Diurnal Variation in Coronary Flow Velocity Reserve in Healthy Men

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Abstract

Background. A number of cardiovascular diseases show diurnal variation. However, it is unknown whether coronary circulation exhibits diurnal variation.

Methods. The flow velocities in the left anterior descending coronary artery of 15 healthy men were measured by transthoracic Doppler echocardiography both at rest and during intravenous infusion of adenosine triphosphate at 7 AM, noon, 5 PM and 9 PM. Coronary flow velocity reserve (CFVR) was calculated as the ratio of hyperemic to basal mean diastolic flow velocity. CFVR at 7 AM was significantly smaller than that at 9 PM ($p=0.001$; 7 AM, 3.23 ± 0.66 ; noon, 3.89 ± 0.86 ; 5 AM, 3.46 ± 0.65 ; 9 PM, 4.41 ± 1.11 , respectively). CFVR at 5 PM was also significantly smaller than that at 9 PM ($p=0.008$).

Conclusions. Diurnal variation in CFVR exists in healthy men. This finding may be related to the diurnal variation in cardiovascular events. (J Echocardiogr 2007; 5: 72-78)

Key words: coronary circulation, diurnal variation, Doppler echocardiography

Introduction

The frequencies of the onset of cardiovascular events such as transient myocardial ischemia, myocardial infarction and sudden cardiac death show marked diurnal variations. They most frequently occur in the morning or have bimodal distribution.[1-4] Hypercoagulability, hypofibrinolysis[5] and increased vascular tone[6] are the factors that have been proposed as underlying pathophysiological triggers of increased cardiovascular vulnerability at this time of day. Blood pressure[7] and sympathetic activation[8,

9] also have been shown to increase in the morning. Furthermore, recently, a growing number of investigations have suggested the existence of diurnal variation in endothelium-dependent function of vascular walls.[10-15] From these findings, we hypothesized that diurnal variation also may exist in coronary circulation.

Coronary flow reserve has been considered an important diagnostic index in coronary artery disease and other impaired coronary microcirculatory diseases such as hypercholesterolemia, diabetes, and hypertension.[16, 17] Impaired coronary flow reserve has been suggested as a surrogate measure of subclinical coronary atherosclerosis, providing an integrated measure of both vascular endothelial function and smooth muscle relaxation.[18]

Recent advances in transthoracic Doppler echocardiography (TTDE) have allowed the measurement of coronary flow velocity and the estimation of coronary flow reserve by measuring coronary flow velocity reserve (CFVR) in a noninvasive and reproducible

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manner.[19-21] The purpose of this study was to investigate whether diurnal variation exists in coronary circulation using CFVR measurement by noninvasive TTDE.

Methods

Study subjects

We studied 15 healthy men with a mean age of 29.5 years (range, 25-37 years). None had a history of hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, obesity or other risk factors for coronary artery disease. All the subjects had normal left ventricular size and function, confirmed by routine echocardiographic examination just before they were enrolled in this study. Measurements of CFVR by TTDE were performed at 7 AM, noon, 5 PM and 9 PM. To minimize the effect of diets on coronary circulation, all the subjects had meals just after collecting echocardiographic data except at 9PM. Subjects were randomly allotted to undergo their first study beginning either in the morning or evening. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all subjects.

Measurements of CFVR

Transthoracic echocardiography was performed with a Sequoia 512 (Siemens, Mountain View, CA) with a high frequency transducer of 5 to 7 MHz. Coronary flow velocity in the left anterior descending artery (LAD) was recorded by pulsed wave Doppler (frequency 3.5 MHz) under the guidance of color Doppler flow mapping and measured by Doppler spectral tracing of flow velocity obtained from first Fourier transformation analysis.[19]

Adenosine triphosphate (ATP) was administered by intravenous infusion (0.14mg/kg/min) for 2 min to record spectral Doppler signals during hyperemic conditions.[22] Example images from one of the subjects are shown in Figure 1. CFVR was calculated as the ratio of hyperemic to basal mean diastolic flow velocity. All studies were continuously recorded on half-inch super VHS videotape, and clips of stopped frames were also stored digitally on magneto-optical disks for off-line analysis. Angle correction was undertaken in each Doppler measurement (mean angle 32°; range, 0-56°).

