## D. 考察

①血圧日内変動に関する検討

脳梗塞発症・脳出血発症について、また脳梗塞死亡・心疾患死亡・脳出血・出血性脳卒中死亡に関して、異なる日内変動パターンやモーニングサージ、異なる時間帯の血圧がそれぞれのリスクに関与していることが明らかになった。

脳梗塞・心疾患に関しては夜中の血圧の関与が高く、日中の血圧の関与が低いことから夜間降圧度が小さいほど発症・死亡リスクが上昇すると考えられる。これらの時間帯の血圧は日中の活動性とは異なり、定常状態の血圧とも考えられ持続的に高い血圧であるという状態が脳梗塞や心疾患に関与しているのではないかと考えられる。

一方で、脳出血に関しては日中の血圧レベル、大きい夜間降圧度、大きいモーニングサージの関与が考えられた。大きい夜間降圧度は日中の大きな血圧上昇と解析上は区別することができないことを考えると、日中活動時にかけての血圧の上昇が脳出血発症に深く関与していると考えられる。

以上のように高血圧に伴って生じる病型によって異なる時間帯の血圧が関与していること、異なる病態によって引き起こされることが確認、再確認された。

高血圧症の診断基準は随時血圧で140/90mmHg 以上と定義されているが最近では仮面高血圧の存在とその不良な予後が報告されており、また各種日内変動それぞれが予後予測能を持っていることも知られてきた。高血圧症は高血圧症によって引き起こされる各種病態の原因となることからその分類が決定され、高血圧症自体がその中に多様性を秘めている。今回の研究では同様に高い血圧であっても、血圧を測定する時点において将来リスクが高くなる疾患が異なってくるということである。

②血圧長期変動に関する検討

これまで自由行動下血圧による 30 分毎の血圧の変動(血圧短期変動)および血圧日内変動は予後との関連が知られていたが、家庭血圧日間変動(血圧長期変動)と生命予後との関連は報告がなかった。本研究は家庭血圧測定による血圧日間変動と脳心血管死亡および脳卒中発症との関連を初めて明らかにした。

24時間自由行動下血圧測定による30分毎の血圧短期変動と家庭血圧日間変動は互いに異なり、それぞれ独自の価値があるものと思われる。24時間自由行動下血圧測定による15－30 分毎の血圧短期変動は予後と関連する。しかし、24 時間自由行動下血圧測定を日常診療において繰り返し測定することは実際的ではない。従って、家庭血圧測定による血圧日間変動でこれを代用し得るかは興味深い。しかし、24 時間自由行動下血圧測定による血圧短期変動と家庭血圧日間変動とは質的に異なるものと考えられる。24 時間自由行動下血圧測定の意義は自由行動下の血圧測定である。一方、家庭血圧測定の意義は統一した測定条件、即ち起床後一時間以内、排尿後、安静 2 分間後、座位にて家庭血圧を測定する“定点観察”である。このように 24 時間自由行動下血圧測定と家庭血圧測定とは異なり、必ずしも互換性はないといえる。実際、血圧短期変動と家庭血圧日間変動との相関を検討した以前の我々の検討では、相関係数は 0.071 から 0.299 と低い。したがって、24 時間自由行動下血圧測定による血圧短期変動と、家庭血圧日間変動とは、一方で他方を代用しうるものではなく、互いに異なる価値を持つと思われる。

家庭血圧測定による血圧日間変動の再現性は本研究において重要と思われる。家庭血圧の平均値については、以前の我々の検討において最低 3 日間の測定が必要であること報告しており、本研究においても3日間以上の家庭血圧測定を必須とした。しかし、本研究では血圧日間変動の指標を血圧の標準偏差として

おり、変動性の評価においては 3 日間では少ない可能性があると考えられた。したがって、家庭血圧測定を 20 日以上測定した対象での分析も併せて実施した。本研究の結果からは、3 日間測定の対象者よりも、20 日以上測定した対象に限定した方が、家庭血圧日間変動と脳心血管死亡および脳卒中との関連が増強しており、より長期の家庭血圧測定が望ましいと考えられる。今後、更なる長期間の測定が必要なのか、あるいは、より短期間の測定で予後予測能はプラトーとなるのかを検討する必要がある。

