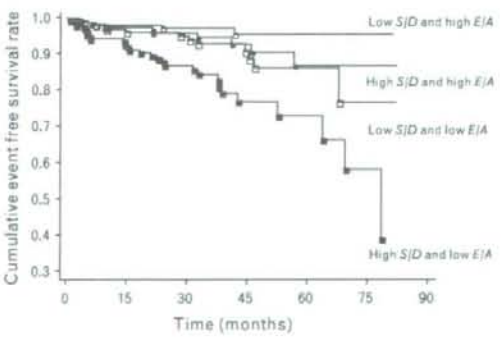
Table 2 Baseline clinical characteristics of study subjects

Variables	*E/A* ratio ≥ median Male ≥ 0.84 Female ≥ 0.82		*E/A* ratio < median Male < 0.84 Female < 0.82	
	Low *S/D* Male < 1.31 Female < 1.51	High *S/D* Male ≥ 1.31 Female ≥ 1.51	Low *S/D* Male < 1.77 Female < 1.81	High *S/D* Male ≥ 1.77 Female ≥ 1.81
n	177	178	175	175
Male (%)	50.9	50.6	50.3	50.3
Age (years)	52.7 ± 14.2§	60.5 ± 9.4†,§	65.7 ± 9.0†	67.6 ± 8.3†
Body mass index (kg/m^2)	24.1 ± 3.7	24.3 ± 3.3	24.4 ± 3.3	24.2 ± 3.0
Duration of hypertension (years)	11.9 ± 10.2§	12.9 ± 9.9§	16.3 ± 10.2†	17.9 ± 10.4†
Smoking status (%)				
Never/past/current	54.0/27.8/18.2	55.4/23.2/21.5	54.3/30.9/14.9	50.3/37.7/12.0
Pulse pressure (mmHg)	60.3 ± 15.1‡	61.0 ± 11.2	64.0 ± 13.7*	65.4 ± 15.0†
Heart rate (bpm)	65.9 ± 8.9	65.9 ± 9.4	67.3 ± 8.5	68.1 ± 7.5
Diabetes (%)	18.6	17.4‡	28.0	29.9*
Total cholesterol (mmol/l)	5.28 ± 0.88	5.25 ± 0.77	5.13 ± 0.79	5.23 ± 0.84
Triglycerides (mmol/l)	1.59 ± 1.53	1.45 ± 0.89	1.49 ± 0.85	1.50 ± 0.76
High-density lipoprotein cholesterol (mmol/l)	1.40 ± 0.44§	1.34 ± 0.40	1.27 ± 0.34†	1.24 ± 0.39†
LAD (cm)	3.54 ± 0.44‡	3.65 ± 0.49	3.67 ± 0.48*	3.66 ± 0.45
LVMI (g/m^2)	123.34 ± 36.28	124.58 ± 31.12	127.35 ± 35.23	132.19 ± 32.58*
Ejection fraction (%)	70.54 ± 8.64	71.76 ± 7.10	71.88 ± 7.74	72.59 ± 7.91*
E/A ratio	1.15 ± 0.28§	1.02 ± 0.17†,§	0.71 ± 0.09†	0.65 ± 0.11†,‡
DcT (ms)	206.2 ± 36.5§	216.7 ± 38.0§	243.0 ± 43.1†	263.7 ± 52.0†,§
S/D ratio	1.19 ± 0.20§	1.66 ± 0.24†,§	1.54 ± 0.19†	2.14 ± 0.33†,§
Peak PV_a-velocity (m/s)	0.26 ± 0.06§	0.28 ± 0.05	0.30 ± 0.08†	0.31 ± 0.10†
ARdur − A_d (ms)	−28.9 ± 30.8	−29.6 ± 28.3	−31.4 ± 28.1	−28.9 ± 26.6
Diastolic filling patterns (%)				
Normal filling	53.7§	44.9§	0†	0†
Impaired relaxation	39.6§	55.1†,§	100.0†	100.0†
Pseudonormal filling	5.6§	0†	0†	0†
Restrictive filling	1.1	0	0	0
Antihypertensive medication (%)	67.2§	79.9†	85.9†	85.9†
Calcium channel blocker	52.9§	62.8§	78.7†	71.8†
Beta-blocker	29.9	31.5	22.3	23.4
ACEI or ARB	32.4	32.0	34.9	38.3
Diuretic	13.5	11.1	18.8	25.6†
Number of CVD events	5	10	13	28†,§

ACEI, angiotensin-converting enzyme inhibitor; A_d, the duration of atrial filling wave; ARB, angiotensin II receptor blocker; *ARdur*, the duration of flow at atrial contraction; A-velocity, the peak of atrial diastolic phase filling; CVD, cardiovascular disease; *DcT*, the deceleration time of early diastolic LV filling; *E/A*, the ratio of peak early to late diastolic filling velocity; E-velocity, the peak of early diastolic phase filling; LAD, left atrial dimension; LVMI, left ventricular mass index; PV_a, pulmonary vein atrial reversal; *S/D*, the ratio of the pulmonary venous systolic velocity to diastolic velocity. Data are mean ± SD or percentage. *$P < 0.05$ and †$P < 0.01$ versus low *S/D* ratio and high *E/A*. ‡$P < 0.05$ and §$P < 0.01$ versus low *S/D* ratio and low *E/A*.

Fig. 2



Cardiovascular event-free survival in four groups stratified by both baseline peak velocity ratio of the pulmonary venous systolic to diastolic wave (*S/D*) and peak transmitral velocity ratio of early diastolic to atrial filling (*E/A*) (log-rank $\chi^2 = 28.064$, $P < 0.01$).

Discussion

The present study demonstrated that the relationship between a high *S/D* ratio and CVD risk is significant, and persisted after multivariate Cox regression analysis including traditional risk factors. The combination of high *S/D* and low *E/A* was a powerful independent predictor of CVD events. Moreover, even in the subgroup with low *E/A*, high *S/D* was a significant predictor of CVD events.

Our results were partially in accordance with a previous report [13] that more than 95% of our study subjects had 'normal diastolic function' or 'mild diastolic dysfunction'. In addition, only 0.3 and 1.4% of the subjects were identified as having a 'restrictive pattern' and 'moderate diastolic dysfunction (pseudonormal pattern)', respectively. Therefore, pseudonormal or restrictive physiology is unlikely to affect the results observed in the present study to a significant degree.

