To better identify patients at high risk for cardiovascular events, several markers of risk have been proposed for use in screening. Recently, oxidative stress and inflammation have been evaluated as potential tools for prediction of the risk of cardiovascular events. Among them, we have measured reactive oxygen species (ROS) formation by mononuclear cells (MNCs), since they may be a possible link between inflammation and oxidative stress. ROS formation by MNCs was measured by a gated flow cytometric assay [1]. MNCs are crucial cells in the genesis of atherosclerotic lesions. MNCs when stimulated have been shown to release ROS, induce lipid peroxidation, release cytokines, and induce adhesion to endothelium, which result in atherosclerosis and cardiovascular events. We have already shown that high glucose [2,3], hyperlipidemia [4], or pressure [5] increases oxidative stress in vitro.

There is evidence that the angiotensin receptor blocker (ARB) has blood pressure (BP)-independent effects on left ventricular (LV) mass. Whether regression of LV mass by ARB is correlated to ROS formation by monocytes has not previously been fully understood. To compare the effects of the ARB valsartan versus the calcium channel blocker amlodipine, ROS formation by MNCs and LV mass were studied in 104 hypertensive patients with LV hypertrophy (LVH). Decrease in ROS formation by monocytes by valsartan was related to decrease in LV mass [6,7].

Inhibitors of 3-hydroxy-3-methylglutary CoA (HMG-CoA) reductase are antilipidemic agents (statins) widely used for the prevention of cardiovascular diseases. Recent studies have suggested that the overall benefits of statin therapy cannot be accounted for solely by its antilipidemic effect. Recently, we have shown that ROS formation by MNCs is related to intima-media thickness (IMT) of human carotid artery [8]. We have also performed the study on the effects of pitavastatin for six months on intima-media thickness (IMT), a marker of carotid atherosclerosis, in hypertensive patients with hyperlipidemia. Pitavastatin 2 mg for six months significantly decreased IMT of these patients [9].

Whether anxiety and depression are associated with increased BP and cardiovascular disease risk is not fully studied. We examined the hypothesis that anxiety and depression lead to increased plasma catecholamines and ROS formation by MNCs in hypertensives. We also studied the role of BP in this effect. Trait anxiety may increase plasma norepinephrine, which resulted in the increase in ROS formation by MNCs independent of BP in hypertensive patients [10].

Because oxidative stress and inflammation are known to play important roles in the pathogenesis of cardiovascular events that occur most frequently in the morning, we studied the association between ROS formation by PMNs or MNCs and morning BP rhythm. These results suggest that both extreme-dippers and morning BP surge type hypertensives may suffer increased ROS formation by MNCs, and that increased ROS formation by MNCs may underlie morning strokes [11].

Thus, we have demonstrated that ROS formation by MNCs is regulated by vascular inflammation. ROS formation by MNCs is also related to LV mass, norepinephrine, IMT, and nocturnal blood pressure (figure 1). We would like to propose that ROS formation by MNCs is a risk factor of cardiovascular diseases.

References

2. Yasunari K, Kohno M, Kano H, Yokokawa K, Minami M, Yoshikawa J. Antioxidants improve impaired insulin-mediated glucose uptake and prevent migration and proliferation of cultured


Figure 1. Relationship between ROS formation by MNCs and CRP, LV mass, norepinephrine, IMT, or nocturnal blood pressure.
ROS Formation by MNCs

- CRP
  - Inflammation
- LV Mass
- Norepinephrine
- IMT
- Nocturnal Blood Pressure