirement between two groups. During a median follow-up of 27.0 months, late organ or limb ischemia, aortic rupture, recurrent dissection, pathological aortic expansion, and aortic surgery occurred in 0, 8, 14, 39, and 26 patients, respectively. Reduction in aortic events was observed in tight HR control group (12.5%) compared to conventional HR control group (36.0%), (Odds ratio: 0.25, C.I.: 0.08 to 0.77, $P<0.01$).

***Conclusions*—**The present study demonstrated that tight heart rate control improved the outcome of medical treatment in patients with aortic dissection. **(*Circulation*. 2008;118[suppl 1]:S167–S170.)**

Key Words: aortic dissection ■ heart rate ■ medical treatment ■ secondary adverse events

Aortic dissection is a catastrophic cardiovascular disease associated with high morbidity and mortality.[1] Blood pressure control using β-adrenergic receptor blocker is widely accepted for treating type B acute aortic dissection.[2] The goal is to lower systolic blood pressure to the lowest level commensurate with adequate vital organ perfusion, usually 100 to 120 mm Hg.[3] Although lowering heart rate is also thought to be important, the target setting of heart rate has not been well established.

We conducted this study to assess whether tight heart rate control, <60 beat per minute (bpm), reduced subsequent adverse events in patients with type B acute aortic dissection.

Methods

Patients

From 1997 to 2005, 224 patients with type B acute aortic dissection were admitted to our institutions within 2 days from the onset. The diagnosis was confirmed by clinical and diagnostic evaluations consisting of combinations by imaging modalities such as contrast-enhanced computed tomography (CT), MRI, or transesophageal echocardiography. The onset was defined as the first instance of pain or discomfort. Patients with the aorta of more than 5 cm in maximum aortic diameter, aortic rupture, systolic left ventricular dysfunction (less than 40% in ejection fraction), ischemic organs disturbance within 3 days after the onset, prior aortic dissection, prior cardiovascular surgery, malignancy, intractable hypertension (systolic blood pressure had not achieved less than 120 mm Hg within 3 days after the onset), or Marfan syndrome were excluded. The remaining 171 patients were enrolled to this study.

Treatment and Long-Term Follow-Up

Propranolol, diltiazem, verapamil, nicardipine, or nitroglycerine were administered intravenously to reduce systolic blood pressure to 100 to 120 mm Hg as initial therapy. Oral antihypertensive agents were also administered in the acute phase. Intravenous antihypertensive agents were tapered as systolic blood pressure achieved to 100 to 120 mm Hg by oral antihypertensive agents. Beta blocker was administered to all patients except those with the contraindication including chronic obstructive pulmonary disease and allergy for the drug. Patients with contraindication for β blocker took diltiazem or verapamil to reduce dP/dt. Plural antihypertensive agents were used to maintain to appropriate systolic blood pressure under 120 mm Hg unless any adverse effects attributable to the drugs were observed.

Heart rates and blood pressure were measured at 6 AM, noon, and 6 PM everyday during the admission. Based on the average heart rate at 3, 5, and 7 days after the onset, patients were divided into 2 groups, tight heart rate (<60 bpm) control and conventional heart rate (≥60 bpm) control groups.

After the discharge, the follow-up information was obtained with clinic visits to our hospital including CT examinations once a year

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Table 1. Univariate Logistic Analysis of Clincal and Demographic Varibles to Predict Aortic Events and Surgical Requirement

	Aortic Events			Surgical Requirement		
Variables	Odds Ratio	(95% CI)	*P* Value	Odds Ratio	(95% CI)	*P* Value
Heart rate	0.538	(0.054–5.412)	0.594	0.203	(0.012–3.571)	0.268
Hemodialisis	0.327	(0.042–2.030)	0.223	0.769	(0.108–15.374)	0.822
Diabetes	1.337	(0.563–3.442)	0.519	1.200	(0.412–4.379)	0.753
Overt AD	0.586	(0.301–1.134)	0.112	0.864	(0.371–2.036)	0.734
Beta blocker	1.363	(0.607–2.988)	0.446	0.658	(0.182–1.889)	0.458
ACEi	1.038	(0.538–2.004)	0.910	1.038	(0.538–2.004)	0.910
ARB	0.717	(0.364–1.418)	0.337	0.717	(0.364–1.418)	0.337
ACEi or ARB	0.929	(0.433–1.932)	0.847	0.929	(0.433–1.932)	0.847
CCB	0.267	(0.192–1.705)	0.366	0.619	(0.192–1.705)	0.366
Statin	0.599	(0.222–1.664)	0.317	0.599	(0.222–1.664)	0.317

AD indicates aortic dissection; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

and interviews with the family physicians, the patient, or the patient's family. The aortic events including late organ or limb ischemia, aortic rupture, recurrent dissection, and aortic expansion of >5 mm, and surgical requirements were compared between the tight heart rate control group and the conventional heart rate control group.

