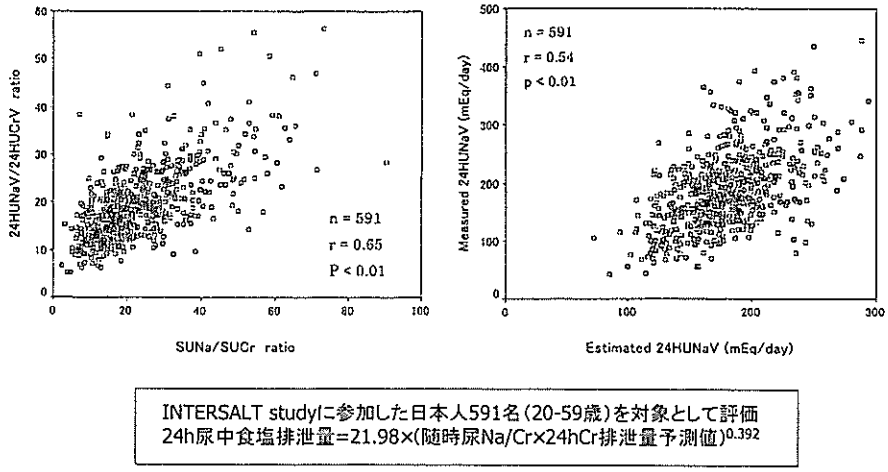

図 2.　スポット尿（随時尿）による食塩摂取量の評価
左は随時尿中 Na/Cr 比（SUNa/SUCr ratio）と 24 時間尿中 Na/Cr 比（24HUNaV/24HUCrV ratio）との関係。
右は随時尿からの計算式による 24 時間尿 Na 排泄量の推定値（Estimated 24HUNaV）と実際の 24 時間尿 Na 排泄量（Measured 24HUNaV）との関係（文献 20 による）

2. 高血圧管理における食塩摂取量評価

これまで述べたように、食塩摂取量の評価にはいくつかの問題がある。すなわち、信頼性が高いと考えられる食事の計測や 24 時間蓄尿でも厳密には十分といえず、またこれらの方法は実施することに難点がある（表 1）。スポット尿の Na/Cr 比や試験紙を用いる方法は簡便であるが、信頼性は低くなる。夜間尿やスポット尿を用いて計算式により求める方法は、信頼性は高くなるが煩雑さも増すことになろう。また、尿の Na 排泄量や質問法により求めた食塩摂取量は、実際の摂取量より少なく表されることにも留意を要する。

このような問題はあるが、各個人の食塩摂取量を評価することは、具体的な数値が分かることから減塩の動機付けや指導、効果判定に有用であり、高血圧の管理において強く推奨される。可能であれば信頼性が高い方法が望ましいが、やや信頼性が低い方法であっても臨床的に有益と考えられる。

表 5.　食塩摂取量評価のガイドライン

評価法	位置づけ	主な適用
24 時間蓄尿による Na 排泄量測定 栄養士による秤量あるいは質問調査	信頼性は高く望ましい方法であるが、煩雑である。患者の協力や施設の能力があれば推奨される。	高血圧専門施設
随時尿での Na、Cr 測定と Na/gCr 比による推定*	信頼性はやや劣るが、簡便であり、実際的な評価法として推奨される。	一般医療施設
早朝尿（夜間尿）での計算式を内蔵した電子式食塩センサーによる推定**	信頼性はやや低いが、簡便で患者本人が測定できることから推奨される。	患者本人

*：早朝尿（夜間尿）を用いてもよい。24 時間尿 Cr 排泄量推計値を含む計算式（表 2-4）を用いれば、信頼性は高まる。

**：試験紙や簡単な塩分計による方法は、簡便であるが信頼性が低く、定量的な評価は困難である。

日本高血圧学会の減塩ワーキンググループは、高血圧管理における食塩摂取量評価について、表 5 に示すガイドラインを提唱する。すなわち、高血圧者の管理においては、できるだけ各個人の食塩摂取量を以下の方法のいずれかにより評価する。