Our results showed that a high *S/D* ratio is independently associated with CVD risk, and suggest that the assessments of PVF by transthoracic echocardiography, simple

Table 3 Combined effects of the peak velocity ratio of the pulmonary venous systolic to diastolic wave (*S/D*) and peak transmitral velocity ratio of early diastolic to atrial filling (*E/A*) ratios as predictors of cardiovascular disease events

	Crude		Risk factor-adjusted model*	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
S/D and *E/A*				
Low *S/D* and high *E/A*	1 (reference)		1 (reference)	
High *S/D* and high *E/A*	1.480 (0.88–2.65)	0.140	1.402 (0.83–2.53)	0.211
Low *S/D* and low *E/A*	1.720 (1.05–3.04)	0.029	1.390 (0.84–2.48)	0.206
High *S/D* and low *E/A*	2.662 (1.72–4.57)	< 0.001	2.158 (1.40–3.70)	0.001
Age, 1 year	1.059 (1.03–1.09)	< 0.001	1.032 (1.00–1.06)	0.040
Diabetes, yes	1.449 (1.10–1.89)	0.010	1.301 (0.98–1.70)	0.067
Pulse pressure, 1 mmHg	1.031 (1.02–1.05)	< 0.001	1.015 (1.00–1.03)	0.116
LAD, 0.1 cm	1.010 (1.00–1.01)	< 0.001	1.002 (1.00–1.01)	0.428
LVMI, 1 g/m^2	1.017 (1.01–1.02)	< 0.001	1.015 (1.01–1.02)	< 0.001

CI, confidence interval; HR, hazard ratio; LAD, left atrial dimension; LVMI, left ventricular mass index. *Adjusted by age, diabetes, pulse pressure, LAD, and LVMI.

methods of assessing left atrial diastolic filling [29,30], are useful for predicting the risk of CVD in essential hypertension. The precise mechanisms by which the risk for CVD becomes higher with increasing *S/D* ratio are unclear; there are, however, several hypothetical mechanisms: LVMI, an established independent predictor of CVD in hypertension [31], was higher in patients with higher *S/D* ratio, but the association between a higher *S/D* ratio and CVD was statistically independent of LVMI in multivariate analysis; in normal LV function, the *S/D* ratio positively correlates with left atrial reservoir function [32], which may reflect the cumulative effect of filling pressures over time; and the activated renin–angiotensin–aldosterone system and brain natriuretic peptide, which are importantly involved in the development of hypertension and CVD, strongly promote myocardial remodeling, resulting in increased *S/D* ratio.

One notable result of this study is that, in essential hypertension, the combination of a high *S/D* and low *E/A* was a powerful independent predictor of CVD events, and this is especially noteworthy because of the relatively short follow-up of this study. More importantly, in the group with low *E/A*, the risk of CVD became higher with increasing *S/D* ratio, and thus, the assessment of *S/D* ratio adds prognostic information especially in subjects with low *E/A*. The fact that the association between the group with high *S/D* and low *E/A* and an increased risk for CVD was present even in those with 'normal diastolic function' or 'mild diastolic dysfunction' suggests that evaluation of both mitral valve flow (MVF) and PVF may help identify essential hypertensive subjects without clinical evidence of CVD who are predisposed to adverse outcomes. This result may have been introduced because of advanced age, higher pulse pressure, and longer duration of hypertension, which are established risk factors for CVD, in subjects with high *S/D* and low *E/A*. On the other hand, the diastole phase of PVF resembles early mitral flow, while systolic forward flow is influenced by left atrial compliance, atrial relaxation, mean left atrial pressure, descent of annuals toward the left ventricular apex, and right ventricular contraction [33]. Previous reports have shown that PV_s associates with LV preload [34] and left atrial pressure [35]. In addition, the *S/D* ratio positively correlates with left atrial pressure in subjects with normal LV function [32]. Thus, in subjects with *E/A* under median values, an increased *S/D* ratio may suggest the presence of worse left atrial function, increased LV preload, and worse right ventricular contraction. Evaluation of pulmonary *S/D* in addition to mitral *E/A* may help to assess not only LV diastolic function, but also left atrial and right ventricular function, and thus may provide clinically sensitive prognostic information in patients with essential hypertension. A previous study [36] as well as the present study found that it was possible to obtain high-quality recordings of PVF in more than 80% of the patients by transthoracic echocardiography with daily practice, and thus, we suggest routine evaluation of not only MVF, but also PVF. With respect to the *ARdur* and peak PV_a velocity, we could not find a significant association between these variables and CVD risk, possibly because these variables are usually normal in mild diastolic dysfunction [37].

A previous report showed that control of hypertension and regression of cardiac hypertrophy improved LV diastolic dysfunction [38]. Because our study population included patients with treated essential hypertension at the beginning of the study, our results suggest the importance of evaluating diastolic dysfunction to assess CVD risk, even in patients receiving antihypertensive medication. These results could, however, underestimate the involvement of blood pressure or PVF itself in the development of diastolic dysfunction and CVD events. Another limitation was the lack of control over occasional changes in the antihypertensive regimens over time. The deceleration time of PV_d, which is also useful for estimating pulmonary capillary wedge pressure as a measure of left atrial pressure [39], was not included in this study because it is useful only in patients with a relatively slow heart rate [40]. Severe mitral regurgitation or severe systolic dysfunction can influence PVF, and our findings may not be applicable to hypertensive patients with these other concomitant conditions.

In conclusion, our findings suggest that impaired diastolic function evaluated by increased *S/D* or decreased *E/A* on the baseline Doppler echocardiography is associated with an increased risk of CVD, and the combination of high *S/D* and low *E/A* may be a powerful predictor of CVD in essential hypertension. PVF evaluation by Doppler echocardiography may provide clinically important prognostic information in patients with essential hypertension.

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生活習慣病からの循環器病克服戦略
—高血圧と慢性腎臓病—

河野雄平

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要旨 高血圧，糖尿病，高脂血症，メタボリックシンドロームなどの生活習慣病は多くの循環器病の危険因子となっており，慢性腎臓病は末期腎不全や循環器病に強く関連している．日本人の高血圧の有病率はきわめて高く，慢性腎臓病もかなり高頻度に認められる．高血圧治療が循環器病や腎障害の予防に有用であることは明らかであるが，高血圧を有しても適切な診断，治療，コントロールがなされていない者は少なくない．残された課題は多いが，ライフスタイル改善による高血圧などの生活習慣病の予防，高血圧や慢性腎臓病の早期発見と治療による循環器病の予防，高血圧および他の危険因子の管理による循環器病の予後改善を目標として，Population strategy と High risk strategy の組み合わせにより，小児から老年者まで全国民に向けての多面的な対策が重要と考えられる．

キーワード 生活習慣病，循環器病，高血圧，慢性腎臓病

はじめに

高血圧，糖尿病，高脂血症，メタボリックシンドロームなどの生活習慣病は，多くの循環器病の危険因子となっている．また，生活習慣病や循環器病に関係する生活習慣として，過食による肥満や運動不足，食塩摂取過剰，ミネラル摂取不足，喫煙，非飲酒および過剰飲酒，全体の食事習慣，ストレスなどが知られている．生活習慣病の予防や治療が循環器病の予防に有効であることは，多くの研究によって示されているが，日本におけるエビデンスは少ない．また，各々の生活習慣病を有する者についても，適切に診断や治療，コントロールがなされているわけではないことが問題である．本稿では，国立循環器病センターによる循環器病克服10年戦略のために準備した高血圧対策を基に慢性腎臓病を加えて概説し，循環器病予防のための課題を示したい．

高血圧

1．背景と現状

高血圧が脳卒中や心筋梗塞，心不全，不整脈，大動脈瘤，閉塞性動脈硬化症，腎不全など，種々の循環器病の主要な危険因子であることはよく知られている．高血圧はまた生命予後に悪影響を及ぼし，認知症にも関係している．血圧が高いことが循環器疾患のリスクを高めることは，正常血圧の範囲においても認められている．たとえば，115／75mmHg 以上では血圧が20／10mmHg 上昇する毎に脳卒中の危険性は約２倍となる[1]（図１）．高血圧の悪影響に