Statistical Analysis

Data are expressed as mean±SD or as proportions. Univariate analysis was performed on all clinical and demographical variables with χ^2 test and Fisher exact test used for categorical variables and Student *t* test used for continuous variables. Univariate logistic analysis was done to evaluate the prognostic values of demographical and therapeutic variables on type B aortic dissection. The aortic event free rate and surgical requirement free rate were estimated by Kaplan–Meier analysis. Odds ratios were given with 95% confidence intervals. A probability value <0.05 was considered statistically significant. JMP6.0.3 (SAS Institute Inc) was used for statistics analysis.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Influences of Demographical and Therapeutic Variables on the Long-Term Aortic Events and Aortic Surgery for the Long-Term Follow-Up

One hundred sixty patients (94%) were followed-up (a median follow-up of 27 months; 6.9 to 57.0 months), and 106 patients (63.5%) had visited our hospital regularly for more than 2 years. The compliance of medications was confirmed in 132 cases (84%) from clinic visits to our hospital and interviews from the family physicians and patients. Ninety-eight percent of those patients were good compliant with medications. Systolic blood pressure was maintained to less than 130 mm Hg at the last clinic visit to our hospital or the family physician in those patients.

Aortic rupture, recurrent aortic dissection, pathological aortic expansion, and aortic surgery occurred in 8, 14, 39, and 26 patients, respectively. Heart failure, organ malperfusion, and renal failure did not occur. When 38 patients were rehospitalized to our hospital because of aortic events including recurrent dissection and impending rupture, the average blood pressure at the admission was 137±20/75±16 mm Hg.

The influences of heart rate, medications, conditions of the false lumen, and compromised disease including hemodialysis and diabetes on the long-term aortic events and surgical requirement were analyzed (Table 1). None of those variables correlated with the long-term aortic events and surgical requirement significantly.

The frequency of aortic events among the groups divided by heart rate control levels per 10 bpm increase was shown in Table 2. The heart rate of <60 bpm control group had less aortic events and aortic surgical requirement than the heart rate of 60 to <70 bpm control group and the heart rate of 70 to <80 bpm control group significantly ($P<0.05$).

Tight Heart Rate Control Versus Conventional Heart Rate Control

There were 32 patients in the tight heart rate (<60 bpm) control group (mean heart rate of 56.6±3.1 bpm) and 139 patients in the conventional heart rate (≥60 bpm) control group (mean heart rate of 71.7±8.2 bpm). All patients in tight HR control group were maintained to heart rate under 60 bpm after discharge from information of clinic visits to our hospital or the family physicians. The demographical data and medications before and after admission, of the patients in the 2 groups are listed in Table 3. Although the age in tight

Table 2. The Frequency of Aortic Event Among Heart Rate Control Levels per 10 bpm Increase

Heart Rate Control Level	Frequency of Aortic Event	Frequency of Surgical Requirement
<60 bpm (n=32)	4 (12.5%)	0
60–70 bpm (n=65)	25 (38.5%)*	13 (20%)*
>70−80 bpm (n=56)	20 (35.7%)*	11 (19.6%)*
>80 bpm (n=18)	5 (27.8%)	2 (11.1%)

bpm indicates beat per minute.

*$P<0.05$ by Fisher exact test compares heart rate control of less than 60 bpm group.