収縮期家庭血圧日間変動は脳心血管死亡の粗死亡率と直線的に関連していた。その一方で、収縮期家庭血圧日間変動高値の者はより高齢で高脂血症、降圧療法および脳心血管病の既往を持つ者の割合が高く、また血圧レベルが高かった。各種危険因子で補正後、収縮期家庭血圧変動と脳心血管死亡との関連は有意ではなくなった。従って、収縮期家庭血圧変動の増大と脳心血管死亡増大の機序として、各種危険因子による動脈硬化により二次的に血圧変動が増大している部分が大きいと考えられた。しかし、拡張期家庭血圧日間変動では危険因子補正後も脳心血管死亡リスクと有意な関連を認め、独立した予後予測能が示唆された。

脳心血管死亡には一週間の周期性が存在することが知られている。心筋梗塞、突然死は月曜日に有意に増大していることが報告されている。この原因として、休養から勤務に移行するというライフスタイル、身体活動の変化が大きく影響していることが考えられている。このようなライフスタイル、労働ストレスおよび身体活動の変化は同時に血圧変動の原因ともなりうると考えられる。したがって本研究において考慮すべき交絡因子と考えられる。本研究では家庭血圧データを収集する際、勤務日・週末を考慮していない。しかしながら、身体活動による血圧変動を除外する目的で、家庭血圧測定を一定の条件つまり、起床後一時間以内、2分間の安静後、座位にて測定するように指導した。したがって、交絡因子としての身体活動の変化はある程度除外されていると考えられる。

本研究では血圧日間変動は初発脳卒中発症リスクと有意に関連した。特に脳卒中の病型を脳梗塞に限定した場合、より予後予測能が増強した。したがって、家庭血圧日間変動と脳卒中発症との関連において、虚血性脳血管障害が大きな位置を占めているものと考えられる。脳出血発症およびくも膜下出血発症については、それぞれ 35 例(1%)および 10 例(0.4%)と頻度が低く今回は検討出来なかった。

本研究では服薬コンプライアンスは調査していないが、服薬コンプライアンスの悪い高血圧患者が血圧変動の増大と不良な予後との関連に寄与している可能性がある。すなわち降圧薬を"間引き"して服用する場合、血圧日間変動の増大が懸念される。また、同時に服薬コンプライアンスの低下は不良な血圧管理と結びついている。実際、薬剤抵抗性高血圧の原因として服薬コンプライアンスの低下が挙げられる。したがって、服薬コンプライアンスは本研究において重要な交絡因子であると考えられる。

## E. 結論

遺伝要因がある特定の環境要因を通して高血圧発症を引き起こし、さらに各疾患を発症するというモデルを考えると、高血圧の有無のみではなく、血圧レベルや血圧日内変動の大きさなどとの比較で遺伝子多型を捉えた方がより病態を反映した解析となるであろう。 また血圧日間変動は脳心血管病の新規の危険因子であると考えられる。したがって、高血圧関連遺伝子の探索において、家庭血圧レベルとともに家庭血圧日間変動も同時に検討することで有益な結果が得られることが期待される。

## F. 健康危険情報

なし

## G. 研究発表

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## H. 知的財産権の出願・登録状況

1. 特許取得
   なし
2. 実用新案登録
   なし
3. その他
   なし

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分担研究報告書

# テーラーメイド医療に向けた新規遺伝子診断法の開発

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**研究要旨**

高血圧・糖尿病の発症や病態に関連する遺伝子多型(とくにSNP)を臨床面で活用し、オーダーメイド医療として結実させるためには、診療の場で簡便・迅速に実施が可能な遺伝子検査法の開発が求められる。わたしたちは、イムノクロマトグラフィー試験紙を用いて簡便に遺伝子型が判定できる遺伝子診断法を開発した。本方法は、一般病院の検査室で特殊機器や専門的技術を要することなく遺伝子検査が可能な画期的な手法である。今後、本方法を用いたベッドサイド遺伝子診断によって、遺伝子型に応じたテーラーメイド生活指導を含む予防医療への展開が可能と考えられる。

## A．研究目的

ゲノム研究の進展によって高血圧・糖尿病に関連した遺伝子多型(そのなかでもとくにSNP と呼ばれるもの)が次第に明らかにされつつある。これらの遺伝子多型を臨床面で活用し、遺伝子多型に応じたテーラーメイド生活指導を含む予防医療を確立するためには、臨床の場への遺伝子診断の導入が不可欠である。そこで必要となってくるのは、診療の場で簡便・迅速に実施することが可能な遺伝子検査法である。