Blood samples

Blood samples were obtained just prior to each TTDE measurement from all subjects to measure serum concentrations of total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol and

glucose.

Statistical analysis

All data were expressed as mean $\pm$ SD. One-way analysis of variance (ANOVA) was used to determine the effect of the time of day. Fisher's protested least-significant difference test was used for the post hoc test. For all analysis, $p < 0.05$ was considered significant.

Results

Complete CFVR data for all four periods were obtained from 12 (80%) of the 15 subjects. The other 3 subjects were excluded because of suboptimal images of Doppler spectral tracing. No patient showed atrioventricular block, chest pain, or palpitation during the administration of ATP in the TTDE studies. No significant differences were found in heart rate, systolic blood pressure and diastolic blood pressure during the administration of ATP (Table 1). Blood pressure and heart rate at baseline and during the administration of ATP did not change significantly among the four periods. Blood glucose level at 7 AM was significantly lower than those of other periods (Table 2). Serum concentrations of lipids including total cholesterol, triglyceride and HDL cholesterol did not change significantly among the four periods.

Diurnal change in mean diastolic velocity and CFVR

Coronary flow velocity data are in Table 1 and

Fig. 1 Coronary flow velocity profiles at baseline and hyperemia obtained from one of the subjects. Top, coronary flow velocity profile at baseline. Bottom, coronary flow velocity profile at hyperemic condition.

Table 1. Hemodynamic and Doppler echocardiographic data

	7:00 AM	Noon	5:00 PM	9:00 PM
HR (beats/min)				
Baseline	61±9	58±11	62±9	58±9
Hyperemia	65±9	64±13	64±11	61±9
Systolic BP (mmHg)				
Baseline	106±13	103±18	104±13	101±11
Hyperemia	100±14	99±17	101±12	95±12
Diastolic BP (mmHg)				
Baseline	57±8	54±11	54±11	52±9
Hyperemia	52±9	53±11	51±10	49±11
MDV (cm/s)				
Baseline	20.9±3.0*	18.6±4.6	17.9±3.5	16.3±3.2
Hyperemia	66.7±13.4	70.4±13.8	61.1±11.2**	71.7±11.9

* p<0.005 versus 9PM, ** p<0.05 versus 9PM, Values are mean±SD.

HR; heart rate, BP; blood pressure, MDV; mean diastolic velocity.

Table 2. Biochemical parameters

	7:00 AM	Noon	5:00 PM	9:00 PM
Lipids (mg/dl)				
T-Cho	176±30	172±33	177±29	174±28
TG	108±49	117±105	99±60	100±69
HDL-Cho	58±10	55±10	57±8	57±9
Glucose (mg/dl)	92±9	118±20*	118±21*	121±19*

*p<0.001 vs. 7:00 AM. Values are mean±SD.

T-Cho; total cholesterol, TG; triglyceride, HDL-Cho; high density lipoprotein cholesterol.

Figure 2. Baseline MDV at 7 AM was significantly greater than that at 9 PM (20.9 ± 3.0 cm/s versus 16.3 ± 3.2 cm/s, $p=0.003$). Hyperemic MDV at 5 PM was significantly smaller than that at 9 PM (61.1 ± 11.2 cm/s versus 71.7 ± 11.9 cm/s, $p=0.04$). CFVR was 3.23 ± 0.66 at 7 AM, 3.89 ± 0.86 at noon, 3.46 ± 0.65 at 5 PM and 4.41 ± 1.11 at 9 PM, respectively (Figure 2). CFVR at 7 AM was significantly smaller than that at 9 PM ($p=0.001$). CFVR at 5 PM was also significantly smaller than that at 9 PM ($p=0.008$). There was neither significant correlation between coronary blood flow velocity nor CFVR and blood glucose level, although blood glucose level at 7 AM was significantly lower than those of other periods.