① 24 時間蓄尿による Na 排泄量測定、あるいは栄養士による食事内容の調査。これらは信頼性が高いが、実施が難しい場合が多い。患者の協力や施設の能力があれば推奨される方法で、高血圧の専門施設に適しているといえよう。

②随時尿の Na/Cr 比による Na 排泄量の推定。信頼性はやや低いが、簡便で実際的であろう。日本人の Cr の 1 日排泄量は約 1 g（約 10 mmol）なので[9]、グラム Cr あたりの Na 排泄量が 100 mmol(100 mEq) であれば食塩 6 g 程度と推定され、減塩指導の参考になると考えられる。ただし、尿 Cr 排泄量は体格や年齢、性などによりかなり異なるので、小柄な女性では Na/Cr 比から推定した値より食塩摂取量は少なく、大柄な男性では多くなることに留意を要する。早朝尿（夜間尿）を用いてもよい。また、計算式（表 2-4）を用いれば信頼性は高まる。

③早朝尿（夜間尿）での計算式を内蔵した電子式食塩センサーによる推定。信頼性はやや低いが、簡便で患者本人が測定できることから推奨される。ただし、家庭での測定を行うにあたっては、食塩セン

サーを個人が購入するか医療施設が貸し出す必要がある。

高血圧の管理における生活習慣修正のガイドラインに従えば、いずれの方法によっても、食塩6 g（Na 100 mmol）/ 日未満であれば食塩制限は守られており、それ以上であれば不十分と判断される。

結　論

食塩摂取量の評価にはいくつかの方法があるが、各個人の摂取量を正確に求めることは困難で限界がある。また、信頼性が高い方法は実施することに難点があり、簡便な方法は信頼性に劣るという問題がある。しかし、食塩摂取量の評価は各個人の摂取量の把握と減塩の実践において有用であり、強く推奨される。

高血圧の管理においては、できるだけ食塩摂取量を以下の3つの方法のいずれかで評価することが望ましい。① 24時間蓄尿によるNa排泄量測定、あるいは栄養士による食事内容の調査。信頼性が高く望ましい方法であるが実施が難しく、主に高血圧専門施設に適する。②随時尿のNa/Cr比によるNa排泄量の推定（グラムCrあたりのNa排泄量）。信頼性はやや低いが簡便で実際的であり、一般医療施設に適している。早朝尿（夜間尿）を用いてもよく、また計算式を用いれば信頼性は高まる。③早朝尿（夜間尿）での計算式を内蔵した電子式食塩センサーによる推定。信頼性はやや低いが、簡便で患者本人が測定できることから推奨される。いずれの方法によっても、食塩摂取量（排泄量）が6 g（Na 100 mmol）/ 日未満であれば食塩制限は守られており、それ以上であれば不十分と判断される。

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7 循環器系

—寝たきりをつくりやすい心臓，脳，血管の病気と未病について—

A 血圧と未病

はじめに

血圧の異常には高血圧と低血圧がある．高血圧は普遍的であるが，動脈硬化を促進し，心肥大や腎障害などの臓器障害をもたらし，脳卒中や心筋梗塞など種々の循環器疾患の主要な危険因子となっている．高血圧による心血管系の変化は自覚症状がなくても進行することから，高血圧を未病として捉える必要があろう．一方，低血圧は比較的少なく，一部を除けば心血管系や生命予後への悪影響は小さく，むしろそれに伴う症状が問題となる場合が多い．本項では，血圧と未病の観点から，高血圧の病態や診断，治療を中心として述べる．

1 高血圧と低血圧

血圧は血管内の圧力で，通常は動脈圧を意味している．心臓の収縮期に最も高く（収縮期血圧），拡張期に最低（拡張期血圧）となる．血圧は心臓や血管，腎臓，神経系や内分泌系などの多くの因子の影響を受け，また精神，身体活動などにより常に変動している[1]．

高血圧は血圧が高い状態で，成人では収縮期血圧 140mmHg 以上，あるいは拡張期血圧 90mmHg 以上が診断基準となる[2]．高血圧は普遍的であり，わが国における有病率は，30 歳以上の成人の 30 %以上で，高齢者では 60 %以上である[3]．高血圧の頻度は年齢とともに高くなるが，収縮期血圧は上昇を続けるのに対し，拡張期血圧は高齢者では低下傾向を示す．また，男性は女性より血圧が高いが，高齢者では性差はほぼ消失する．