Table 3. Patients Characteristics and Medications

	Tight HR Control Group	Conventional HR Control Group	*P*
Demographics			
No. of patients	32	139	
Mean HR	56.6±3.1 bpm	71.7±8.2 bpm	
Mean systolic BP, mm Hg	108±6	110±31	N.S.
Mean diastolic BP, mm Hg	60±5	60±6	N.S.
Mean age, y	74.1±10.3	69.1±11.7	0.02
Male, n (%)	24 (75.0%)	88 (63.3%)	N.S.
Hemodialisis, n (%)	1 (3.1%)	4 (2.9%)	N.S.
Intramural hematoma, n (%)	17 (53.1%)	80 (57.6%)	N.S.
Medications			
Beta-blocker, n (%)	25 (78.1%)	110 (79.1%)	N.S.
ACEi or ARB, n (%)	23 (71.9%)	102 (73.4%)	N.S.
ACEi, n (%)	16 (50.0%)	72 (51.8%)	N.S.
ARB, n (%)	10 (31.3%)	48 (34.5%)	N.S.
CCB, n (%)	29 (90.6%)	122 (87.8%)	N.S.
Statin, n (%)	4 (12.5%)	14 (10.1%)	N.S.
Prehospitalanti-hypertensive m edication, n (%)	28 (87.5%)	128 (92.1%)	N.S.
Atrialfibrillation, n (%)	1 (3.1%)	6 (4.3%)	N.S.
COPD, n (%)	2 (6.3%)	12 (8.6%)	N.S.
Period until the relief of pain since the admission, n (%)	1.3±0.6	1.3±0.7	N.S.
Length of ICU stay, days	4.0±1.6	5.0±5.4	N.S.
Length of hospital stay, days	20.0±9.9	23.6±8.8	N.S.

HR indictes heart rate; bpm, beat per minute; BP, blood pressure; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensisn receptor blocker; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit. Results are displayed as absolute values and mean values (1±D). *P* compares tight HR control group and conventional HR control group.

HR control was significantly higher than that in conventional HR group, there was no significant difference in the other parameters between the 2 groups.

The frequency of aortic events between tight heart rate control group and conventional heart rate control group was shown in Table 4. Reduction in aortic events was observed in tight HR control group (12.5%) compared to conventional HR control group (36.0%; Odds ratio: 0.25, C.I.: 0.08 to 0.77, $P=0.0059$), and aortic surgery in the chronic phase significantly reduced in tight HR control group compared to conventional HR control group (0% versus 18.7%, $P=0.005$). A subgroup analysis in aortic intramural hematoma also showed that reduction in aortic events was observed in tight HR control group compared to conventional HR group (5.9% versus 31.3%, $P=0.036$). Kaplan–Meier aortic event free and surgical requirement free curves in two groups were showed in Figures 1 and 2.

Discussion

We evaluated the effect of heart rate on the prognosis of patients with type B aortic dissection under appropriate blood

Table 4. Secondary Adverse Events Between Tight Heart Rate Control Group and Conventional Heart Rate Control Group

	Tight HR Control Group (n=32)	Conventional HR Control Group (n=139)	*P*
Total aortic events, n (%)	4 (12.5%)	50 (36.0%)	0.011
Aortic expansion, n (%)	3 (9.4%)	36 (25.9%)	0.060
Recurrent aortic dissection, n (%)	1 (3.1%)	13 (9.4%)	N.S.
Aortic rupture, n (%)	1 (3.1%)	7 (5.0%)	N.S.
Aortic surgery, n (%)	0	26 (18.7%)	0.005

HR indicates heart rate.
P compares tight HR control group and conventional HR control group.

pressure control and demonstrated that tight heart rate control of <60 bpm reduced aortic events and surgical requirement in the long-term follow-up.

Patients suffering acute distal aortic dissection are at significantly lower risk of early death from complications of the dissection than are those with proximal dissection.[3] A large retrospective series involving patients from both Duke and Stanford universities has, by multivariate analysis, shown that medical therapy provides an outcome equivalent to that of surgical therapy in patients with uncomplicated distal dissection.[4,5]

Aggressive medical treatment of aortic dissection was first advocated in 1960s.[6,7] The authors established reduction of systolic blood pressure and diminution of the rate of left ventricular ejection (dP/dt) as the 2 primary goals of pharmacological therapy. Beta blocker has been recommended to administer to reduce dP/dt especially. Antihypertensive drugs have been administered in incremental dose until the achievement in the appropriate systolic blood pressure. There have been several reports that β-blocker had the favorable effects on aortic diseases.[8,9] The present study, however, did not reveal that the use of β blocker improved the prognosis significantly and showed that there was no significant difference of uses of β blocker between tight heart rate control group and conventional heart rate group, although the administered dose of β blocker might be different between 2 groups because of the intention treatment based on systolic blood