国立循環器病センター 高血圧腎臓内科
別刷請求先：河野雄平 国立循環器病センター 高血圧腎臓内科部長 〒565-8565 大阪府吹田市藤白台５－７－１
（平成19年５月９日受付，平成19年７月20日受理）
Strategy for Overcoming Lifestyle-related Cardiovascular Diseases : Hypertension and Chronic Kidney Disease
Yuhei Kawano
Key Words : lifestyle-related disease, cardiovascular disease, hypertension, chronic kidney disease

ついては，わが国の疫学研究においても明瞭に示されている[2]．

高血圧はきわめて普遍的な疾患であり，わが国の高血圧患者は約3,500万人と推定される．第5次循環器疾患基礎調査では，30歳以上の男性は50%近くが，女性は約35%が高血圧を呈していた(図2)．高齢者ではその頻度はさらに高く，約2/3が高血圧と診断される．しかし，普遍的であっても高血圧の悪影響は明らかであり，むしろそれゆえに高血圧は循環器病の最大の危険因子となっている．

降圧治療が脳卒中や心筋梗塞，心不全，腎不全などの予防に効果的であることは，多くの大規模臨床

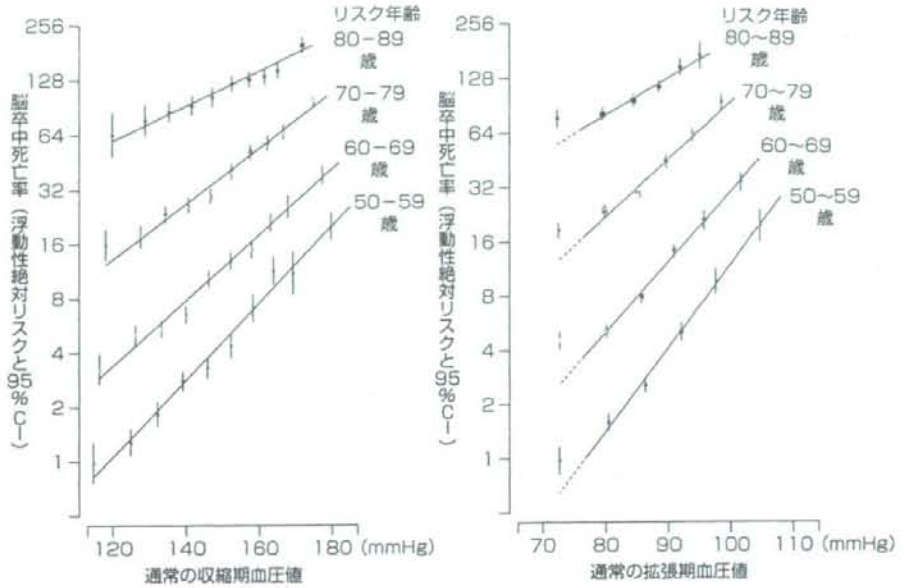

図1　前向き疫学研究のメタアナリシスによる年齢と血圧値からみた脳卒中死亡率[1]

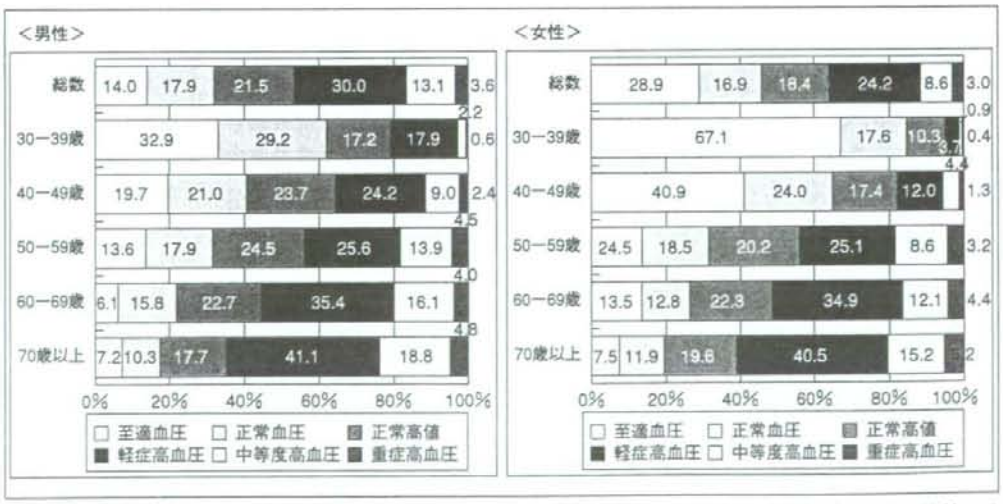

図2　厚生労働省第5次循環器疾患基礎調査（2000年）における性・年齢階級別の血圧区分（2回の平均値による）
http://wwwdbtk.mhlw.go.jp/toukei/kouhyo/indexkk_18_1.html

試験により証明されている[3][4]．降圧薬による治療はまた，全死亡率を低下させる．しかし，これまでに得られた知見の多くは欧米の成績であり，わが国におけるエビデンスは少ない．さらに，高血圧と診断されても適切な治療を受けていない者や，治療を受けても血圧がコントロールされていない者が多いことが問題である．

高血圧者の大部分は原因を特定できない本態性高血圧であるが，これには遺伝因子と環境要因（生活習慣）がともに関与すると考えられる．高血圧の遺伝子については，近年の研究でかなりの成果が得られたが，まだ解明されているわけではない[5]．しかし，環境要因による高血圧の発症にも遺伝因子が関与すると考えられる．高血圧に関係する生活習慣として，肥満，運動不足，食塩摂取過剰，ミネラル摂取不足，喫煙，過剰飲酒，ストレスなどが知られている．わが国では食塩摂取はまだ多く，過食と運動不足にともない肥満者は激増している．カリウム，カルシウム，マグネシウムの摂取は不足ぎみであり，大量飲酒者は少なくなく，社会的なストレスは多い．生活習慣の修正（非薬物療法）は重要であるが，降圧効果は比較的小さく，実行と維持が困難であり，長期効果は明らかではない[6]．

血圧測定は高血圧の診断や管理に必須であり，わが国では検診が普及している．しかし，血圧測定を受けずに高血圧が見逃されている者は少なくないと考えられる．また，全国民が検診を受けたとしても，それで十分とはいえない．随時血圧測定で高血圧と診断される者の約20%は白衣高血圧であり，不要な薬物治療をうける可能性がある．逆に，随時血圧で正常血圧と診断される者の約10%は仮面高血圧であり，放置されて予後不良となる恐れがある[7]．高血圧の診断や治療において，24時間血圧測定や家庭血圧測定の有用性は明らかであるが，これらは十分に活用されてなく，保険適応にもなっていない．

2．今後の課題

21世紀の循環器病予防のためには，高血圧などの生活習慣病対策がきわめて重要であろう．ライフスタイル改善による生活習慣病の予防（高血圧，糖尿病，高脂血症の有病率を低下させる），生活習慣病の早期発見と治療による循環器病の予防（高リスク者を減らし脳卒中，心臓病を減少させる），生活習慣病および危険因子の管理による循環器病の予後改善（脳卒中，心臓病の再発を防ぎ予後を改善させる）ことが主要目標となる．そのためには，Population strategy と High risk strategy の組み合わせ（国民全体への啓発や検診と有病者への適切な治療），小児から老年者まで全国民に向けて（小児期からの生活習慣病予防と高齢者の健康寿命延長），保健医療関係者と社会の活動および交流（集学的研究と産官学の協力による多面的アプローチ）といったストラテジーが必要と考えられる．