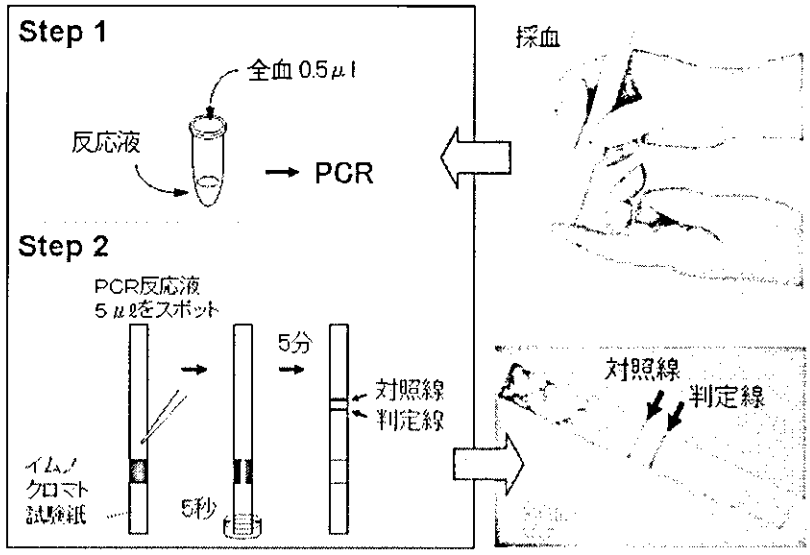
現在、さまざまな遺伝子多型の検出法が知られているが、現時点では一般病院や診療所などの臨床の現場で施行が可能な SNP 検出法は存在しない。近年注目されている DNA チップなどの SNP 検出法は、もともとヒトゲノム解析研究のために開発されたものであり、大量検体における多項目の SNP 検出を目的とし、ハイテクを駆使した特殊高額機器と専門的な技術が必要である。一方、臨床の場で必要とされる SNP 検出は、専門的技術をもたない一般臨床検査技師・医師・看護師によって、短時間のうちにベッドサイドや外来診療の場で判定できることが求められる。

本分担研究の目的は、わたしたちが独自に開発した新しい SNP 検出法を用いることにより、一般医療機関において遺伝子多型をその場で検出できる遺伝子診断法を確立し、オーダーメイド医療が実施できる基盤を確立することにある。

## B．研究方法

本分担研究の中核となる遺伝子多型検出法は、DNA を抽出することなく血液 0.5 μℓを直接使用し、2ステップの操作を行うだけの簡便・迅速な手法である(次ページの図参照)(Hum Mutat 2003;22:166-172)。遺伝子多型の有無は、イムノクロマト試験紙上に現れる紫色の判定線によって、肉眼的におこなう。本方法(CASSOH 法と命名)は、基本的にはアレル特異的オリゴヌクレオチド・ハイブリダイゼーションをベースとしているが、これまでの常識を覆す短い検出プローブ(～10-mer)と競合プローブの併用などによってミスマッチ形成の効率を1/100 以下に低下させ、従来にない高い信頼性と再現性を得ることに成功している。また、こ

れまで長時間をかけて厳密な温度・塩濃度条件の管理下で行う必要があったプローブの洗浄過程を、クロマトグラフィー展開中に数分で、しかも室温で行うことが可能となった。必要な試薬はすべて最初に混和されているため操作途中での反応液追加は不要で、手技的にはインフルエンザウイルス迅速検出検査などに極めてよく似ている。採血から2時間以内に SNP の遺伝子型判定が可能である。




本年度は、CASSOH 法の臨床応用を実際に検証することを目的として、既知の各種薬物代謝酵素遺伝子多型について、その検出系を確立するための検討を行った。

(倫理面への配慮)

本研究は、直接ヒトを対象とした研究を行うものではなく、また遺伝子解析そのものを目的とする研究を行うものでもない。本研究で標準検体 DNA を検査法の検定に用いることについては、すでに東北大学医学部倫理委員会の審査を受け、承認されている(承認番号 2003-105)。

## C. 研究結果

以下に示すような8種の薬物代謝酵素遺伝子多型/薬物標的分子多型について CASSOH 法による検出法を確立することができた(遺伝子名・(SNP)・表現型の順に記載):