高血圧は全身の細動脈硬化や大血管の粥状硬化，心肥大や腎障害をもたらし，心血管系の主要な危険因子となり，生命予後にも悪影響を及ぼす（表1）．高血圧が関与する疾患には，脳出血や脳梗塞などの脳卒中，心筋梗塞，心不全，不整脈などの心疾患，腎不全，大動脈瘤や閉塞性動脈硬化症といった血管疾患などがあり，これらの心血管疾患のリスクは血圧値に伴って増加する[4]（図1）．臓器障害や予後に関しては，若年者では拡張期血圧も重要であるが，高齢者では収縮期血圧がより強く関連する．高血圧は頭痛やふらつき感，動悸などの自覚症状を伴うこともあるが，無症状のことが多い．しかし，無症状であっても心血管系への悪影響は明らかであり，高血圧は silent killer とも称される．一方では，軽症ながら種々の自覚症状を伴う場合もある．

表1　高血圧による臓器障害と心血管病[2)]

脳
脳出血・脳梗塞
無症候性脳血管障害
一過性脳虚血発作
認知機能障害
心　臓
左室肥大
狭心症・心筋梗塞
心不全
腎　臓
蛋白尿
腎障害・腎不全
（血清クレアチニン　男性≧1.3mg/dL，女性≧1.2mg/dL）*
血　管
動脈硬化性プラーク
頸動脈内膜-中膜壁厚＞0.9 mm*
大動脈解離
閉塞性動脈疾患
眼　底
高血圧性網膜症

（*2003ESH-ESC ガイドラインに準拠）

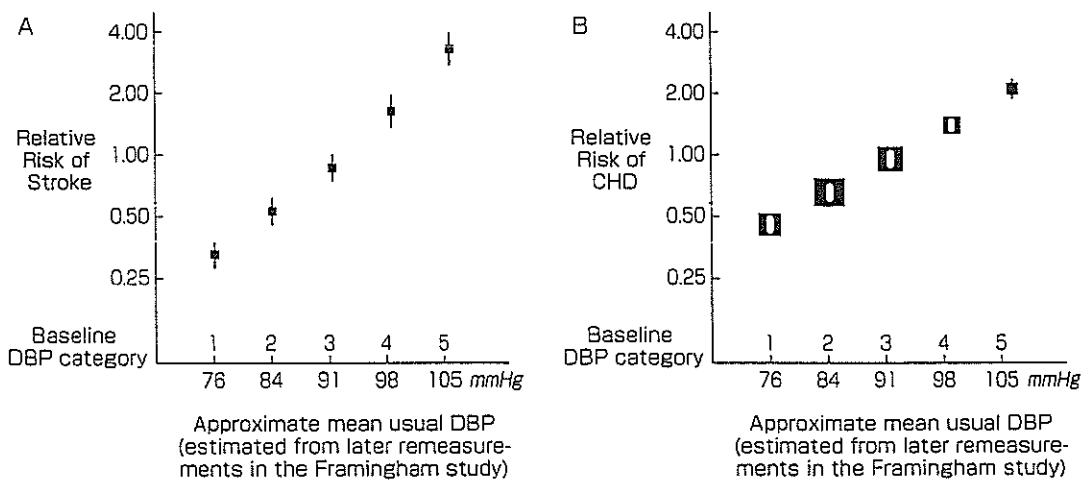

図1　疫学研究における拡張期血圧に別の脳卒中（左）および虚血性心疾患（右）の相対危険度[4)]

低血圧は，血圧が低い，あるいは体位などによって血圧が低下する病態である[1]．成人では収縮期血圧100mmHg未満が低血圧とされる．起立性低血圧は，立位の血圧が臥位より20mmHg以上低いことで診断される．低血圧の頻度は高血圧に比べると低く，最近の研究では成人における慢性低血圧者の頻度は，男性で0.2％，女性で1.0％と報告されている[5]．