高血圧の診断や治療は容易になってきたが，まだ今後に残された問題点は多い．循環器病克服10年戦略における高血圧領域の重要な研究課題を，表1に示す．

基礎研究および開発研究に関しては，分子生物学，遺伝子工学による研究では高血圧や血管作動性物質についての種々の疾患モデルを用いて，高血圧の成因とそれによる心血管障害の機序を明らかにすること，ゲノムおよびプロテオーム情報による創薬研究ではミレニアム・ゲノム・プロジェクトやプロテオーム・プロジェクトなどの成果を受けて，高血圧と関連する心血管病に対する新しい治療薬を開発すること，トランスレーショナル研究と臨床応用ではそれらの研究成果を臨床応用し，新しい効果的な高血

表1　高血圧対策の研究課題

(1)基礎研究および開発研究
①高血圧と心血管障害の分子生物学，遺伝子工学による研究
②高血圧治療薬のゲノムおよびプロテオーム情報による創薬
③新しい高血圧治療のトランスレーショナル研究と臨床応用
(2)疫学研究
①生活習慣と高血圧のゲノム疫学および臨床疫学による解明
②高血圧に効果的な生活習慣改善の長期の介入と検証
③高血圧に対する Population strategy の構築と実践
(3)臨床研究
①高血圧治療による循環器病予防の臨床試験
②高血圧の原因遺伝子，病態修飾遺伝子の解明
③ゲノム情報の個別的な生活習慣改善，薬物療法への応用
④家庭血圧，24時間血圧モニタリングによる至適降圧治療の確立
⑤白衣高血圧および仮面高血圧の解明と対策
(4)社会的課題
①高血圧について，全国民への啓発と教育
②小児から高齢者まで，全国民の血圧測定
③家庭血圧測定による高血圧の予防と管理
④高血圧の予防と治療のための生活習慣への社会的アプローチ
⑤高血圧対策による循環器病予防の医療経済的検討

圧の予防，治療法を開発することが重点課題となろう．

疫学研究に関しては，ゲノム疫学および臨床疫学研究では高血圧に関連する生活習慣をさらに明らかにするとともに，食塩や肥満など各々の生活習慣による血圧変化に関係する遺伝子を同定すること，効果的な生活習慣改善の介入と検証として長期の介入試験により血圧や予後への効果や実行可能性（継続性）などを明らかにすること，population strategyの構築と実践では高血圧の診断や予防，治療についての社会的アプローチを含めた効果的な対応策を作り実行することが重要である．

臨床研究に関しては，進行中の，および新しい高血圧治療の大規模臨床試験の推進により，高血圧治療による循環器病予防の日本人におけるエビデンスを得ること，ミレニアム・ゲノム・プロジェクトなどにより得られた遺伝子研究の成果をさらに発展させ，高血圧の原因遺伝子，病態修飾遺伝子を解明すること，薬剤感受性遺伝子の研究を推進し，前向き臨床試験を行い，遺伝子情報をとりいれた効果的で個別的な高血圧治療を確立すること，進行中およびこれからの無作為臨床試験を遂行し，家庭血圧や24時間血圧に基づいた至適降圧治療を確立すること，白衣高血圧および仮面高血圧の実態と原因，予後，治療効果を明らかにし，これらへの管理方針を確立することが重点課題となる．

社会的課題として，高血圧についての全国民への啓蒙，教育および指導のための官公庁や自治体，学会などによる体制を作る必要があり，全国民が定期的な血圧測定を受ける体制を作るとともに，高血圧者および正常高値血圧者への適切な対策をとらねばならない．さらに家庭血圧への知識と理解を深めて，測定をさらに普及させる必要がある．食塩制限や肥満対策など高血圧の予防と治療に有効な生活習慣改善を，産官学の協力により推進することも重要である．また，高血圧の管理による循環器病予防の医療経済的効果について，生活習慣改善と薬物治療，家庭血圧や24時間血圧測定などについて検討を要する．

慢性腎臓病

わが国における末期腎不全による透析患者数は増加を続けており，医療経済的にも大きな問題となっている[8]（図3）．末期腎不全の原因は，以前は慢性糸球体腎炎などの腎疾患が主であったが，最近は糖尿病性腎症が最も多く，高血圧による腎硬化症も増加している．喫煙や肥満も腎障害の原因となり，生活習慣や生活習慣病は腎臓にも密接に関係していることになる．また，透析患者の最大死因は心不全などの循環器疾患であり，腎機能低下や蛋白尿は循環器疾患の予知因子である．循環器疾患患者の予後は腎障害があれば不良であることも示されている．したがって，循環器疾患の予防や予後改善には，腎臓を含めた対策がきわめて重要と考えられる．

腎臓と高血圧は密接な関係があり，腎機能が低下すれば血圧は上昇し，高血圧は腎障害をもたらす．降圧治療が腎保護に働くことは明らかで，高血圧治療の普及とともに日本人の血圧値は低下し脳卒中は減少したが，末期腎不全は増加している．人口の高齢化や糖尿病の増加が大きな要因であろうが，腎不全の予防と予後改善は今後の重要な課題である．また，腎障害をともなう場合には130／80mmHg未満とする厳格な血圧管理が推奨されているが[9]，この目標が達成されていない場合が多いことも問題となっている．

最近，慢性腎臓病（Chronic kidney disease：CKD）という概念が提唱され，普及している．これは腎障害（形態的または機能的な異常），あるいは糸球体濾過率（GFR）60ml/min／1.73m²未満の腎機能低下が3カ月以上持続するものである[9]．たとえば，蛋白尿などの尿異常が続けば腎機能は正常でも慢性腎臓病であり，腎機能低下が続けば尿所見は正常でも慢性腎臓病となる．慢性腎臓病を有する者は少なくなく，とくに高齢者や循環器疾患患者においては高率に認められる．慢性腎臓病はGFRによりステージが分けられ，米国ではそれに応じた診療計画が示されている[10]（表2）．わが国における慢性腎臓病対策はまだ始まったばかりであるが，末期腎不全の予防だけでなく循環器疾患の予防のためにも重要な課題であり，今後の対策の強化が望まれる．最近日本腎臓学会よりCKD診療ガイドが刊行されたので参照されたい[11]．

おわりに

高血圧および慢性腎臓病の現状と，循環器病の予防と予後改善のための今後の課題について述べた．日本人の高血圧の有病率は依然としてきわめて高く，降圧治療の普及により血圧管理は容易にはなってきたが，残された問題も多い．また，慢性腎臓病は高