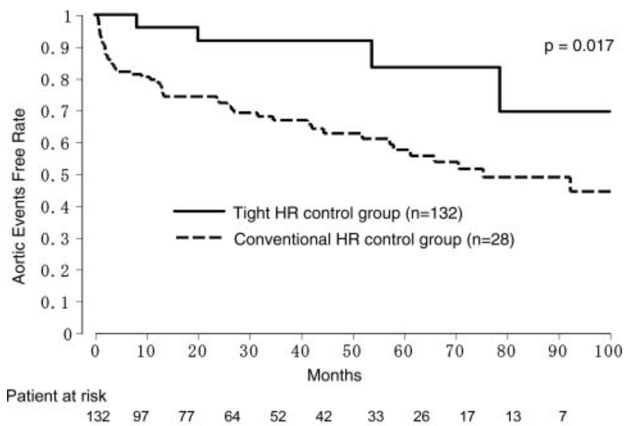

Figure 1. Kaplan–Meier aortic event free curves from tight heart rate control group and conventional heart rate control group.

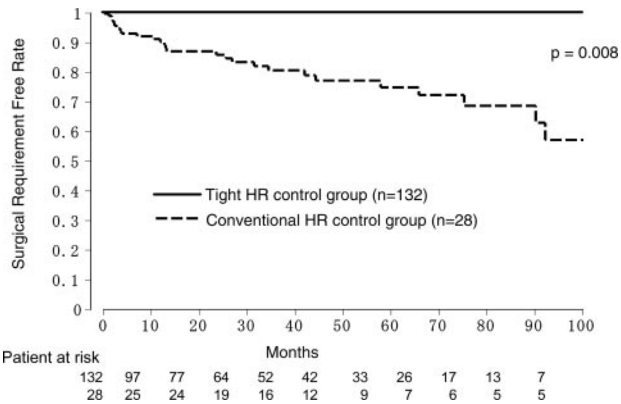

Figure 2. Kaplan–Meier surgical requirement free curves from tight heart rate control group and conventional heart rate control group.

pressure. Angiotensin converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) were also reported to improve the prognosis of aortic diseases.[10,11] This study could not disclose the significant effects of ACE inhibitor or ARB on the prognosis in patients with type B acute aortic dissection.

Heart rate reduction has been though to be an essential management. However, the mandatory setting of heart rate control for aortic dissection has not been established. The present study demonstrated that tight heart rate control of <60 bpm significantly decreased the secondary adverse events in type B aortic dissection compared to conventional heart rate control of ≥60 bpm, although heart rate did not correlate with the aortic events in patients with heart rate of ≥60 bpm.

The managements and the prognostic difference of overt dissection and aortic intramural hematoma have been controversial.[12–14] A subgroup analysis regarding aortic intramural hematoma in the present study indicated that the benefit of tight HR control for the prevention of aortic events was observed in this population.

There are several potential limitations in our study. First, this study was an observational study, although there was no significant difference in baseline characteristics and medications between tight heart rate control group and conventional heart rate control group. Second, the heart rate receptivity of medications and automatic nerve activity might influence the results of our study. They could recommend that βblocker should be administered in incremental dose to reduce automatic nerve activity sufficiently, and the heart rate of <60 bpm might be a landmark to determine the dose of βblocker. Third, heart rate control group was divided on the average of heart rate at 3 days, 5 days, and 7 days after the onset. The accurate level of heart rate control might require the average of heart rate using Holter ECG and the precise examination of heart rate during the chronic phase, although we evaluated heart rate 3 times a day during hospital stay and the level of heart rate control in the chronic phase was similar to that in the acute phase. Fourth, this was a single-center study experience that could reflect a certain referral population, limiting our ability to apply these findings to general population. Fifth, the sample size was relatively small and further large studies could be required to validate our findings. Sixth, it was unclear whether heart rate reduction could effect on visceral or peripheral malperfusion in this study because these events did not occur in this study population.

Conclusions

The present study demonstrated that tight heart rate control of <60 bpm improved the outcome of medical treatment in patients with aortic dissection. Further studies involving larger number of patients in a prospective multi-center setting may be needed to establish the management of heart rate for aortic dissection. Nevertheless, this study might provide an evidence for the medical therapy in acute aortic syndrome and we recommend medical treatment with a combination of the incremental dose of β blocker based on the tight heart rate control of <60 bpm and vasodilators for systolic blood pressure control of <120 mm Hg.

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Disclosures

None.

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