低血圧は種々の原因によるが，交感神経の器質的障害による場合は起立性低血圧を示し，予後はあまりよくない[1]．自律神経の機能的障害による血管迷走神経失神は，通常は無症状であるが急性の低血圧と徐脈を呈する．非自律神経性の低血圧には，心疾患，血管拡張，血液量減少などがあり，重篤な病態の反映であることが少なくない．明らかな原因がないものは本態性低血圧といわれ，若年女性に多い．無症状のことも倦怠感などの自覚症状を伴うこともあるが，予後は良好である．

2 高血圧の診断

高血圧は収縮期140mmHg以上，あるいは拡張期90mmHg以上であるが，血圧値によりさらに細分化される．日本高血圧学会のガイドライン（JSH 2004）による分類を表2に示す[2]．高血圧は軽症，中等症，重症に分けられ，収縮期血圧は高く拡張期血圧は正常な場合は収縮期高血圧と呼ばれる．正常血圧であっても高めであれば心血管系のリスクが増大することから，130～139/85～89mmHgは正常高値血圧とされる．

高血圧の診断は1度だけの血圧測定によるべきではなく，繰り返しの測定によってなされるべきである．診察室では高血圧で24時間血圧や家庭血圧は正常の者は少なくなく，白衣高血圧と呼ばれる（図2）[6]．逆に，検診や診察室では正常であるが日常の血圧は高い場合もあり，仮面高血圧と呼ばれる．白衣高血圧は，持続性高血圧に比べれば予後は良好であるが，臓器障害を伴うことや持続性高血圧に移行する場合があり，無害とはいえない．仮面高血圧は，臓器障害の進行や予後不良が示されており，注意すべき病態と考えられる．

高血圧の診断においては，高血圧の重症度と，他の心血管危険因子，および高血圧の原因についての評価が必要である．心電図や心エコーにより心肥大の有無を，尿や血液検査により腎

表2　成人における血圧値分類[2]

分類	収縮期血圧		拡張期血圧
至適血圧	＜120	かつ	＜80
正常血圧	＜130	かつ	＜85
正常高値血圧	130～139	または	85～89
軽症高血圧	140～159	または	90～99
中等症高血圧	160～179	または	100～109
重症高血圧	≧180	または	≧110
収縮期高血圧	≧140	かつ	＜90

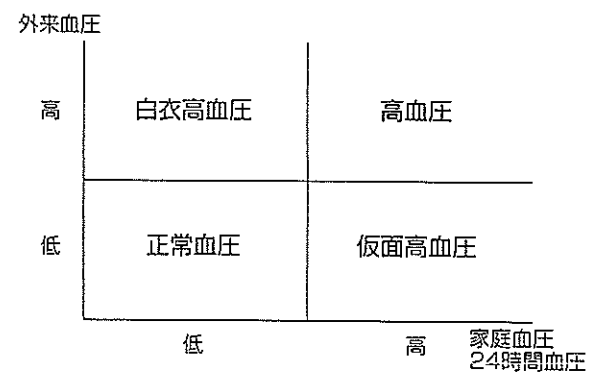

図2　外来（随時）血圧と家庭あるいは24時間血圧による血圧分類

障害の有無を調べる．胸部X線では心や大動脈，眼底検査では細動脈が観察できる．高血圧以外の危険因子では，喫煙，糖尿病，脂質代謝異常，肥満，微量アルブミン尿，高齢，心血管病の家族歴などが重要である．高血圧患者の診療に当たっては，血圧値と危険因子，臓器障害などによりリスクを層別化して治療方針を決定することが重要となる[2)]．

高血圧患者の大部分（約90％）は原因を特定できない本態性高血圧で，一部（約10％）は他に原因を有する二次性高血圧である[1, 2)]．本態性高血圧の成因は完全には解明されていないが，遺伝因子と環境要因が関与し，後者には食塩，肥満，アルコール，運動不足，ミネラル不足，ストレスなどの生活習慣が含まれる．二次性高血圧の中では，腎性高血圧が最も多い．これには腎実質性高血圧と腎血管性高血圧がある．副腎性高血圧には，原発性アルドステロン症やクッシング症候群，褐色細胞腫などがある．薬剤も高血圧の原因になることがあり，注意を要する．

