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# Concentrations of endothelin-1 associated with aging of prehypertension patients in Denpasar and Badung districts, Bali, Indonesia



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## ABSTRACT

**Introduction:** Hypertension is a major health problem in the world. Prehypertension increases the risk of developing hypertension. Aging often accompanied with an elevation of blood pressure. Endothelin-1 is a potent vascular vasoconstrictor which its concentration is related to various cardiovascular diseases including hypertension. However, it is still unclear whether aging is related to endothelin-1 activation. Therefore, this study aims to determine the correlation between age and serum endothelin-1 concentration in patients with prehypertension.

**Methods:** This is a community-based and cross-sectional study which was conducted in Denpasar and Badung regencies, Bali-

Indonesia. A total of 75 prehypertension patients were involved in the study.

**Results:** Spearman Correlation analysis demonstrated that age was strongly correlated with endothelin-1 levels in the patients with prehypertension,  $R = 0.290$  ( $p = 0.012$ ). Age was also positively correlated with systolic blood pressure  $R = 0.235$  ( $p = 0.042$ ). In contrast, there was no correlation between age with diastolic blood pressure,  $R = 0.037$  ( $p = 0.750$ ).

**Conclusion:** In conclusion, endothelin-1 concentration were correlated with the age of patients with prehypertension.

**Keywords:** age, blood pressure, endothelin-1

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## INTRODUCTION

Hypertension is one of the major health problems in the world. WHO data in 2002 showed that hypertension ranked third as the cause of death in the world. In 2004, hypertension contributed to 12.8% or around 7.5 million from 58.8 million deaths worldwide. In 2010, the prevalence of hypertension throughout the world was 31.1%.<sup>1</sup> In Indonesia alone the prevalence of hypertension was 26.5%.<sup>2</sup> Hypertension is a major risk factor for coronary artery disease, stroke, heart failure, and kidney failure.<sup>3</sup>

Prehypertension is a predictor of an increased risk of hypertension. Predictors of hypertension onset varied widely, but it showed a consistent association with previous blood pressure. Based on data from the *Framingham Heart Study*, patients with history hypertension for at least four years, 5% of them were within optimal blood pressure, 18% of patients with normal blood pressure, and 37% of patients with prehypertension.<sup>4</sup> People with prehypertension have contributed an additional 31% risk of coronary artery disease compared to individuals with normal blood pressure. They also have a higher risk of stroke and total cardiovascular events (49% and 44%, respectively).<sup>5</sup> Prehypertension often associated with damage of target organs such as early atherosclerosis,

damage on small blood vessels, coronary artery calcification, vascular remodeling, and left ventricular hypertrophy.<sup>4</sup>

Hypertension often occurs with aging. In general, over time there were increased systolic blood pressure and diastolic pressure. However, diastolic blood pressure level ups until the age of 50, and then gradually decreases afterward. Increased blood pressure associated with the aging process was in part due to the alteration of the heart and arteries structures, especially the structure of the large arteries. This structural changes cause stiffness in blood vessels and shifting in systolic and diastolic blood pressure.<sup>6</sup>

Endothelin-1 is an endogenous vasoconstrictor of blood vessels, which was first discovered by Yanagisawa et al.<sup>7</sup> Endothelin consists of 3 isopeptides which are endothelin-1, endothelin-2, and endothelin-3. Human endothelial cells only produce endothelin-1 in vascular smooth muscle. Endothelin-1 works by binding to specific receptors in vascular smooth muscle then causes vascular vasoconstriction and increased blood pressure. Endothelin-1 is the most potent and most dominant endogenous vasoconstrictor in the human cardiovascular system where its strength is 100 times greater than noradrenaline.<sup>8,9</sup> Increased endothelin-1 mediated vasoconstriction has been linked to the etiology of some cardiovascular

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pathologies, including hypertension. There is strong evidence in animal models that age associated with elevated endothelin-1 activation. However, data regarding the influence of age on endothelin-1 system activation in human adults are limited.

Bali is one of the most tourist destinations in the world. Denpasar and Badung regencies both are the center of the tourist activities in Bali. Residents of both regions came from various parts of Bali and as well as outside Bali. Due to the influence of tourism and modernization era, the population in this area tends to have a modern habit as their new lifestyle including adding fast food to their daily meal. The increased number of cardiovascular diseases including prehypertension, which mostly will transform into hypertension.