Observer variability

Interobserver and intraobserver variabilities for measurement of Doppler velocity recordings were 5.0% and 3.9%, respectively.

Discussion

To our knowledge, the present study is the first to show that diurnal variation in coronary circulation exists in clinical setting. Significant diurnal variations

were demonstrated for both resting coronary blood flow velocity and CFVR. Namely, resting coronary blood flow was greatest at 7 AM, and CFVR was smallest at 7 AM and second smallest at 5 PM.

Diurnal variation in coronary circulation

It has become evident that diurnal variation exists in the time of the onset of acute cardiovascular events.[1-4] Nevertheless, little is known about diurnal variation of coronary artery function, although some investigations reported diurnal changes in resting coronary blood flow in canine models[23] or diurnal variation of coronary response to vasodilator drugs.[24, 25] Recently, many studies have described the existence of diurnal variations in endothelial function, indicating several competing results.[10-15] Some of these studies demonstrated morning attenuation of endothelial function in the brachial arteries in healthy subjects, suggesting these changes might contribute to the diurnal pattern of cardiovascular vulnerability.[10, 15] Indeed, endothelial dysfunction in the brachial arteries appears to be correlated with both cardiovascular disease status and prognosis.[26, 27] However, flow-mediated dilation of brachial arteries does not evaluate

Fig. 2 Baseline mean diastolic velocities, hyperemic mean diastolic velocities, and Coronary coronary flow velocity reserves at the four time points. Dotted lines indicate individual data in each subject. Solid line indicates average data and standard deviation of all the subjects.

response of the coronary circulation directly, as shown that this parameter was not an independent predictor of cardiovascular outcome.[27]

Assessment of CFVR by TTDE

Coronary flow reserve has been considered as a parameter of physiological changes in the coronary circulation reflecting the function of large epicardial arteries and microcirculations,[16-18] providing an integrated measure of both vascular endothelial function and smooth muscle relaxation.[18] We measured flow velocity change, not coronary flow rate, in the epicardial coronary artery. However, it has been reported that changes in coronary flow velocities during drug-induced hyperemia closely reflect changes in coronary blood flow, and there is good agreement between CFVR as assessed from the flow velocity and coronary

flow reserve by positron emission tomography.[28, 29] In addition, good agreement has been found between CFVR assessed with TTDE and Doppler guide wire examination.[19]

The techniques used for assessment of coronary circulation, such as invasive Doppler guide wire or expensive positron emission tomography, are not ideal for clinical purposes, especially if serial measurements are required as in the present study. This is one of the reasons why few investigations have reported about diurnal variation in coronary circulation. Assessment of CFVR by TTDE is completely noninvasive and reproducible. This method has already been used for serial measurements of CFVR.[30, 31] Thus, the method we used in the present study was the most suitable one for serial measurements of CFVR.

Diurnal variation of CFVR

The occurrence of ischemic episodes demonstrates diurnal variation with a peak in the morning or bimodal circadian distribution with a prominent peak during morning and a second less prominent peak during evening.[1-4] In the present study, we observed smallest CFVR at 7 AM and second smallest CFVR at 5 PM. This biphasic change of CFVR coincides with the phenomenon of bimodal circadian distribution in the occurrence of ischemic episodes. However, periods of these smaller CFVR were not totally consistent with data from Hjalmarson et al, who observed a lower second peak in the incidence of myocardial infarction in the evening between 6 PM and 12 midnight.[4] One conceivable explanation for this fact is that decreased CFVR may not instantaneously link to a cardiovascular event, although it relates to the initiation or progress of pathological processes that proceed gradually and over several hours. In addition, a number of investigations implied that the potential mechanisms for a diurnal variation in cardiovascular events involved so many endogenous factors (i.e., autonomic nervous function, catecholamine, responsiveness to norepinephrine, hypercoagulability, hypofibrinolysis, and vascular tone) and exogenous influences (i.e., rest-activity cycle, stressful events, and postural changes).[32] Together, these factors, not only CFVR, are assumed to contribute to a diurnal variation in the incidence of cardiovascular events.