1) ALDH2・(1459G>A)・アルコール代謝遅延

2) CYP2C19・(681G>A)・ジアゼパム、オメプラゾールなどの代謝遅延

3) NAT2・(341T>C、590G>A、857G>A)・イソニアジド代謝遅延

4) TPMT・(719A>G)・メルカプトプリンなどの代謝遅延

5) UGT1A1・(211G>A)・イリノテカン代謝遅延

6) Mitochondria・(1555A>G)・アミノグリコシド系抗生剤による難聴

いずれの遺伝子多型検出においても、シークエンス法によって遺伝子型が決定された標準検体を対象として、遺伝子多型の有無をクリアカットに判定することが可能であった。

## D. 考察

現在の遺伝子多型(とくに SNP)検出法は、ヒトゲノム解析研究のために開発・研究された技術(例:DNA チップ)を基礎としており、国内外のバイオ関連企業が次々と市場に送り込む新しい方法は、高額な特殊機器の使用を前提としている。また、簡便迅速な遺伝子変異検出を謳う手法も、ハイテクを駆使した専用機器が必要である。一般病院や診療所でそのような高額機器を導入することは困難であるとともに、分子生物学の専門教育・訓練を受けていない臨床検査技師が実施するにはきわめて敷居が高い。

臨床の現場で求められる薬理遺伝学的多型の検出は、ヒトゲノム解析研究のように同時に多くの患者における数千種類の SNP タイピ

ングをおこなう必要はない。重要なことは、一個人の検査結果が、その場ですぐに得られることである。わたしたちの考案した CASSOH 法は、low technology で、迅速・簡便・安価に、1人の検体を対象に少項目の SNP 検出を行うという発想の下に生まれたこれまでに類を見ない手法である。この CASSOH 法は、今回検討した8種類のSNP検出に応用可能であったことから、その汎用性が実証されたものと考えられる。

イムノクロマトグラフィーという手法そのものは、現在、医療の現場において妊娠判定・インフルエンザウイルス感染などの様々な迅速診断に用いられており、臨床検査技師や看護師レベルで盛んに実施されている。これらはいずれも遺伝子診断ではないが、医療従事者にとって親しみのある手法である。今後、イムノクロマトグラフィーという媒体を用いることによって、臨床の現場に抵抗なく遺伝子検査を普及することが期待できる。

## E．結論

イムノクロマトグラフィー試験紙を用いて簡便に遺伝子型が判定できる遺伝子診断法を開発し、薬物代謝酵素遺伝子多型/薬物標的分子多型の検出に応用した。本方法は、一般病院の検査室で特殊機器や専門的技術を要することなく遺伝子検査が可能な画期的な手法である。本方法を用いて、臨床的有用性の高い疾患発症関連SNPの検出系を確立することにより、遺伝子型に応じたテーラーメイド生活指導を含む予防医療への展開が可能と考えられる。

## F．健康危険情報

該当なし

## G．研究発表

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## H．知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

# III. 研究成果の刊行に関する一覧表

# 研究成果の刊行に関する一覧表

雑誌

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
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# Ⅳ．研究成果の刊行物・別刷

— Review —

# Epidemiology of Hypertension Based on Ambulatory Blood Pressure Monitoring and Self-Measurement of Blood Pressure at Home

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Measurements of ambulatory blood pressure (ABP) and of home blood pressure (HBP) as an adjunct to casual/clinic BP (CBP) measurements are currently widely used for the diagnosis and treatment of hypertension. We have monitored a rural cohort of people from the population of Ohasama, Japan, with respect to their prognosis and have previously reported that ABP and HBP are superior to CBP for the prediction of cardiovascular mortality. We examined the prognostic significance of white-coat hypertension for mortality and found that the relative hazard for the overall mortality of patients with white-coat hypertension was significantly lower than that for true hypertension during 5-year observation period but observed that the development of sustained hypertension was more frequent in patients with white-coat hypertension than those with true normotension during 10-year observation period. Our results also confirmed that day-by-day variability as well as short-term blood pressure variability (as measured every 30 min) was independently associated with cardiovascular mortality. In addition, research has recently focused on isolated systolic hypertension and pulse pressure as independent risk factors for poor cardiovascular prognosis. The Ohasama study also clearly demonstrated that isolated systolic hypertension and increased pulse pressure, as assessed by HBP, were associated with an increase in the risk of cardiovascular mortality. Concerning diurnal blood pressure variation, the relative hazard for cardiovascular mortality increased in non-dippers and inverted dippers while that in extreme dipper did not. The Ohasama study also clearly demonstrated that nocturnal BP levels in hypertensive patients with extreme dipper were significantly higher than those in normotensive subjects. The Ohasama study showed that the level and variability of hypertension as assessed by ABP and HBP are independent predictors of cardiovascular morbidity and mortality. It also demonstrated an independent association between the prognosis of hypertension and each component of ABP and HBP, indicating the prognostic significance of these blood pressure measurements.