So far, a study examining the relationship between endothelin-1 concentrations with aging in prehypertension patients were lacking. Besides, the role of aging on endothelin-1 activation is still unclear. Regarding those reasons, the objective of this study was to understand the correlation between age and endothelin-1 concentrations in prehypertensive patients in Denpasar and Badung regencies, Bali-Indonesia.

## METHOD

This is a cross-sectional community-based study, aimed to determine the correlation between aging and the concentration of endothelin-1 in patients with prehypertension. The study was conducted in Denpasar and Badung regencies from January until March 2017. The stratified random sampling method was used to determine the sampling region. The study in Denpasar carried out in Sumerta Kelod and Pedungan Vills, while in Badung carried out in Kedongan and Nusa Dua Vills. The prehypertensive patient is defined as a patient with a systolic blood pressure of 120-139 mmHg or diastolic blood pressure of 80-89 mmHg after the blood pressure measurement in a proper sitting position. Inclusion criteria were prehypertensive patients with age of 18-59 years old and willing to participate in the study by signing informed consent. While the exclusion criteria were patients with preexisting chronic kidney disease and pregnant women. A total of 75 prehypertensive patients who met the criteria was involved in this study. The patients Endothelin-1 concentration was measured by ELISA, using a quantitative sandwich-enzyme immunoassay method and expressed in units of pg / mL.

In order to determine the correlation between aging and endothelin-1 levels, Pearson test will be utilized in the if normally distributed. In contrary, the Spearman non-parametric test will be used if the data distribution is not normal.

## RESULT

A total of 75 prehypertensive patients were involved in the study. The study subjects consisted of 39 men (52%) and 36 women (48%), with a median age of 48 (19-59). The distribution of education levels was quite diverse. The highest frequency was 38 high school graduates (50.7%), followed by 12 undergraduates (16%), 9 master graduates (12%), 5 elementary school students (5.7%), 5 without any education (5.7%), 4 diplomas (5.3%), 1 junior high school graduate (1.3%), and 1 professor (1.3%). Median systolic blood pressure was 128 (105-139) mmHg, and the median diastolic blood pressure was 82 (65-89) mmHg. The average endothelin-1 level is  $1.45 \pm 0.35$  pg / mL.

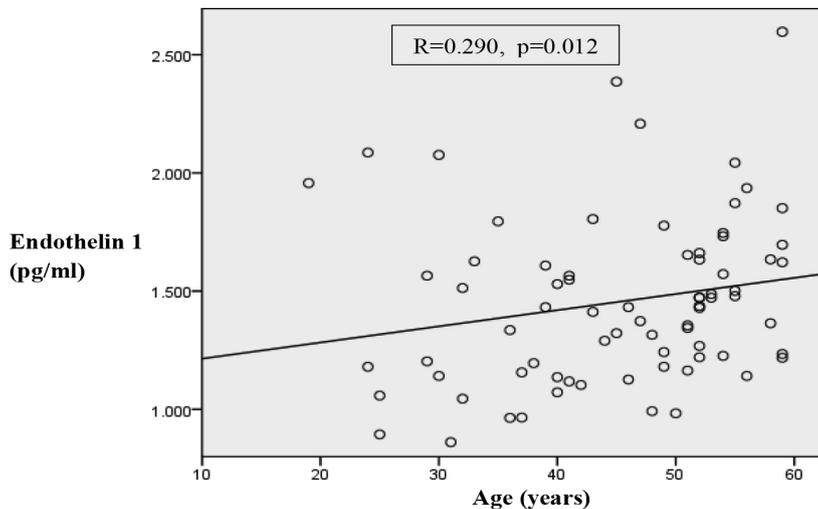
Due to the age of patients is not normally distributed, even after it has been transformed, the Spearman non-parametric test was utilized in this study. The result showed that age was positively correlated with endothelin-1 levels in prehypertension patients with correlation efficiency 0.290 ( $p = 0.012$ ) (Figure 1)

