white matter and gray matter. Apparent diffusion coefficiency (ADC) maps demonstrated hyperintensity in these lesions (Fig. 1). The findings of magnetic resonance (MR) angiography were normal. Initially, central nervous system involvement through small vessel vasculitis was suspected, but because of its characteristic clinical features and radiological findings, a provisional diagnosis of reversible posterior leukoencephalopathy syndrome was considered. Antibiotics, continuous intravenous heparin and epoprostenol were started to treat her inflammation, hypercoagulable state and pulmonary hypertension. Her consciousness and vision recovered gradually and completely normal. Extubation was done 7 days later. A follow-up MRI performed on day 36 after admission showed complete resolution of the affected lesions (Fig. 2), and the elevated C-reactive protein, thrombin-antithrombin III complex, plasmin-$\alpha_2$plasmin inhibitor complex, and D-dimer level had subsided to normal levels (Table 1). On 71 days after administration, she was discharged under warfarin treatment.

Discussion

We here report a case of reversible posterior leukoencephalopathy syndrome caused by hypercoagulable state without hypertension. This case indicates that reversible posterior leukoencephalopathy syndrome is induced by cerebrovascular endothelial dysfunction, which is induced not only by high blood pressure but also hemostatic dysfunction.

Reversible posterior leukoencephalopathy syndrome is characterized clinically by altered mental status, headache, seizures, and visual disturbances, and T_2-weighted and diffusion-weighted MRI findings of a hyperintense region in the parietal-occipital lobe involving lesions of the white matter, basal ganglia, brain stem, cerebellum, and gray matter (*1*, *18*). Analysis of ADC maps suggests that such abnormalities are caused by vasogenic edema rather than by ischemia (*18*). In the past, reversible posterior leukoencephalopathy syndrome has been considered to occur mainly in the posterior lobe and to be reversible disease as per its name. More recently, however, the syndrome has been considered irreversible in the manner of cerebral infarction or hemorrhages if the underlying causes are not treated, and the involved lesions are no longer considered specific to the posterior region (*19*). Our case also demonstrated that the abnormality is not restricted to the white matter or posterior lobe, but also occurs in the gray matter and anterior lobe. For this reason, we should reconsider the definition of reversible posterior leukoencephalopathy syndrome and decide on more appropriate terms described precisely.

Reversible posterior leukoencephalopathy syndrome is mostly associated with abrupt and severe hypertension occurring at eclampsia or acute renal failure, *etc.* However, it is also seen in patients treated with immunosuppressive or cytotoxic agents such as cyclosporine or tacrolimus (*1*), and in patients with connective tissue diseases such as systemic lupus erythematosus (*3*), and thrombotic microangiopathic states such as thrombotic thrombocytopenic purpura (*4*). Because some cases of the latter (*1*, *3*, *4*) occur even in the absence of hypertension, the pathogenesis of reversible posterior leukoencephalopathy syndrome is multifactorial, although the most fundamental mechanism is disruption of cerebral vascular endothelial cells.

The endothelium are now considered as the largest "organ" in the body, and play a critical role not only in separating the vascular wall from circulation, but also in regulating blood pressure and inhibiting platelet aggregation, coagulation, inflammation, oxidative stress, and cell migration and proliferation (*5*). Because endothelium are distributed systemically, such abnormalities are participating diffuse vascular beds damages (*12*, *13*) even though specific site is prone to be more or less (*20*). Because the cerebral endothelial cells form a blood-brain-barrier for preventing excess flux of ions, amino acids, and peptides into the brain through adherens and tight junctions (*21*), the interaction between endothelial cells and other factors could be more complex than at other sites. There are several well known risk factors for cerebral endothelial cell damage, including hypertension, diabetes, hyperlipidemia, smoking, aging, and obesity (*6*, *7*, *22*). Recently, several other possible factors have been suggested to play a role—*i.e.*, hyperhomocysteinemia, inflammation, infection, and hypercoagulability (*23*, *24*)—although further evidence will be needed to confirm these relations. Nevertheless there are still many deteriorating factors to be remained undetermined (*16*, *17*), so we have to break such enigmas and promote the strategies for preventing and treating cerebrovascular disease (*25*).