**Key words** —— blood pressure, home measurement, ambulatory monitoring, variability, pulse pressure, heart rate

## INTRODUCTION

The most vital blood pressure information related to hypertension in clinical practice is the casual/clinic blood pressure (CBP). Blood pressure information for epidemiological purposes is generally also obtained in medical environments similar to those used for mass screening. Several questions have, however, recently been posed regarding the true representativeness of CBP, so research has focused on the other ways of measuring blood pressure, such as ambulatory blood pressure (ABP) monitoring and self-measured blood pressure at home (HBP). Each method of blood pressure measurement has its own specific features.

Since 1985, we have been conducting an epide-

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**Table 1.** Referece Values of Home BP Value by JNC-VI and 1999 WHO/ISH

| | HBP value (Ohasama) (mmHg) | Reference value (mmHg) |
|---|---|---|
| Hypertension | ≥ 138/≥ 83 | ≥ 135/≥ 85 |
| Cox model (non-parametric) | | (JNC-VI) |
| Normotension | | |
| Cox model (non-parametric) | 120–127/72–76 | |
| Corresponding value of 140/90 mmHg (Clinic BP) | 123/77 | < 125/< 80 (WHO/ISH) |
| Mean home BP value + 1 S.D. (with normal Clinic BP value) | 125/77 | |

miological survey of hypertension using ABP and HBP in Ohasama, in the northern part of Japan. Ohasama initially had a population of 9400, but this has now dropped to 6800. Over the past 18 years, we have obtained 3000 ABP monitorings from subjects aged 20 years and over, and 5000 HBP measurements from subjects aged 7 years and over, as well as outcome and information on risk factors and predictors. One of the initial purposes of the study was to define reference values for these measurements with respect to prognosis in a long-term prospective study.

## REFERENCE VALUES OF AMBULATORY BLOOD PRESSURE AND SELF-MEASURED BLOOD PRESSURE

Several methods are available for obtaining these reference values. The first involves the distribution criteria, for example mean + S.D., mean + 2 S.D. or 95$^{th}$ percentile value of the reference population. A meta-analysis of distribution criteria using an international database has been conducted.[1] These values provided us with the distribution of ABP and HBP levels in the population, but the clinical significance of these values is still uncertain.

Another method uses correspondence criteria, which derives ABP and HBP levels corresponding to a casual blood pressure of 140/90 mmHg or 160/95 mmHg. Such values were obtained in the Ohasama study,[2] the PAMELA study,[3] the Belgian population study[4] and others. The relationship between CBP and ABP or HBP has not, however, been well enough characterized to obtain sufficiently accurate corresponding values (the correlation coefficient of the relationship between CBP and ABP or HBP having been calculated to be approximately 0.5).

The most meaningful reference values would be provided by a long-term prospective study based on the resultant cardiovascular morbidity and mortality. Several observational and interventional studies are currently ongoing world-wide, of which the Ohasama study started first and is the only study aiming to provide such reference values. Subjects from the Ohasama population aged 40 years and over were followed up for an average of 5 years.[5–7] ABP and CBP values were classified equally into quintiles on the basis of blood pressure level, the relationship between blood pressure level and cardiovascular mortality being analyzed by a Cox regression model adjusted for age, sex and drug treatment.

No specific tendency was observed in systolic CBP in the 1300 subjects ≥ 40 years followed. In subjects in the highest quintile of systolic ABP, however, a significant increase in relative hazard was observed. A tendency towards an increased relative hazard was also observed in the lowest quintile. The higher predictability of HBP when compared with CBP was also confirmed in the Ohasama study.[5,6,8] These results were cited in the Sixth Report of the Joint National Committee[9] and 1999 World Health Organization/International Society of Hypertension guidelines[10] (Table 1), and were the basis of the reference values (Table 1) for ABP monitoring and HBP measurements given in these guidelines.

