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学 位 論 文 題 目	Relationship of four blood pressure indexes to subclinical cerebrovascular diseases assessed by brain MRI in general Japanese men (一般日本人男性において脳 MRI で評価した潜在性脳血管疾 患と血圧指標の関係)
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論文内容要旨

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学位論文題目	Relationship of four blood pressure indexes to subclinical cerebrovascular diseases assessed by brain MRI in general Japanese men (一般日本人男性において脳 MRI で評価した潜在性脳血管疾患と血圧指標の関係)		
<p>Purpose: A relevant amount of publications reported the association of blood pressure (BP) indexes, which are, systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), and mean arterial pressure (MAP) to subclinical cerebrovascular diseases (SCVDs). Nevertheless, the association is inconclusive and further understanding of the pathophysiological mechanisms of BP indexes and SCVDs is needed. The purpose of our study was to clarify the magnitude of the association of BP indexes measured at two different visits on SCVD outcomes assessed by MRI in community-dwelling Japanese men.</p> <p>Methods: The study population was the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA), a community-based observational study of general Japanese men from Kusatsu city in Shiga Prefecture. The total number of participants at Visit 1 [2006-2008] was 1094 between the age of 40-79. The participants were asked for a second visit (Visit 2) between 2010 and 2014, and the number then was 853, and again were asked to participate in an MRI visit between 2012 and 2015 in which the number complied was 740. Participants with history of myocardial infarction, stroke with symptoms, and participants with any missing data were excluded and the analyzed participants were 616.</p> <p>At both Visit 1 and 2, office BP was measured clinically following strictly the criteria of The Japanese Society of Hypertension Guidelines and the average from each visit was used to calculated four office BP indexes (SBP, DBP, PP, MAP). Following the classification of the Japanese Braindock guideline which is similar to Fazekas grading, five SCVD MRI outcomes were dichotomized as: Lacunar infarction= presence (≥ 1 lesion) or absence. Periventricular hyperintensity (PVH)= presence (Fazekas grade ≥ 2) or absence. Deep subcortical white matter hyperintensity (DSWMH)= presence (Fazekas grade ≥ 3) or absence. Microbleeds= presence (≥ 1 microbleed) or absence. Intracranial artery stenosis (ICAS)= presence ($\geq 1\%$ stenosis) or absence. Covariates adjusted in statistical analysis models were: age, BMI, HbA1c, LDL-C, HDL-C, smoking status, drinking status, hypertension medication, diabetes mellitus medication, and dyslipidemia medication.</p>			

- (備考) 1. 論文内容要旨は、研究の目的・方法・結果・考察・結論の順に記載し、2千字程度でタイプ等を用いて印字すること。
2. ※印の欄には記入しないこと。

Multivariable logistic regression adjusting for covariates was used to estimate the odds ratio (OR) and 95% CI of each prevalent SCVD for 1-SD higher office BP indexes. Statistical significance was set at $P < 0.05$ and all analyses were performed on SAS version 9.4.

Results: Among the 616 eligible participants mean age \pm SD was 63.6 ± 9.2 years at Visit 1 and 68.2 ± 8.1 years at Visit 2. Multivariable adjusted OR for the presence of MRI outcomes per 1-SD higher of each office BP index (SBP, DBP, PP, and MAP) at Visit 1 and Visit 2 revealed that SBP at Visit 1 associated with lacunar infarction, DSWMH, microbleeds, and ICAS, and at Visit 2 associated with lacunar infarction, microbleeds, and ICAS. DBP at both visits associated with lacunar infarction, PVH, and DSWMH, with a slightly higher OR at Visit 2 than at Visit 1 for microbleeds. Visit 1 and Visit 2 PP associated with lacunar infarction and ICAS, while Visit 2 PP only associated with microbleeds.

Considerations: Almost all BP indexes showed distinct associations between two visits of BP indexes and MRI assessed SCVDs. This is consistent with previous studies, however, we found association of SBP and DSWMH not reported before, while we did not find association between PP and PVH, DSWMH, or microbleeds. This might be due to differences in genetic and environmental backgrounds between populations like age, gender, and ethnicity. Visit 1 and 2 BP indexes showed almost similar associations to SCVDs, which were consistent with previous studies, however, the association was slightly stronger for microbleeds at Visit 2, which could be due to difference in underlying pathophysiological mechanisms. Recent increase in SBP, DBP seems to associate more with the pathophysiological pathway of microbleeds, whereas the progression of the other SCVDs is gradual and could vary in time to the onset of the outcome which could explain the stronger relationship of BP indexes at Visit 1 to the outcomes lacunar infarction, PVH, DSWMH, and ICAS. This is important for clinicians to carefully assess and separately evaluate four BP indexes as a tool for early prevention of potential stroke while considering cerebrovascular risk factors.

Conclusions: In conclusion, our study showed two different periods' measured BP indexes were associated to some but not all SCVDs. The distinct association of each periods' BP index to SCVDs helps understand particular pathophysiological mechanisms that are yet to be confirmed. Deliberate evaluation of each BP index separately, in addition to conventional cerebrovascular risk factors, may be used as a tool for early prevention of potential stroke.

別紙様式9（課程博士・論文博士共用）

博士論文審査の結果の要旨

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論文審査委員			
<p>(博士論文審査の結果の要旨)</p> <p>本論文では、滋賀県下の健康住民コホートによる疫学調査を行い、高血圧症と無症候性MRI脳病変との関連性を評価することにより、以下の点を明らかにした。</p> <ol style="list-style-type: none"> 1) 准臨床動脈硬化症の滋賀疫学研究(SESSA)のうち、血圧測定（ホームおよびオフィス）などの調査を約5年間のインターバルで2回受け、かつ頭部MRI画像検査を受けた616例を対象に、収縮期血圧(SBP)、拡張期血圧(DBP)、脈圧(PP)、平均動脈圧(MAP)の各血圧(BP)インデックスを指標とし、MRI上のラクナ梗塞、脳室周囲高シグナル、深部白質高シグナル、微小出血、頭蓋内動脈狭窄の潜在性脳血管障害(SCVD)各所見との関連性を統計学的に評価した。 2) すべてのBPインデックスは、それぞれの程度に脳MRI病変と相関した。 3) 従来の報告に比して、新たにSBPと深部白質高シグナルに相関を見出したが、一方、PPと深部白質異常や微小出血の間には相関を認めなかった。 4) 血圧の1回目評価と2回目評価を用いた解析では類似した結果であったが、微小出血については2回目評価との相関性がやや強かった。 5) ホームおよびオフィスでの血圧は類似の相関性を示したが、オフィスでの血圧の方がいくらか強い相関を示した。 <p>本論文は、高血圧の各インデックスが無症候性脳病変の原因として、いかに関与するかについて新たな知見を与えたものであり、また最終試験として論文内容に関連した試問を実施したところ合格と判断されたので、博士（医学）の学位論文に値するものと認められた。</p> <p style="text-align: right;">(令和3年1月26日)</p>			