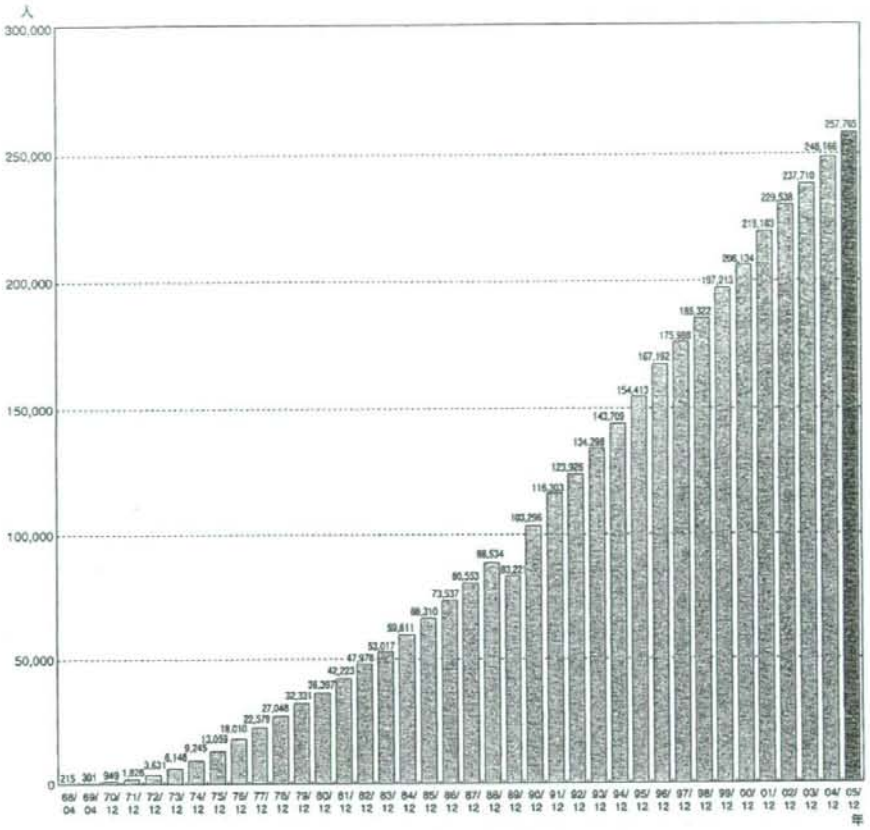

図3　日本における慢性透析患者数の推移[9]

表2　慢性腎臓病の重症度分類と臨床行動計画[10]

Stage	重症度の説明	換算GFR値 (mL/min/1.73m²)	診療計画
	リスクの増大 CKD危険因子が存在する。 （DM，高血圧など）	≧90	①CKDスクリーニングの実施 （アルブミン尿など） ②CKD危険因子の減少に努める。
1	腎障害（+） GFRは正常または亢進	≧90	CKDの診断と治療の開始 －併発疾患comorbidityの治療 －CKD進展を遅延させる治療 －心血管疾患リスクを軽減する治療
2	腎障害（+） GFR軽度低下	60～89	CKD進行を予測
3	腎障害（+） GFR中等度低下	30～59	CKD合併症を把握し治療する。 （貧血，血圧上昇，二次性副甲状腺機能亢進症など）
4	腎障害（+） GFR高度低下	15～29	透析または移植を準備する。
5 5D	腎不全 透析期	<15 透析	透析または移植の導入 （もし尿毒症の症状があれば）

血圧にも密接に関連しているが，末期腎不全や循環器病の予防の面からも，その対策が重要である．基礎および臨床研究の進歩と集団管理および個別管理により高血圧と慢性腎臓病の効率的な管理がなされれば，多くの循環器病が予防でき，健康寿命の延長が期待できるであろう．

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Masked Hypertension: Subtypes and Target Organ Damage

YUHEI KAWANO, TAKESHI HORIO, TETSUTARO MATAYOSHI, AND KEI KAMIDE

Division of Hypertension and Nephrology, National Cardiovascular Center, Fujishirodai, Suita, Osaka, Japan

Masked hypertension has been drawing attention recently because this condition is often seen in untreated and treated individuals and is associated with target organ damage and a poor cardiovascular prognosis. Although masked hypertension is defined as normal office blood pressure with elevated ambulatory or home blood pressure, there are several subtypes. Morning hypertension is the most common form of masked hypertension, and is caused by natural circadian variation, evening alcohol consumption, and the use of short-acting antihypertensive drugs. Daytime hypertension may be caused by lifestyle factors such as habitual smoking and mental or physical stress. Nighttime hypertension is seen in various conditions that produce non-dipping status, including a high salt intake, renal dysfunction, obesity, sleep apnea, and autonomic failure. Advanced target organ damage such as increases in the left ventricular mass, carotid artery intima-media thickness, and urinary albumin excretion, is often present both in untreated and treated subjects with masked hypertension. In our study, the presence of the reverse white-coat effect is independently associated with those indices of organ damage among treated hypertensive patients. It is important to identify individuals with masked hypertension, to evaluate them with including the search for the subtype, and to treat each patient appropriately according to the cause of this condition.

Keywords masked hypertension, target organ damage, ambulatory blood pressure monitoring, home blood pressure

Introduction

Masked hypertension, which is also called reverse white-coat hypertension or isolated ambulatory hypertension, has been drawing attention recently (1–3). Masked hypertension is defined as normal office blood pressure (BP) with elevated ambulatory or home BP. Although the term of masked hypertension was originally applied to untreated subjects, this condition is also frequently seen in treated hypertensive

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Address correspondence to Yuhei Kawano, MD, PhD, Division of Hypertension and Nephrology, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan; E-mail: ykawano@hsp.ncvc.go.jp

patients. The prevalence of masked hypertension has been reported to be about 10% in normotensive (defined by casual BP) subjects and about 20% among treated hypertensive patients (1,4–6). There is increasing evidence that masked hypertension is associated with advanced target organ damage and a poor cardiovascular prognosis (7–11).

Masked hypertension can be classified into several subtypes according to the pattern of ambulatory BP and underlying mechanisms. These subtypes include morning, daytime, and nighttime hypertension (3). Detecting the subtype and underlying mechanism may be helpful for the appropriate management of each patient with masked hypertension. Regarding the target organ damage in masked hypertension, obtained information may not be enough, especially for treated patients. In this review, we describe the subtypes and organ damage of masked hypertension, including the results of our studies.

Subtypes of Masked Hypertension

Morning Hypertension

Morning hypertension is the most common form of masked hypertension (see Table 1). The circadian rhythm of BP is well known. Usually, BP elevates sharply with waking in the early morning, decreases slightly from the late morning to early afternoon, increases again in the early evening, decreases in the late evening, and then falls largely with sleeping. It has been shown that home BP in the early morning is somewhat higher than that in the late evening (6,12). It is possible that this physiological change in BP causes masked hypertension, if office BP is measured in the late morning or early afternoon in the absence of the white-coat effect. Morning hypertension is also caused by lifestyle-related factors such as habitual alcohol intake. We observed that evening alcohol consumption decreases nighttime BP but increases daytime BP in

Table 1
Subtypes of masked hypertension

Subtypes	Causes	Management
Morning hypertension (morning surge)	Natural circadian rhythm	Alcohol restriction
	Alcohol	Long-acting drug
	Antihypertensive drug (short-acting)	Evening drug administration
		Alpha blockers (evening)
Daytime hypertension (worksite hypertension)	Smoking	Smoking cessation
	Stress (mental, physical)	Stress management
		Beta blockers (morning)
Nighttime hypertension (non-dipper)	Salt, renal dysfunction	Salt restriction
	Obesity, sleep apnea	Weight reduction
	Autonomic failure	Diuretics
		Treatment of sleep apnea

hypertensive patients (12,13). This alcohol-induced BP elevation is most obvious in the early morning.

