CHAPTER I
INTRODUCTION

Endothelial cells are specialized cells lining in luminal surface of blood vessels and forming capillary. They regulate blood flow and delivery of oxygen and nutrients to peripheral tissues through releasing a number of factors affecting vascular smooth muscle tone, hemostasis and vasculogenesis (1). For instance, under physiologic condition endothelial cells constitutively secrete nitric oxide (NO) and prostacyclin to maintain vasodilation and inhibit platelet activity, ensuring adequate blood flow to hypoxic tissues.

Cadmium, a divalent transition metal is toxic to human cells. The use of cadmium in the manufacturing of metals plating and batteries produces significant industrial sources of environmental cadmium contamination. High-level cadmium exposure occurs through oral ingestion of contaminated food and water in highly contaminated area (2). Low-level exposure may arise from cigarette smoking in general population (3).

Several studies suggest that cadmium exposure may be associated with vascular disorders such as atherosclerosis and hypertension (4-6). High prevalence of hypertension has been reported in population of Mae Sot District, Tak Province where cadmium contamination was pervasive. (7). Therefore, the vascular endothelium may be an important target of cadmium toxicity. An in vivo study demonstrated that cadmium decreased endothelial NO synthase (eNOS) protein levels, resulting in impairment of vascular function and hypertension in rats (8). An In vitro study demonstrated that cadmium attenuated NO production by blocking eNOS phosphorylation without any change in eNOS protein levels in immortal hybrid endothelial cell lines (9).

Nitric oxide (NO) is synthesized constitutively by eNOS in the vascular endothelium. It promotes blood flow to tissue locally through mediation of vasodilation and platelet inhibition. The reduction of NO levels in blood circulation

may represent an impaired endothelial function. In vitro studies suggest that cadmium could disrupt endothelium functions by (i) reduction of NO synthesis by the inhibition of eNOS phosphorylation (9) and decreased eNOS protein levels (8), (ii) and oxidative stress and free radical consumption of NO (10). Acute cadmium intoxication in animals could induce oxidative stress and NO depletion (11, 12). Previous data from our colleague revealed that the plasma nitrite levels of cadmium-exposed subjects live in Mae Sot District, Tak Province (urinary cadmium > 5 µg/g creatinine) were lower than those of control subjects (urinary cadmium < 0.5 µg/g creatinine) (13) suggesting an endothelial dysfunction in chronically cadmium-exposed subjects.

Because the mechanism underlying decreased NO levels in cadmium-exposed subjects had never been studied in human primary endothelial cells, we peformed two parts of experiments. First, we determined the potential NO consumption by plasma of control and cadmium-exposed subjects by a chemiluminescence NO detector. Soluble thrombomodulin was measured as marker of endothelial dysfunction. Second, we studied the effect of cadmium on primary endothelial cells from human coronary artery (human coronary artery endothelial cells, HCAECs). The cytotoxicity of cadmium on HCAECs was evaluated using MTT assays. The NO synthesis from HCAECs was determined by measuring the nitrite levels in supernatant and cell lysate. Furthermore, the effects of cadmium on eNOS expression and phosphorylation at serine 1177, which was related to increased eNOS activity, were examined.