

| | |
|---------|--|
| 氏名 | エイジロ スギヤマ エヂソン EIJIRO SUGIYAMA EDISON |
| 学位の種類 | 博士 (医学) |
| 学位記番号 | 甲第 485 号 |
| 学位授与年月日 | 平成 27 年 3 月 18 日 |
| 学位授与の要件 | 自治医科大学学位規定第 4 条第 2 項該当 |
| 学位論文名 | 日本人の高齢高血圧患者における心電図上の左室肥大と心血管疾患との 関連 |
| 論文審査委員 | (委員長) 教授 小山 信一郎 (委員) 准教授 多賀 直行 准教授 宮下 洋 |

論文内容の要旨

1 研究目的

Our aim was to assess whether electrocardiographic left ventricular hypertrophy (ECG-LVH) is associated with a higher risk of cardiovascular disease (CVD) events, independent of 24-hour blood pressure (BP) and circulating levels of norepinephrine and hemostatic factors.

2 研究方法

In 514 older hypertensive patients (mean age 72.3 years; 37% men), we assessed ambulatory BP values, circulating levels of norepinephrine and hemostatic factors (plasma fibrinogen, prothrombin fragment 1+2 (F1+2), von Willebrand factor (vWF), and plasminogen activator inhibitor-1 (PAI-1)), and the presence or absence of ECG-LVH (Sokolow-Lyon voltage ≥ 3.5 mV). The incidence of CVD events (i.e., myocardial infarction and stroke) was prospectively ascertained.

3 研究成果

During an average 41 months of follow-up (1,751 person-years), 43 stroke and 3 myocardial infarction events occurred. At baseline, patients with ECG-LVH had higher mean 24-hour BP (148.8/83.8 mmHg vs. 135.7/77.2 mmHg) and circulating norepinephrine levels (404.6 pg/ml vs. 336.3 pg/ml) compared to those without ECG-LVH; the difference remained unchanged after adjustment for age, gender, smoking status, presence of diabetes mellitus, and antihypertensive medication uses at follow-up time (all $P < 0.01$). Cox proportional hazards models suggested that the hazard ratio (HR; 95% confidence interval (CI)) of CVD events for those with ECG-LVH was 4.4 (2.3-8.2), and the association between ECG-LVH and incident CVD events remained significant after adjustment for high 24-hour BP ($\geq 130/80$ mmHg), nocturnal SBP, circulating norepinephrine and fibrinogen levels (HRs, 3.5-4.2. all $P < 0.001$).

4 考察

Although the association of LVH and CVD events in hypertensive patients is well established, the reason beyond remain unclear. There are at least two important determinants of LVH: i.e., hemodynamic factors and nonhemodynamic factors. Hemodynamic factors include high BP. In particular, higher 24-hour BP and higher nocturnal BP has been shown to be associated with LVH in hypertensive patients. Previous evidence by LIFE (*Hypertension* 44:48-54, 2004) and JATOS study (*Circ J* 74:938-945, 2010) showed that the association between ECG-LVH and CVD event was independent of several conventional cardiovascular risk factors including office BP. However, these studies did not used ambulatory BP including nocturnal BP as adjustment factor, which is known more strongly associated with target organ damage than office BP. Our study complement and extent the prior evidence (*Am J Hypertens* 21:464-470, 2008. *Hypertension* 62:518-525, 2013. *J Hypertens* 32:921-928, 2014) by showing that the association between Sokolow-Lyon ECG-LVH and the risk of CVD events was independent of high 24-hour BP and high nocturnal SBP, particularly in elderly hypertensive patients. Our data shows each of ECG-LVH (HR, 4.42; 95% CI, 2.37-8.22; $P = 0.0001$) and high 24-hour BP (HR, 4.33; 95% CI, 1.65-11.33; $P = 0.003$) or nocturnal BP (HR, 3.15; 95% CI, 1.37-7.24; $P = 0.007$) was independently associated with increased risk for CVD events. An interaction of ECG-LVH with high 24-hour BP or high nocturnal BP on cardiovascular risk was not observe, which might be owing to statistical insufficient of small CVD events.

Nonhemodynamic factors such as neurohumoral and coagulation factor might be another candidate to explain the cardiovascular risk of LVH. These factors share an etiology of LVH and cardiovascular events. Schlaich *et al.* (*Circulation* 108:560-565, 2003) suggested that despite same BP level, neurohumoral activity was high in hypertensive LVH compare to hypertensive without LVH. Our findings indicated that circulatory norepinephrine level was significantly higher in hypertensive patients with ECG-LVH compare to hypertensive without ECG-LVH. Each of ECG-LVH (HR, 4.03; 95% CI, 2.16-7.53; $P = 0.0001$) and circulatory norepinephrine level (HR, 1.00; 95% CI, 1.00-1.00; $P = 0.01$) was independently associated with increased risk for CVD events. An interaction of ECG-LVH with norepinephrine level on CVD events was not observed, which might be due to statistical insufficient of small CVD events. Lip *et al.* (*Am J Cardiol* 80:1566-1571, 1997) suggested that those with echocardiographic LVH had higher circulating fibrinogen levels compare with those without LVH. We observed that circulating levels of fibrinogen, F1+2, vWF, and PAI-1 were not significantly different between those with and without ECG-LVH. The reason of this discrepancy remained uncertain. However racial differences may exist in the circulating levels of hemostatic factors and their impacts on cardiovascular events.

In our study, the association between ECG-LVH and CVD events could not be explained by high 24-hour BP, higher nocturnal SBP, and higher circulating levels of norepinephrine and hemostatic factors. Other potential mechanism unmeasured in the present study that share a

common etiology of LVH and CVD events such as sleep apnea, neurohumoral factors (circulating levels of angiotensin, aldosterone, and natriuretic peptide) and salt sensitivity are required in further investigations to determine whether the association between ECG-LVH and CVD events observed in our study is independent of these uncontrolled factors.

5 結論

In older hypertensive patients, ECG-LVH was associated with a higher risk of CVD events, independent of ambulatory BP parameters and circulating norepinephrine and fibrinogen levels.

論文審査の結果の要旨

本論文は、高血圧のある高齢者において、心電図による左室肥大所見と心血管イベントのリスクについて、後ろ向き研究を行ったものである。その結果、高血圧のある高齢者において、心電図による左室肥大所見がある群は、ない群と比較して有意に心血管イベントを増加させ、これは、外来での血圧測定、血漿中ノルエピネフリン濃度およびフィブリノーゲン濃度とは、独立した因子である事を示した。

本研究については、すでに 2014 年に *Am J Hypertens* に論文として掲載されており、また平成 27 年 1 月 29 日に開催された学位審査委員会において行われ学位論文に相応しいものであることが評価された。

最終試験の結果の要旨

本論文は、高血圧のある高齢者において、心電図による左室肥大所見と心血管イベントのリスクについて、後ろ向き研究を行ったものである。その結果、高血圧のある高齢者において、心電図による左室肥大所見がある群は、ない群と比較して有意に心血管イベントを増加させ、これは、外来での血圧測定、血漿中ノルエピネフリン濃度およびフィブリノーゲン濃度とは、独立した因子である事を示した。

本研究については、すでに 2014 年に *Am J Hypertens* に論文として掲載されており、また平成 27 年 1 月 29 日に開催された学位審査委員会において、プレゼン・質疑応答の内容について審議された結果、学位論文に相応しいものであることが評価された。