Morning hypertension is often seen among treated hypertensive patients, particularly in those who are taking short-acting antihypertensive drugs in the morning. Such medication does not maintain the antihypertensive efficacy for 24 hours, resulting in BP elevation in the early morning. The use of long-acting drugs or evening administration of antihypertensive drugs is helpful to control morning hypertension. Because the sympathetic nervous system plays an important role in the morning BP elevation through alpha receptor-mediated vasoconstriction, the administration of alpha blockers in the evening may also be effective to attenuate the morning BP surge (14).

Daytime Hypertension

Daytime hypertension is caused by lifestyle-related factors such as habitual smoking and daily stress (see Table 1). Smoking cigarettes acutely elevates BP, and smokers show a higher daytime BP on a smoking day compared with nonsmokers or a nonsmoking day (15). Mental or physical stress also acts to elevate daytime BP, particularly during working (16). We also observed that daytime BP but not nighttime BP is higher during usual daily life than during a hospital stay in hypertensive patients (17). When habitual smokers or subjects experiencing stress visit clinics, their BP may be normal because they can take a rest without smoking in the waiting room. The cessation of smoking and control of daily stress is recommended for subjects with daytime hypertension. Beta blocker usage may be effective to control stress-related hypertension.

Nighttime Hypertension

Although BP usually falls at night, the nighttime BP dip is blunted or absent in a considerable portion of normotensive and hypertensive subjects. Some individuals show a rise in BP during sleep. This non-dipper pattern is often seen in salt-sensitive subjects on a high-salt diet; patients with renal dysfunction; obese subjects, particularly those with sleep apnea; and patients with autonomic failure; and may cause masked hypertension (see Table 1). It should be mentioned that many non-dippers also show morning hypertension because their BP continues to increase during the night until waking up.

Previous studies by our institute have shown that treatment with a low-salt diet or a diuretic decreases nighttime BP effectively in hypertensive patients (18,19). Weight reduction is recommended for obese subjects. Continuous positive airway pressure treatment is effective to lower nighttime as well as 24-hour BP in patients with sleep apnea (20). It is also important to use long-acting antihypertensive drugs to control nighttime BP.

Identifying the Subtypes

The diagnosis of masked hypertension is obtained by the use of ambulatory BP monitoring (ABPM) or home BP measurement in comparison with office BP. The Japanese guidelines for the management of hypertension (JSH 2004) support the use of ABPM and home BP measurement, particularly for the diagnosis of white-coat hypertension and masked hypertension (21).

To identify the subtypes of masked hypertension, ABPM is superior to home BP measurement because it provides multiple BP readings throughout 24 hours. However, the

application of ABPM to all hypertensive subjects is not practical, and a single ABPM may not be enough to represent the individual's 24-hour BP profile. Self-measurement of BP in the morning and evening at home appears to detect morning hypertension. Daytime hypertension can be detected through additional BP measurement at home or worksite during the daytime. ABPM is particularly suitable for the diagnosis of nighttime hypertension. The detection of nighttime hypertension by home BP measurement is difficult; however, new devices with timers, such as OMRON HEM-747IC, can determine BP during sleep. The widespread application of such devices may easily identify the subtypes of masked hypertension without using ABPM.

Target Organ Damage in Masked Hypertension

Numerous studies have examined the relationship between ambulatory BP or home BP and cardiovascular complications. It has been shown that ambulatory BP and home BP are more closely related to hypertensive organ damage and cardiovascular prognosis than office BP (22–26). Therefore, it is not surprising that subjects with masked hypertension are prone to develop target organ damage.

Untreated Subjects

It has been shown that subjects with masked hypertension have advanced target organ damage and a poor cardiovascular prognosis compared to normotensive subjects. Liu et al. measured target organ abnormality by echocardiography and arterial ultrasonography in untreated subjects with sustained normotension, masked hypertension, and sustained hypertension (27). They demonstrated that left ventricular mass and carotid wall thickness are greater in subjects with masked hypertension compared to those with sustained normotension, and are similar to those with sustained hypertension. Lurbe et al. also showed that young patients with masked hypertension have a higher left ventricular mass index than normotensive subjects (28). It is likely that a majority of masked hypertensives are overlooked because of normal office BP, resulting in the progression of target organ damage.

Treated Patients

Advanced target organ damage is also seen in treated patients with masked hypertension. We determined the left ventricular mass index, carotid artery intima-media thickness, and urinary albumin excretion in 332 treated hypertensive patients (29,30). In our study, all of these indices of target organ damage in patients with masked hypertension were significantly higher than those with controlled hypertension or white coat hypertension, and were even higher than those with sustained hypertension (see Figure 1). Cuspidi et al. examined left ventricular mass index and urinary albumin excretion in treated hypertensive patients at baseline and after an average follow-up of 30 months (31). They observed that these parameters decreased in patients with controlled ambulatory BP but not in those with masked hypertension.

Subtypes and Organ Damage

A number of studies have shown that the non-dipper pattern or the level of nighttime BP is associated with advanced organ damage and a poor prognosis (22–24,32,33). In the PAMELA study, nighttime BP was the best predictor of future cardiovascular death