## WHITE-COAT HYPERTENSION

White-coat hypertension — reproducible hypertension in the medical setting and normotension in the non-medical setting — is more accurately defined using normative values of ABP and HBP. The

Ohasama study examined the prognostic significance of white-coat hypertension.[11] According to the Cox proportional hazard model, the relative hazard in white-coat hypertensive patients was similar to that seen in true normotensive subjects, whereas true hypertension and reversed white-coat hypertensive subjects (masked hypertension: hypertension in the non-medical setting and normotension in the medical setting) carried a significantly higher relative hazard of cardiovascular mortality. Recent analysis demonstrated that the development of sustained hypertension was more frequent in patients with white-coat hypertension than in those with true normotension during 10-year observation period.

In the Ohasama population, 24.8% of the 117 subjects with hypertension measured by CBP (systolic blood pressure [SBP] ≥ 160 mmHg and/or diastolic blood pressure [DBP] ≥ 95 mmHg) were normotensive when measured by 24 hr ABP monitoring (SBP < 125 mmHg and DBP < 75 mmHg). The results again suggest that ABP and HBP have more predictive power and are more representative of individual blood pressure than in conventional CBP.

## BLOOD PRESSURE VARIABILITY AND PROGNOSIS

Both new techniques for blood pressure measurement have several advantages over CBP, these advantages essentially being mediated by multiple measurements of blood pressure over a given period.[12] ABP monitoring, for example, provides 50–100 measurements during the course of a day, whereas HBP monitoring provides more than 60 measurements during the course of a month. Such detailed information enables a wider scope of parameters to be derived from the data set, such as 30 min blood pressure variation, circadian blood pressure variation, day-by-day variation and the weekly and yearly variation of blood pressure and provides additional information, including multiple measurements of heart rate, which are not available from CBP measurements.

### Circadian Blood Pressure Variation

Circadian blood pressure variation (a higher blood pressure level during the day and a lower one at night) is usually observed both in subjects with normotension and in those with essential hypertension. Under several pathophysiological conditions, however, circadian blood pressure variation is diminished, even in patients with essential hypertension, sometimes being inverted to show a nocturnal elevation of blood pressure. Subjects who showed normal nocturnal dipping were called dippers, whereas those with diminished nocturnal dipping or a nocturnal elevation of blood pressure (inverted dippers) were classified as non-dippers. (Kario *et al.* have used the term 'extreme dipper' for subjects with a nocturnal dip of 20% or more of diurnal blood pressure).[13]

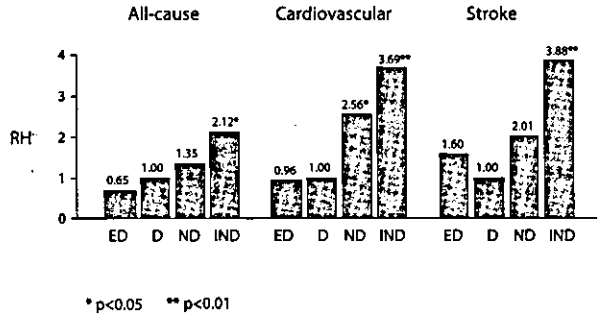


**Fig. 1.** Circadian Blood Pressure Variation and All Cause Mortality, Cardiovascular Mortality and Stroke Mortality in Ohasama Population[17]

*p*-Values are expressed *vs* relative hazard 1. ED: extreme dippers, ND: non-dippers, D: dippers, IND: inverted dippers.

The Ohasama study examined the relationship between diurnal blood pressure level and circadian blood pressure variation.[14] The amplitude of nocturnal dipping increased with the increase in diurnal blood pressure level, and it should be noted that the nocturnal blood pressure level rose according to the elevation of diurnal pressure level. These results suggest that mean daily blood pressure in hypertensive subjects should be lower over 24 hr. A significantly higher relative hazard for cardiovascular mortality, especially for stroke mortality was observed in non-dippers and inverted dippers, while the relative hazard for cardiovascular mortality in extreme dippers was similar to that in normal dippers (Fig. 1).[15]

The nocturnal blood pressure level in hypertensive extreme dippers needs to be identified: in this group, it was significantly higher than was encountered in normotensive subjects (Fig. 2).[16] Thus, extreme dipper hypertensive subjects do not have an inappropriately low blood pressure level. If circadian blood pressure variation were associated with a risk of cardiovascular complications in extreme