In our case, there were no well known cardiovascular risk factors and used no cytotoxic agents, but there was only a transient hypercoagulable state corresponding with the event. Because the patient was complicated with systemic sclerosis with pulmonary hypertension, we think that systemic endothelial dysfunction played an important role in the pathogenesis (*26*), but the event synchronized with inflammatory symptoms followed by a hypercoagulable state. Although we were unable to determine the trigger for such process, infection was perhaps the most likely candidate, since the symptoms and all of the inflammatory markers were ameliorated by using antibiotics. Such synergic effects produced a transient hypercoagulable state, as shown by the elevations in thrombin-antithrombin III complex, plasmin-$\alpha_2$plasmin inhibitor complex, and D-dimer level. Because thrombocytopenia and a reduction in the fibrinogen level were also seen concomitantly, we conjecture that the underlying pathogenesis involved disseminated intravascular coagulation. Although there have been previous reports of normotensive reversible posterior leukoencephalopathy syndrome, this is the first case to be involved in coagulation abnormality (*4*, *27*). Our case was successfully treated with anticoagulation therapy using heparin, but since we have no control case, the usefulness of this regimen cannot be conclusively deter-

mined. But now reversible posterior leukoencephalopathy syndrome is considered to be possibly irreversible damaged without treatment, we have to keep in mind that it could be induced by hypercoagulable state, and cope with it by anticoagulation therapy to avoid any hangover.

In this completely normotensive case, the typical clinical findings of reversible posterior leukoencephalopathy syndrome were triggered by a hypercoagulable state without any blood pressure variation, and the case was successfully treated with anticoagulation therapy using heparin. Thus, this case indicates that reversible posterior leukoencephalopathy syndrome is induced by cerebrovascular endothelial dysfunction, which is induced not only by high blood pressure but also hemostatic dysfunction.

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Loss of Diurnal Rhythms of Blood Pressure and Heart Rate Due to High Fat Feeding

Ruri Kaneda and Kazuomi Kario

Obesity is the most prevalent nutritional disorder in developed countries[1] and plays an important role in cardiovascular morbidity through multiple mechanisms,[2] including well-known risk factors such as hypertension, diabetes, and dyslipidemia.[3–8]

Previous studies have shown that being overweight is associated with increased cardiac output[9] and resting heart rate, with decreased heart rate variability,[10] and with increased prevalence of nondipping status,[11] which is considered to be prognostic indicators of cardiovascular mortality[12,13] and morbidity[14,15] in humans.

Sympathetic nervous system activity is increased in patients with essential hypertension per se;[16] and the adrenergic factors represent one of the mechanisms involved in determining blood pressure (BP) variability[17] including the nondipping pattern of BP. We have the data that diurnal BP variation in elderly hypertensive individuals was significantly associated with neurohumoral factors regulating circulating blood volume. Nondippers appeared to have α- and β-adrenergic subsensitivity, which may be induced by their chronic exposure to high norepinephrine levels.[18]

On the other hand, overactivity of the sympathetic nervous system is a common feature of obesity in humans and in animal models. Study of regional sympathetic nerve activity in obese humans using norepinephrine spillover has demonstrated that obesity is associated with increased sympathetic activity to the kidney, a key organ of cardiovascular homeostasis.[19] Chronic hyperinsulinemia is also associated with a high output, low resistance hemodynamic state, persistent baroreflex downregulation, and episodic (postprandial) sympathetic dominance.[20] Accordingly, decrease of heart rate and BP variability or nondipping status in obese subjects might be caused by overactivity of the sympathetic nervous system.

Consistent with the report by Carroll et al,[21] which shows high fat feeding in rabbits caused immediate losses of diurnal rhythms of BP and heart rate that were independent of weight gain and BP elevation, there are some reports that show an increase of whole day mean arterial pressure and heart rate, rapid abolition the normal diurnal rhythm of mean arterial pressure and heart rate, and increase of low-frequency energy of systolic BP variabilities were shown at an early but not at a late phase after an hyperlipidic and hypercaloric diet.[22,23] Another study also reported that a high fat diet induces abdominal obesity, hyperinsulinaemia, and arterial hypertension, with a left ventricular hypertrophy associated with a biphasic change in autonomic activity. This biphasic change consists of an early and long-lasting decrease in parasympathetic nervous system activity and an early but transient increase in sympathetic activity.[10] The autonomic nervous system changes are dependent on the time course of obesity development. Therefore, the importance of immediate sympathetic nerve activation with overfeeding is clear. However, it is indispensable to investigate the association with several other factors including FFA, insulin, leptin, and the renin-angiotensin system, which might account for the increased sympathetic outflow associated with obesity.[24]

In the future, it is necessary to clarify the time course of these factors in adipose tissue or in circulation, which are strongly associated with obesity and affect the diurnal variation of BP and heart rate. Clarification of these points would shed some light on the pathophysiology of obesity–hypertension and find a new time-dependent therapeutic target.