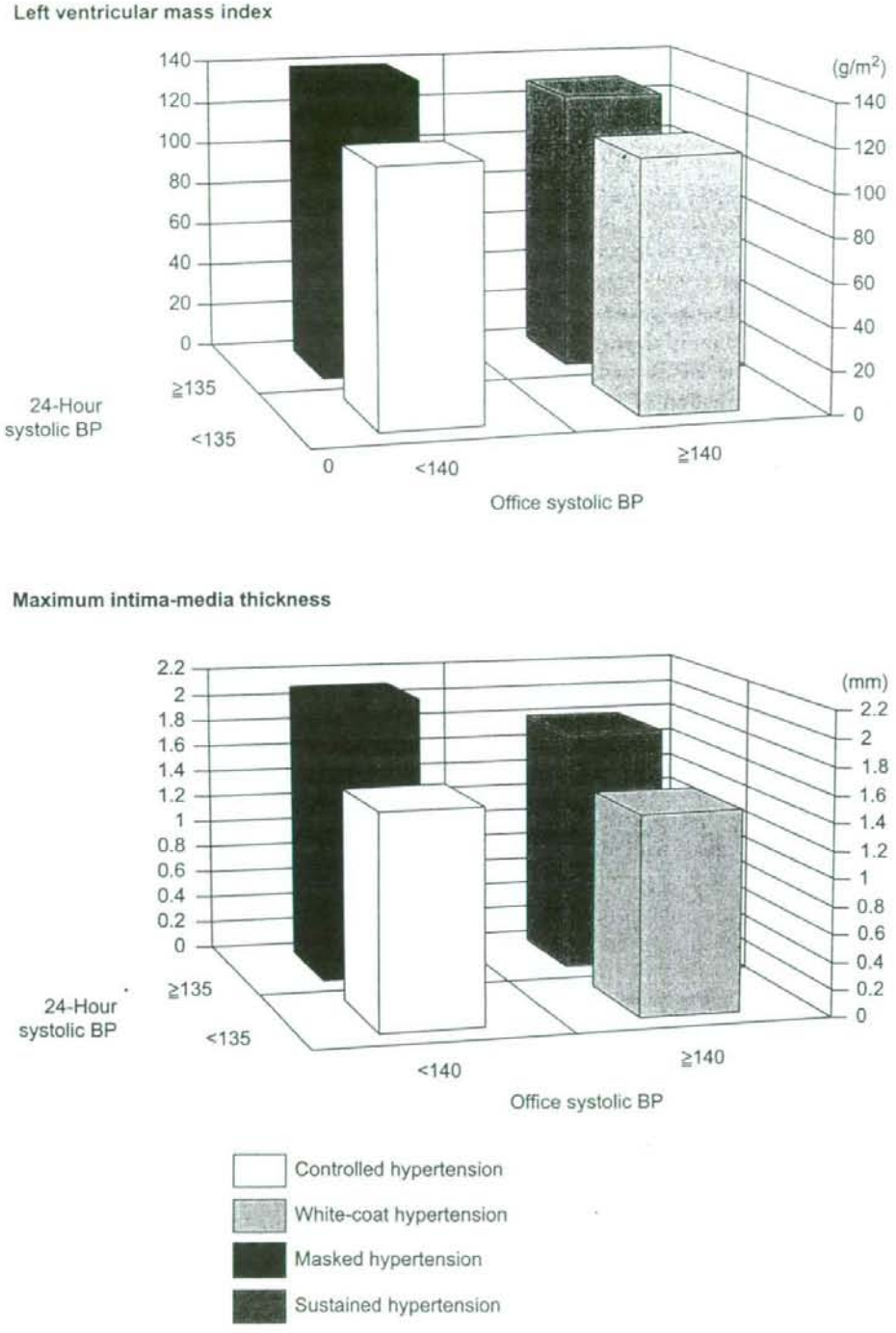

Figure 1. Left ventricular mass index and carotid artery maximum intima-media thickness in treated patients with controlled hypertension, white-coat hypertension, masked hypertension, and sustained hypertension, adopted from (29).

among office BP, home BP, and ambulatory BP parameters (24). Therefore, it is likely that nighttime hypertension is prone to develop organ damage such as left ventricular hypertrophy, carotid atherosclerosis, and impaired renal function.

It is well known that cardiovascular events occur frequently in the early morning when BP increases rapidly. Kario et al. have shown that the morning surge in BP is independently associated with silent and clinical cerebrovascular disease, and morning hypertension is the strongest independent risk factor for stroke in elderly hypertensives (34,35). It is also reported that the morning rise in BP correlates with the left ventricular mass index or hypertrophy in hypertensive patients (36,37), and high morning BP is associated with a loss of functional independence in elderly subjects (38). Therefore, morning hypertension appears to play a role in the target organ damage and cardiovascular events.

The association of daytime BP with organ damage and prognosis is less recognized, although daytime BP is a main determinant of average 24-hour BP. In the PAMELA study, the contribution of daytime BP to cardiovascular mortality was relatively weak compared with nighttime BP (24). However, it has been shown that mental stress is related to the progression of carotid atherosclerosis and cardiovascular mortality (39,40). It is possible that subjects with daytime hypertension are also susceptible to the development of target organ damage.

Conclusion

There are several subtypes of masked hypertension. Morning hypertension is caused by natural circadian variation, evening alcohol consumption, and short-acting antihypertensive drugs. Daytime hypertension may be caused by smoking and stress. Nighttime hypertension is seen in various conditions that lead to a non-dipping status. Advanced target organ damage is often present both in untreated and treated subjects with masked hypertension. All three subtypes of masked hypertension seem to be associated with organ damage, although the relative risk of those subtypes remains to be clarified. It is important to identify individuals with masked hypertension, evaluate them (including identifying the subtype), and treat each patient appropriately according to the cause of this condition.

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特集　循環器疾患の発症・増悪関連遺伝子―最近の話題―

高血圧と関連遺伝子*

神出　計**
河野雄平**
友池仁暢***

Key Words：hypertension, SNP, pharmacogenomics, tailored medicine

はじめに

高血圧症の9割以上は本態性高血圧(essential hypertension：EHT)であり，わが国で3,000万人以上罹患者がいると考えられているように，EHTはもっとも頻度の高い生活習慣病である．さらに，多くのEHT患者は家族歴を有し，遺伝の血圧の変化に対する寄与率は30～50%あると推定されている[1]．したがって，高血圧の原因遺伝子を同定することがもたらすインパクトは計り知れないものがあると考えられる．しかしながら，多因子疾患であるEHTには原因遺伝子が複数存在する可能性が示唆されており[2]，現在報告されているものの多くは高血圧関連遺伝子多型である．とくに，一塩基多型(single nucleotide polymorphism：SNP)はタイピングの容易さから高速タイピングに適しており，近年，多数の検体を用いた解析に頻用され，さらにSNPタイピングによるゲノム網羅的解析も多くなされるようになった．ポストゲノム時代を迎えた当初から，SNPを解析することによって高血圧の発症を予測し，治療薬の選択を行うテーラーメード医療の確立に期待がかけられてきた．

わが国でも2000年から5年計画で開始された癌，高血圧，糖尿病，痴呆，喘息に対するテーラーメード医療の確立と，ゲノム創薬を目標に掲げた遺伝子解析計画，ミレニアム・ゲノムプロジェクト(MGP)が2005年3月末に予定期間を終了したが[3]，これにより高血圧の予防・診断・治療に関する理解は一段と深まった．高血圧診療におけるテーラーメード医療の実現に着実に近づきつつあるが，当面の課題も明らかになった．これらを要約すると，高血圧が遺伝因子以外の多くの因子，とくに年齢，性別，食物，肥満，精神的ストレスなど，環境要因にも影響を受けやすい多因子疾患であること，血圧という表現型が変動性の大きいもので，人的に定めた140/90mmHg以上が高血圧といった定義しかないこと，さらには原因となる遺伝的素因を有していてもすべての症例で高血圧が発症するとは限らず，遺伝浸透率は必ずしも高くないなどである．いずれにせよ，MGPを機にゲノム研究の基盤は整備され，得られた膨大なゲノム情報はここ数年のうちに高血圧領域においても臨床の現場に応用されていくことは間違いないと考えられる．本稿では，国立循環器病センターにおいて行われたMGPならびにその後(ポストミレニアム研究)における高血圧関連遺伝子に対するSNP解析を紹介し，高血圧のテーラーメード医療の

* Recent topics in genetic analysis for hypertension.

** Kei KAMIDE, M.D. & Yuhei KAWANO, M.D.：国立循環器病センター内科高血圧腎臓部門〔〒565-8565 吹田市藤白台5-7-1〕；Division of Hypertension and Nephrology, Department of Internal Medicine, National Cardiovascular Center, Suita 565-8565, JAPAN