On the other hand, resting coronary flow velocity was greatest at 7 AM. This fact coincides with heightened sympathetic activity in the morning,[8, 9] and may relate to increased myocardial oxygen demand

linking to cardiovascular events.

Alteration of CFVR

Several factors such as blood pressure and heart rate have been known to affect CFVR and alter values of CFVR in same subjects.[33] In the present study, however, both blood pressure and heart rate did not change among the four periods and therefore they should not affect CFVR significantly. It has also been reported that CFVR might be reduced by hyperglycemia[34] or hyperlipidemia.[18, 35] Although blood glucose level at 7 AM was lower than at any other periods, CFVR was smallest at 7 AM in the present study. And, serum concentrations of lipids were similar among the four periods. These suggest that diurnal variation of CFVR has neither significant relation to glucose concentration nor lipids concentrations at least in healthy men.

One possible mechanism is diurnal variation of endothelial function in coronary artery. Part of the adenosine-induced myocardial hyperemic blood flow response is mediated by the vascular endothelium because its effects can be reduced by inhibiting NO synthesis.[36, 37] In addition, the use of intravenous ATP as an alternative to adenosine has been confirmed previously.[22, 38] Our finding of attenuated CFVR in early morning coincides with previous studies that reported similar attenuation of endothelial function in early morning.[10, 15] However, these studies about endothelial function in brachial artery showed no data to address the issue of second smallest CFVR at 5 PM. In addition, endothelial function in brachial artery could not necessarily be equated with that in coronary artery, although the association between brachial and coronary reactivity is modest to good.[39] We had no available data with regard to coronary endothelial function, and further investigation is needed to address this issue.

Another possible cause of diurnal variation in CFVR is diurnal variations in alpha-sympathetic activity and its related vascular tone.[6] It has been indicated that adrenergic system played an important role in limiting both the epicardial vasodilator effect of adenosine and the coronary blood flow velocity.[40] It is possible that increased alpha-sympathetic activity attenuated CFVR in the present study.

In the present study, we noted remarkable change of CFVR from 4.32 at 5PM to 6.80 at 9PM in one of the studied subjects. This subject had no significant change in blood glucose, lipids, or hemodynamics,

compared with other subjects. On the other hand, it has been reported that some other factors, such as emotional stress, could affect coronary flow measurements.[41] These other factors might possibly cause dynamic change of CFVR as seen in this subject. We need further investigation to clarify the mechanisms which underlie the dynamic change of CFVR observed in this subject.

Study limitations

First, we cannot identify the specific mechanisms that underlie the diurnal variation in CFVR. It is known that so many factors may have effects on the CFVR measurements. Further investigation is required to identify the mechanisms responsible for the diurnal variation in CFVR. Second, we measured CFVR in the LAD only in the present study. But as the subjects had no evidence of coronary artery disease, CFVR in LAD can be assumed to represent other coronary territories. Furthermore, we studied young healthy volunteers without any risk factors and medications, and it is still questioned whether our results are applicable for patients with coronary artery disease. However, this is also a strength of this study because we could exclude the possibility that vasoactive medications could have obscured the diurnal variation in CFVR or that poor controlled hyperglycemia, hyperlipidemia, or hypertension, elicited by abstinence from medications, could have effected on the CFVR measurements.

Conclusions

There is diurnal variation in both resting coronary flow velocity and CFVR in healthy men. This finding may be related to the previously reported diurnal variation in endothelial function or alpha-sympathetic activity and may lead to the diurnal variation in cardiovascular events.

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