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□ EDITORIAL □

"Cocktail" Antihypertensive Chronotherapy for Perfect Control of Morning Hypertension in Diabetic Patients

Key words: hypertension, morning hypertension, diabetes, chronotherapy, target organ protection

It is well-known that cardiovascular events occur more frequently in the morning (1). Ambulatory blood pressure (BP) varies along with various physical and psychological factors and this BP variability may be a risk for cardiovascular events (2, 3). In recent years, clinical research using ambulatory BP monitoring (ABPM) or self-measured home BP monitoring has clarified that morning BP and BP surge are more closely related to target organ damage and cardiovascular risk than clinic BP (4–14). Also, in hypertensive patients treated with antihypertensive medication, even patients whose clinic BP is well controlled, the morning BP level prior to taking medication is often high (15–17). Therefore, morning hypertension is currently the 'blind spot' in the clinical practice of hypertension.

As diabetes is one of the worst conventional cardiovascular risk factors. In our recent study on asymptomatic hypertensive patients with and without type 2 diabetes, silent cerebral damage including silent cerebral infarcts, decreased functional neuronal mass, and reduced cerebrovascular reserve were advanced in hypertensive patients with diabetes (18). Hypertensive patients were classified into four groups and the risk of multiple silent cerebral infarcts was comparable between diabetic patients with white-coat hypertension (WCHT) and nondiabetic patients with sustained hypertension (19). The patients with both diabetes and sustained hypertension had the highest risk for multiple silent cerebral infarcts. Cardiac remodelling is also advanced in diabetes; in hypertensive patients, the presence of diabetes increases the relative wall thickness (20). Concentric hypertrophy, which is the worst prognosis, was more frequently found in diabetic hypertensive patients.

Nighttime and morning BP levels should be monitored more closely in diabetic patients. In a cross-sectional study in newly-diagnosed type 2 diabetic normotensive patients, morning BP levels and morning BP surge were significantly increased in patients with microalbuminuria compared to those without microalbuminuria (21). In another study on type 2 diabetic patients, those with morning BP hypertension (morning BP level measured at home >130/85 mmHg) had marked frequencies of diabetic renal disease, retinopathy, microvascular disease and vascular complications, including coronary artery disease and cerebrovascular disease (22). In this study, hypertension defined by clinic BP level was not associated with these complications. Diabetic patients, particularly those with autonomic nervous dysfunction, are also likely to have a nondipping pattern of nocturnal falls in BP, which might precede microalbuminuria, leading to a poor prognosis (23). Nighttime BP is associated with a poor prognosis in diabetic patients (24).

In the international guidelines including the guideline of management of hypertension of the Japanese Society of Hypertension, target BP levels are lower for diabetic patients than nondiabetic patients. In addition, the persistent BP control for a 24-h period achieves more effective prevention for target organ damage and cardiovascular events particularly in these patients. However, in the practical sense, 24-h BP control is very difficult in diabetic patients particularly in those with nephropathy. In this issue, Kuriyama et al tried a unique antihypertensive medication for diabetic patients with nephropathy, whose BP was poorly controlled as morning hypertension (self-measured morning BPs >130/85 mmHg) (25).

See also p 1239.

Their special medication consists of calcium channel blockers and/or diuretics given in the morning, an angiotensin receptor blocker given in the evening, together with alpha1-blockers given at bedtime. Actually, the "cocktail" medication successfully reduced morning BP levels with a significant reduction of urinary protein excretion. Considering that neurohumoral factors including sympathetic nervous activity and the renin-angiotensin-aldosterone system are activated in the morning, this sequential combined chronological medication could be physiologically considered as a specific medication for morning hypertension. In recent reports, a long-acting angiotensin receptor blocker (26), and the bedtime dosing of an alpha1-blocker (27) or an angiotensin-converting enzyme inhibitor (28) were effective for controlling morning hypertension.

In addition to the standard clinical practice of hypertension, and following the guidelines issued on the subject, an important next step should be the specific combined chronobiological management targeting the higher blood pressure in the morning in order to achieve a more beneficial outcome particularly in high-risk hypertensive patients such

as in those with diabetes and/or chronic kidney disease.

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Caution for Winter Morning Surge in Blood Pressure

A Possible Link With Cardiovascular Risk in the Elderly

Kazuomi Kario

There are variations in the onset of cardiovascular events. As diurnal variation, most studies have shown an increased incidence of acute cardiovascular events such as acute myocardial infarction, sudden cardiac death, and stroke in the morning.[1] In addition, weekly and seasonal variations in the cardiovascular events have also been reported.[2] These variations may be closely associated with ambulatory blood pressure (BP) variations. In this issue, Modesti et al report an interesting study demonstrating weather-related change in ambulatory BP profile.[3] In their study, in addition to poorly controlled nighttime BP in hot days, cold weather was significantly associated with increased morning BP surge in elderly subjects, even when they were treated with a higher number of antihypertensive drugs per day in cold weather. This cold weather–augmented morning BP surge may partly account for an increased number of cardiovascular events in the cold morning during the winter season.