*** Hitonobu TOMOIKE, M.D.：国立循環器病センター病院長

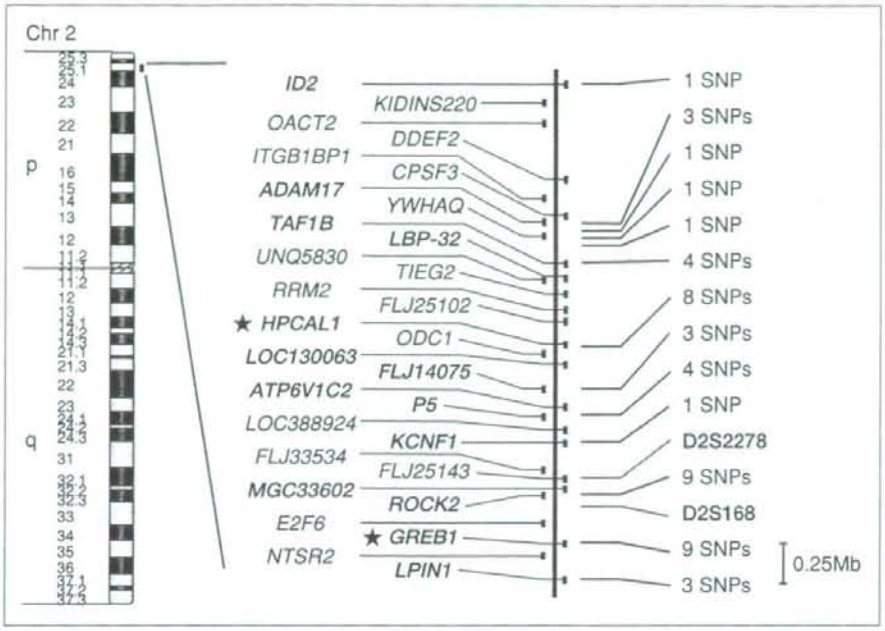

図1　選択されたSNPsと有意差を示した遺伝子(文献[7]より改変引用)

確立に今後，何がなされるべきかについて展開したい．

高血圧原因遺伝子

高血圧への遺伝素因の関与は多岐にわたる．EHTの病態の根幹をなすレニン・アンジオテンシン系(renin-angiotensin system：RAS)や交感神経系(sympathetic nervous system：SNS)の活性化，食塩感受性やインスリン抵抗性の形成など，すべての機序に遺伝因子は関与すると考えられる[3]．これまで数多く行われてきた候補遺伝子アプローチによる高血圧原因遺伝子同定の試みは，アンジオテンシン変換酵素(angiotensin converting enzyme：ACE)I/D多型に代表されるように，RASやSNSの受容体や酵素の遺伝子をターゲットにして，ケース・コントロールを用いた解析が主流となってきた．一方で，欧米では大規模な高血圧の患者家系を用いた連鎖解析，ならびに高血圧の兄弟・姉妹を集めて解析する同胞対解析などのゲノムスキャンが数多く行われてきたが，再現性の高い結果に達していない．しかしながら，複数の報告をまとめると高血圧に関連を示した遺伝子座には報告の重なりが認められる[4]．とくに染色体2番短腕(2p)は6つの異なった国や地域の集団から得られた解析で高血圧遺伝子座とされている[4]．さらに，この染色体2pの領域はイタリア，サルディニア地方の高血圧家系の連鎖解析で，26.5～27.1cMと非常に狭い領域にピークがあることが報告され[5]，また，われわれ日本人に遺伝的バックグラウンドが似ているとされる中国からも，同部位を含む2番に高血圧遺伝子座があると報告されている[6]．したがって，この領域に存在する遺伝子が日本人EHTに関連する可能性が考えられる．われわれはこの領域に注目し，高血圧原因遺伝子の同定を試みた[7]．イタリア，サルディニアからの報告でピークを示したマイクロサテライトマーカー(D2S2278-D2S168)の近傍に存在し，高血圧との関連が示唆される遺伝子を候補にあげ，それぞれの遺伝子のSNPを日本人を対象としたSNP情報の公開データベースであるJSNP(http://snp.ims.u-tokyo.ac.jp/)より，両アレル頻度10%以上のSNPsを選別し(図1)，計14遺伝子，47SNPsに対して1,880人の地域住民のタイピングをTaqMan法で行った．その結果，血圧値ならびに高血圧の頻度いずれにも有意な関与を認めた遺伝子は*HPCAL1*(hippocalcin-

表1 MGPにおけるゲノム網羅的解析

患者群	対照群
<一次タイピング 約10万SNPs>	
188検体 性別：男性 発症年齢：30～59歳 家族歴：1親等以内にあり BMI：25未満 血圧：SBP＝＞160 and/or DBP＝＞100 or 降圧薬服用	752検体 JSNP標準頻度 もしくは 752検体 痴呆・糖尿病・癌 喘息のケースサンプル
<二次タイピング 約2,000SNPs>	
752検体 性別：男女 発症年齢：30～59歳 家族歴：1親等以内にあり BMI：問わない 血圧：SBP＝＞160 and/or DBP＝＞100 or 降圧薬服用	752検体 性別：男女 年齢：50歳以上 家族歴：なし BMI：問わない 血圧：SBP＜＝130 and DBP＜＝85 or 降圧薬非服用
<三次タイピング 約100SNPs>	
619検体 患者群—対照群の選別基準は二次タイピングと同じ	1,406検体 患者群—対照群の選別基準は二次タイピングと同じ

（文献[8]より改変引用）

like-1）と*GREB1*（gene regulated by estrogen in breast cancer）に存在する計3つのSNPsであった[7]．これらの遺伝子が血圧調節に関与する機序は現段階では不明であるが，日本人高血圧感受性遺伝子と推測される．

わが国でのSNPを用いたゲノムワイドスキャンを用いた関連研究（genome wide association study：GWA）はMGPの中でもっとも重点が置かれた研究であった．高血圧領域では愛媛大学の三木哲郎教授を中心とする全国の大学と国立循環器病センターなどによる高血圧部会が結成され，遺伝子検体と臨床情報を共有してゲノムワイドに高血圧感受性SNPの相関解析（case-control association研究）が行われた．表1に示すように3つの症例－対照集団を用い，第1集団では厳しい基準で選んだ高血圧集団を用いて，ゲノム網羅的な約8万SNPをアレル頻度で解析し，有意性（オッズ比＞1.4, $P<0.015$）を示したSNPに対し，さらに別の症例－対照集団を用い同様の解析を行って有意性を示したSNPに絞り込み，最終的に第3の症例－対照集団（コホート集団）でも有意性を示した3 SNP, *ADD2*（$P=1.7\times10^{-5}$），*KIAA0789*（$P=0.0001$），*M6PR*（$P=0.0003$）を高血圧感受性遺伝子多型とした[8]．これらのSNPの機能的意義は今後明らかにされることが期待されるが，*ADD2*（adducin beta）は2pに存在し，前述のこれまでのゲノムスキャンで重なりの多かった領域に存在し，最近米国から*ADD2*を含む染色体2番もpositional candidate gene法により，*ADD2*のSNPが血圧ならびに降圧薬の効果にも有意な関連性を示したとの報告[9]もあり大変興味深い．一方，GWAでは昨年，高血圧を含む7つの疾患それぞれ約2,000人と共通の正常コントロール者3,000人を対象とし，DNAマイクロアレイによる50万SNPを検討する研究が発表されている[10]．これによると，クローン病や1型・2型糖尿病ならびに関節リウマチなどで$P<10^{-5}$を示す大変強い関連性をもつSNPが検出されたが，高血圧では強い関連性を示したSNPは見出されていない．このことは，これまでにもいわれてきたように高血圧における関連遺伝子を同定することの難しさの一面を示している．

候補遺伝子アプローチにおいては，腎臓での水・電解質代謝にかかわる遺伝子がEHTの重要なターゲットと考えられる（表2）．事実，メンデル型遺伝を示す稀な遺伝性高血圧疾患であるLiddle症候群では上皮型ナトリウム・チャンネル（ENaC）遺伝子が原因と考えられ，この遺伝子の