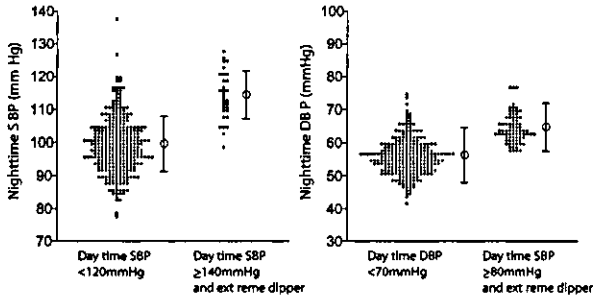


**Fig. 2.** The Nocturnal Blood Pressure Level in Daytime Normotensive Subjects and in Extreme Dippers with Daytime Hypertension[18]

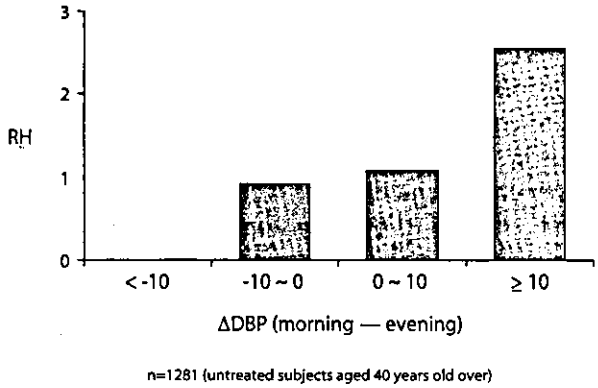


**Fig. 3.** Relative Hazard (RH) for Cardiovascular Mortality in Relation to Morning High Blood Pressure Determined by the Difference Between Home BP in the Morning and That in the Evening ($n$ = 1281 Untreated Subjects aged 40 years and Above)[19]

dippers, a greater amplitude and slope for nocturnal dipping and higher 24 or daytime ABP levels would therefore be postulated.

## Morning Hypertension

The morning rise of blood pressure represents a mirror image of nocturnal dipping. As described for nocturnal dipping, the morning rise has several measurable factors - the blood pressure level itself and the amplitude and slope of the morning rise.

The clinical significance of the high morning blood pressure was suggested by the results of the Ohasama study in terms of its examination of the relative hazards ratio for cardiovascular mortality on the basis of the difference in blood pressure between morning and evening HBP. The higher the morning blood pressure was relative to the evening blood pressure, the greater the relative hazard ratio of cardiovascular mortality that was seen (Fig. 3).[17] Controlling the morning blood pressure seems to give a better prognosis in the hypertensive population. Recently Kamoi *et al.* reported that in normotensivie patients with diabetes mellitus on the basis of clinic BP, only those with high BP in the morning obtained by HBP had severe target organ damage, suggesting that morning BP has a specific clinical relevance to hypertensive complications.[18]

## Blood Pressure Variability and Heart Rate Variability

ABP monitoring provides us with information on blood pressure every 30 min as well as on heart rate variability and average blood pressure and heart rate. The issue remains, however, of whether blood pressure variability *per se* has any prognostic significance. The clinical significance of heart rate variability has scarcely been studied in the general population, and the prognostic significance of blood pressure variability for cardiovascular mortality has not been investigated at all in this group. The poor prognosis of subjects with reduced heart rate variability has, however, been widely recognized in several types of cardiovascular disease.

In the Ohasama Study, we obtained 30 min blood pressure and heart rate variability by means of indirect ABP monitoring in the general population, following subjects for up to 10 years. We can therefore examine the prognostic significance of blood pressure variability, heart rate variability and combinations of these variables.[19] We obtained ABP and heart rate in 1542 subjects aged 40 years and over. The variability of blood pressure and heart rate was estimated as the standard deviation of the daytime or night-time average, measured every 30 min.

Quintile analysis was initially applied to the baseline blood pressure variability, subjects being subdivided into five equal groups according to the distribution of the baseline blood pressure variability. There was a significant linear relationship between daytime systolic ABP variability and relative hazard for cardiovascular mortality (Fig. 4). The highest quintile of daytime systolic blood pressure variability revealed a significant increase in relative hazard for cardiovascular mortality. In analyzing the association between heart rate variability and prognosis, participants were subdivided into three groups: those with a heart rate variability less than the mean minus 1 S.D., greater than the mean plus 1 S.D. and values in between. Cardiovascular mortality increased linearly with the decrease in daytime and