Ambulatory BP also exhibits significant diurnal variation, and an abrupt BP surge in the morning has been suggested as a possible trigger for cardiovascular events. Previously, there were several areas of evidence indicating the importance of morning BP surge on cardiovascular disease. There are 2 relatively small prospective studies to support the possible risk of morning BP surge and cardiovascular events. The first is the Jichi Medical School (JMS) ambulatory blood pressure monitoring (ABPM) study (Wave 1) on elderly hypertensive patients[4]; the other is a French study on hypertensive patients.[5] In the JMS ABPM, a prospective study of 519 elderly hypertensive patients with mean age of 72 years, brain MRI was conducted to assess silent cerebrovascular disease together with 24-hour ABPM at baseline. The prognosis for stroke was studied during the follow-up period of 41 months. Both the sleep–trough surge (morning BP level minus the lowest nocturnal BP) and waking surge (morning BP minus prewaking BP) were significantly associated with stroke risk independently of 24-hour BP levels and nocturnal BP dipping. A recent French prospective study of 507 patients with hypertension found similar results.[5] Hypertensive patients were divided into quartiles of waking surge, defined as morning systolic BP measured on standing minus systolic BP before rising. Although there were no significant differences in the 24-hour BP levels between each group, cardiovascular complications occurred more frequently during the follow-up period in the higher quartile groups. In the multivariate analysis, the waking morning BP surge was significantly associated with cardiovascular risk independent of age and 24-hour BP level.

Morning BP surge is also significantly associated with hypertensive target organ damage. In the JMS ABPM study (Wave 1), silent cerebral infarct was measured by brain MRI at baseline and was more frequently detected in the morning surge group than in the nonsurge group, particularly multiple silent cerebral infarcts.[4] Exaggerated morning BP surge also appeared to increase hypertensive heart disease. In our community-dwelling subjects, sleep-rough surge adjusted for morning physical activity was significantly correlated with left ventricular (LV) mass index, assessed by echocardiography,[6] as found in the French study.[5] Morning BP minus evening BP assessed self-measured BP, also independent determinants of LV mass in hypertensive patients.[7] In addition, hypertensive patients with morning BP surge had prolonged corrected QT interval (QTc) duration and QTc dispersion compared with those without morning BP surge.[8] These QTc abnormalities found in the morning BP surge groups were only significant in the morning period. Spectral analysis of heart rate variability showed that the low frequency power/high frequency power ratio, an indirect index of sympathetic activity, was significantly higher in the morning BP surge group than in the nonsurge group. Thus, in the surge groups, increased sympathetic activity in the morning leads to prolonged QTc dispersion. As this increased QTc dispersion is reported to be associated with LV hypertrophy and cardiac arrhythmia, exaggerated morning BP surge also appears to be associated with increased risk of cardiac arrhythmia and sudden death in the morning in hypertensive patients. More recently, untreated hypertensive patients with morning BP surge had increased carotid intima-medial thickness (IMT) and higher levels of inflammatory markers, such as interleukin (IL) 6 and C-reactive protein, than those without morning BP surge.[9] Another recent study also demonstrated that increased time rate of BP variation in the morning was independently associated with increased carotid IMT in untreated hypertensive patients.[10] These studies indicated that morning BP surge would be potential cardiovascular risk in hypertensive patients.

Increased sympathetic activity, particularly α-adrenergic component, increases vascular tone in the resistance arteries and may contribute to the morning BP surge. In fact, the bedtime dosing of α-adrenergic blocker reduced preferen-

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tially morning BP levels and morning BP surge than ambulatory BPs during another period, particularly in those with advanced hypertensive cerebrovascular disease.[11] As the cold stimulation is also known to have pressor effect predominantly through α-adrenergic activation, cold weather would augment morning BP surge synergically through α-adrenergic activation. Psychological stress also predominantly activates α-adrenergic activity, and the recent study using 7-day (24-hour) ambulatory BP monitoring demonstrated that morning BP surge was the greatest on Monday among days of the week in community-dwelling subjects.[12] This Monday morning surge in BP may be in accord with clinical evidence that cardiovascular events more frequently occur in the morning on Monday. Thus, variations in ambulatory BP would be parallel to the incidence of cardiovascular events. Various peaks of ambulatory BP may be additively or synergically associated with each other to increase the risk of cardiovascular disease. Further experimental and clinical studies are necessary to clarify the impact of these variations of cardiovascular risk on cardiovascular disease in hypertensive patients.

Thrombotic tendency such as endothelial cell dysfunction, platelet activation, and hypercoagulable and hypofibrinolytic states is potentiated in the morning. Fibrinogen, a well-established thrombotic risk factor, has seasonal variations with a winter peak in the elderly.[13] Thus, particularly in winter, in addition to conventional antihypertensive therapy, specific strategy targeting morning BP and its surge would practically achieve more effective prevention for cardiovascular events in the morning in elderly hypertensive patients.

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