This study also determines a relationship

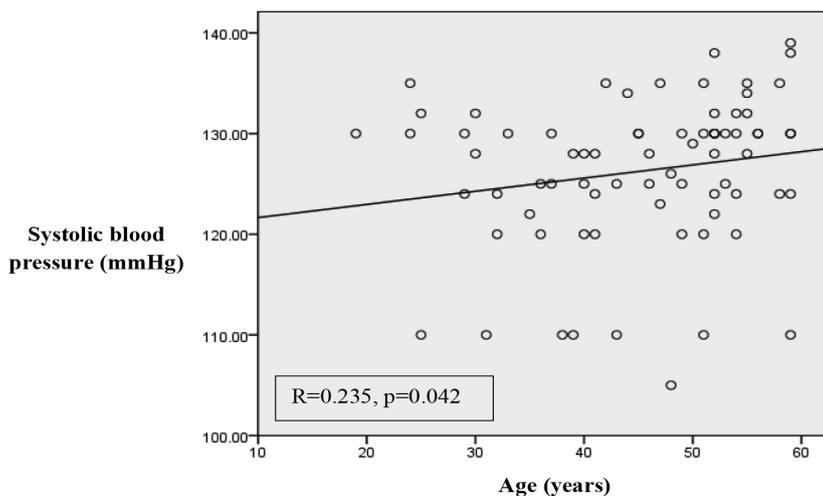
**Table 1. Baseline Characteristics of Study Subjects**

Characteristics	Frequency (%), mean $\pm$ SD, or median (min-max)	Kolmogorov- Smirnov test (p)
Gender		
Men	39 (52%)	
Women	36 (48%)	
Age	48 (19-59)	0.001
Education levels		
Without any education	5 (6.7%)	
Elementary school	5 (5.7%)	
Junior high school	1 (1.3%)	
Senior high school	38 (50.7%)	
Diploma	4 (5.3%)	
Undergraduate	12 (16%)	
Master graduate	9 (12%)	
Professor	1 (1.3%)	
Systolic blood pressure	128 (105-139) mmHg	<0.0001
Diastolic blood pressure	82 (65-89) mmHg	<0.0001
Endothelin-1	1.45 $\pm$ 0.35	0.200*

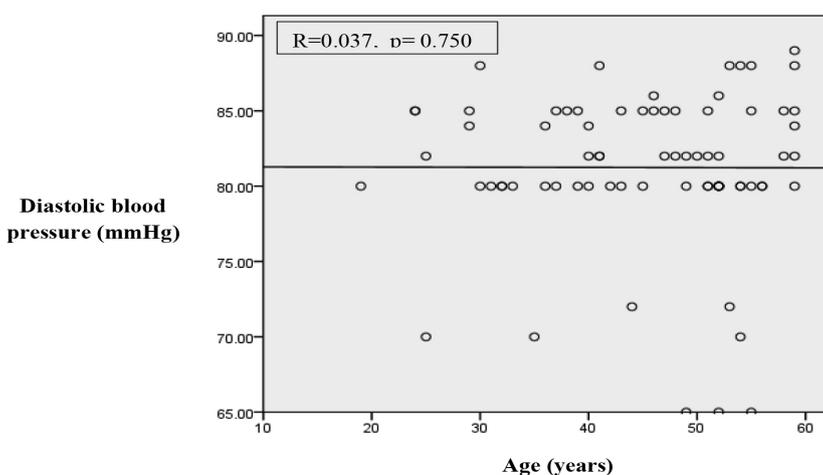
\*: Normal data distribution; SD: standard deviation; BMI: body mass index; min-max: minimum-maximum



**Figure 1.** Correlation between age and Endothelin-1 concentration of patients with prehypertension



**Figure 2.** Correlation between age and systolic blood pressure of patients with prehypertension



**Figure 3.** Correlation between age and diastolic blood pressure of patients with prehypertension

between age and both systolic and diastolic blood pressure. Based on the Spearman analysis, age was also positively correlated with systolic blood pressure with a correlation coefficient of 0.235 ( $p = 0.042$ ).

Based on the Spearman test, there is no correlation between age and diastolic blood pressure with a correlation coefficient of 0.037 ( $p=0.750$ ).