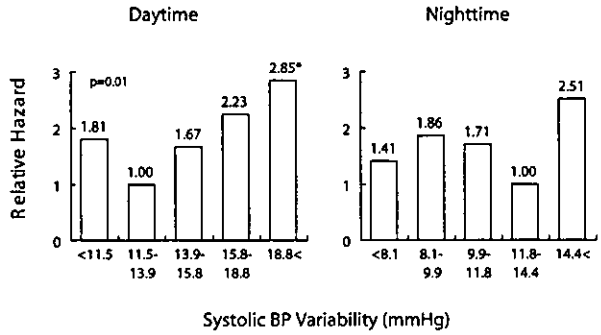


**Fig. 4.** Relative Hazard for Cardiovascular Mortality in Relation to Blood Pressure Variability Determined by Ambulatory BP Monitoring[19]
$p < 0.05$ *vs* relative hazard 1.

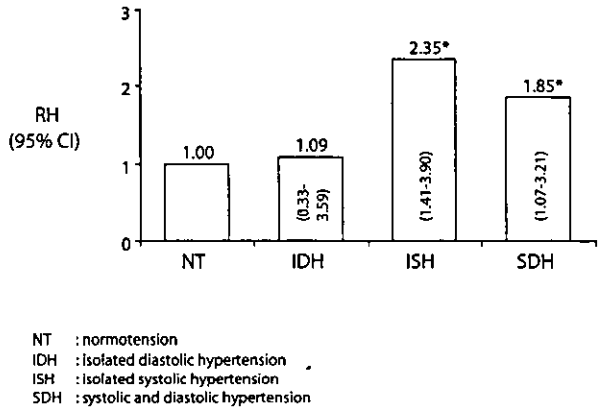


**Fig. 5.** Relative Hazard for Cardiovascular Mortality in Isolated Systolic Hypertension (ISH) in Comparison to Normotension (NT)[20]
$p < 0.00$ *vs* NT.

the night-time heart rate variability. These results suggest that blood pressure variability and heart rate variability are associated with cardiovascular mortality independently of each other.

We then examined the risk of cardiovascular mortality associated with a combination of daytime ABP variability and heart rate variability. Daytime systolic blood pressure variability was divided into two by the cut-off point to separate the fourth and third quintiles of daytime systolic blood pressure, that is, 15.8 mmHg. Daytime heart rate variability was also divided into two groups by the cut-off point at the mean minus 1 S.D. of heart rate variability, that is 7.2 bpm. Subjects whose daytime systolic ABP variability was more than 15.8 mmHg and whose daytime heart rate variability was less than 7.2 bpm had an extremely high relative hazard for cardiovascular mortality. The clustering of high blood pressure variability and low heart rate variability increases cardiovascular mortality risk synergistically.

Recent analysis demonstrated that day-by-day variability of BP obtained by HBP also has a prognostic significance; the high day-by-day variability of BP associates poor prognosis.

## PULSE PRESSURE

It has recently been reported that pulse pressure is a powerful determinant of cardiovascular outcome, and we also found this to be true in the Ohasama population aged 40 years and over.[20] The relative hazard for cardiovascular mortality was highest in isolated systolic hypertension defined on the basis of HBP measurements, greater even than that for combined systolic and diastolic hypertension, suggesting that pulse pressure is the best determinant of cardiovascular mortality (Fig. 5).

## HEART RATE

As mentioned above, heart rate is automatically available from ABP monitoring and HBP measurements. The prognostic significance of heart rate has recently been confirmed in several large-scale cohort studies. We also examined the prognostic significance of heart rate obtained from HBP monitoring.[21] Simultaneous measurements of blood pressure and heart rate at home were obtained in 1500 subjects from Ohasama over 40 years of age. Measurements were taken in the morning for 21 days, the relationship between the average of these parameters and the outcome being examined. Relative hazard for cardiovascular mortality increased linearly with increase in heart rate even after adjusting for blood pressure level, suggesting that heart rate is an independent predictor of cardiovascular mortality. It is surprising that heart rate is even better than blood pressure for prediction.

## CONCLUSION

If HBP measurements become the gold standard because of their high predictive power and reliability, they could also be used for population screening. The exclusion of false-negative and false-posi-

tive cases by means of HBP measurement could result in highly cost-effectiveness for screening and treatment of hypertension. Further qualitative and quantitative improvements in measuring hypertension are expected to introduce additional information besides blood pressure level obtained by ABP monitoring and HBP measurements.

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