One of the pathogenesis of hypertension is an imbalance between vasoconstrictors and vasodilators of blood vessels, which triggers endothelial dysfunction. Endothelin-1 is the most potent endogenous vasoconstrictor in the human body where its strength is 100 times greater than noradrenaline.<sup>8,9</sup> Endothelin is produced by the breakdown process of proteolytic from its large precursor BIG-endothelin-1 by endothelin converting enzyme (ECE). Endothelin-1 is mostly released into smooth muscle. The activity of endothelin-1 is determined by two endothelin receptors, which are ETA receptors located in vascular smooth muscle and ETB receptors located in vascular smooth muscle and endothelial surface. The binding of endothelin-1 with ETA receptors and ETB in vascular smooth muscle cells activates the phospholipase C-inositol triphosphate pathway, which then increases intracellular calcium then causes phosphorylation of myosin kinase and contraction of smooth muscle. Endothelin-1 plays an essential role in the pathogenesis of various cardiovascular diseases since it is not only acting as a vasoconstrictor of blood vessels, but also stimulating fibrous tissue formation and inhibiting Nitric Oxide (NO) endothelial synthesis. Endothelin-1 stimulates platelet aggregation, cell adhesion, and proliferation of vascular smooth muscle cells and mural fibroblasts, which are components of atherosclerosis. Endothelin-1 also activates leucocyte chemotaxis and inflammation in blood vessels by stimulating cytokines such as interleukin-6 and tumor necrosis factor- $\alpha$ , as well as proinflammatory mediators such as NF- $\kappa$ B. These are central factors in the inflammatory component in atherosclerosis.<sup>7</sup>

This study reported that age was positively associated with the concentration of endothelin-1 in prehypertensive patients with  $R = 0.290$  ( $p = 0.012$ ). A similar study by Guilder et al. has shown that the effect of endothelin-1 vasoconstrictor was greater in healthy old men compared with the younger.<sup>10</sup> As it is known, one of the major risk factors for cardiovascular patients is hypertension. As we get older, there is also an increased in endothelin-1 concentrations which leads to increasing vasoconstrictor activity in blood vessels and can trigger prothrombotic processes. Both processes contribute to endothelial dysfunction.

This condition will generate prehypertension then leads to hypertension later on.<sup>7</sup>

Aging is an independent cardiovascular risk factor. However, most studies reported that daily exercise extremely effective to attenuate the enhancement of endothelin-1 concentration induced by aging.<sup>10</sup> Therefore regular exercises should be advised to prehypertensive patients to prevent increased concentration of endothelin-1 levels, which may reduce the risk of hypertension. To date, the pharmacologic approaches to reduce endothelin-1 levels in hypertension such as endothelin converting enzyme inhibitors, endothelin-1 receptor antagonists, HMG CoA reductase inhibitors (statins), and calcium channel blockers are still controversial.<sup>7</sup>

This study also found that age was positively correlated with systolic blood pressure with  $R = 0.235$  ( $p = 0.042$ ), however it did not correlate with diastolic blood pressure with  $R = 0.037$  ( $p = 0.750$ ). The characteristics and definitions of hypertension related to aging have changed with time. Based on data from the Framingham Heart Study, systolic blood pressure increases at the age ranging from 30-84 while diastolic blood pressure shows a varied pattern. Diastolic blood pressure will increase until the age of 50 and then decreases in the age of 60-84. This causes an isolated systolic hypertension.<sup>6,11</sup>

Increased blood pressure related aging is associated with arteries and arterioles stiffness. The stiffness of large arteries is caused by atherosclerosis and calcification, which cannot be separated from the role of endothelin-1. This leads to earlier reflected pressure waves from the arterioles towards the heart during blood pressure wave propagation. This pressure to the wave is transmitted from the arterial towards the heart during blood pressure wave propagation. These pressure waves arrive back during systole increasing central systolic blood pressure and widening pulse pressure.<sup>11</sup>

The increase in diastolic blood pressure up to the age of 50 is mostly due to increased peripheral vascular resistance in small vessels. However, both large artery stiffness and peripheral vascular resistance contribute toward the increase in systolic blood pressure, while diastolic blood pressure increases with peripheral vascular resistance but decreases with the increase in large artery stiffness. Although peripheral vascular resistance may initiate hypertension, it is the acceleration of large artery stiffness that leads to the steeper rise in systolic blood pressure after fifth decades of life.<sup>11</sup>

## CONCLUSION

Patients with prehypertension and advancing age have higher endothelin level which results in

increased blood pressure. Aging is an independent risk factor for hypertension. However, increasing level of endothelin-1 related aging is likely to be prevented by routine exercises to avoid prehypertension or hypertension in the future.

## CONFLICT OF INTEREST

The author declares that she doesn't have any competing interest regarding manuscript.

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## AUTHOR'S CONTRIBUTIONS

Luh Gede Sri Yenny developed the conceptual framework of study, preparing the manuscript, statistical analysis, and data synthesis.

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