3 高血圧の治療

1）治療の原則

高血圧患者の診療に当たっては，個々の患者のリスクを評価し，治療の開始時期や方法について考慮する必要がある[2)]．高血圧者は治療しなければ正常血圧者に比べて予後不良であり，治療により予後は改善することが証明されている．したがって，高血圧は管理する必要がある．

高血圧の治療においては，生活習慣の修正（非薬物療法）と薬物療法がともに重要である．目標血圧は，一般的には140/90 mmHg未満で，腎疾患や糖尿病を伴う場合や若年者では130/85mmHg未満が望ましい．家庭血圧や24時間血圧は高血圧の診断や治療に高い意義を有しているが[7)]，これらは一般に外来血圧より低い．家庭血圧では135/85 mmHg以上であれば高血圧であり，目標とする血圧値もこれ未満となる[2)]．

2）生活習慣の修正

生活習慣の修正は，高血圧の基礎的な治療法として推奨されている．JSH2004のガイドラインを表3に示すが，食塩制限，野菜や果物の摂取とコレステロール制限や飽和脂肪の制限，適正体重の維持，運動，アルコール制限，禁煙が基本となる[2)]．生活習慣の修正は有用であるが，降圧効果が比較的小さいことと，達成と維持が困難な点が限界となる[8)]．

食塩制限の効果には個人差があるが，1 g当たり約1 mmHgの降圧が期待できる．日本人の食塩摂取は平均11～12 g/日と多いが，6 g未満が望まれる[2, 8)]．カリウム，カルシウム，マグネシウムといったミネラルは，摂取不足が高血圧に関係する．野菜と果物，低脂肪の乳製品に富む食事をとれば，かなりの降圧が期待できる．

減量の効果は明らかで，1 kg当たり1 mmHg程度の血圧低下が期待できる[8)]．減量はまた，糖・脂質代謝に好影響を及ぼす．運動は減量にも有効であるが，これとは独立した降圧効果がある．ウォーキングのような比較的軽い運動を，定期的に行うことが勧められる．

アルコールは，1日30ml以内（ビール1本まで），女性はその半量までが望ましい．しかし，

飲酒制限の24時間平均血圧への効果は小さく，アルコール摂取量と循環器病や全死亡との間にはU型やJ型の関係があるので，禁酒すべきではない[8,9]．喫煙は動脈硬化を促進し，心血管予後や生命予後に重大な悪影響を及ぼすことから，禁煙が強く勧められる．

食事や生活に関するその他のことでは，魚油や食物繊維には軽度の降圧や脂質代謝改善の効果がある．ストレスも高血圧や心血管事故に関係するので，ストレスの多い生活は避けることが望ましい．

3）薬物療法

薬物治療の有用性は主に降圧効果そのものによるので，積極的な適応のない場合には主要降圧薬の中から適するものを第一次薬として用いる[2,10]（表4）．薬剤の選択に当たっては，患者の年齢や性，心血管危険因子，臓器障害，心血管病，降圧薬の副作用などを考慮する．主な降圧薬は，Ca拮抗薬，アンギオテンシン受容体拮抗薬，アンギオテンシン変換酵素阻害薬，利尿薬，β遮断薬，α遮断薬である．

表3　生活習慣の修正項目[2]

1）食塩制限6g/日未満
2）野菜・果物の積極的摂取* コレステロールや飽和脂肪酸の摂取を控える
3）適正体重の維持：BMI（体重(kg) ÷ [身長(m)]^2）
4）運動療法：心血管病のない高血圧患者が対象で，有酸素運動を毎日30分以上を目標に定期的に行う
5）アルコール制限： エタノールで男性は20～30mL/日以下，女性は10～20mL/日以下
6）禁煙
生活習慣の複合的な修正はより効果的である

*ただし，野菜・果物の積極的摂取は，重篤な腎障害を伴うものでは，高K血症をきたす可能性があるので推奨されない．また，果物の積極的摂取は摂取カロリーの増加につながることがあるので，糖尿病患者では推奨されない，

表4　降圧薬選択の基本[2]

• 降圧薬治療の有用性は主に高圧効果そのものによる．
• 積極的な適応のない場合には，主要降圧薬の中から最も適するものを第一次薬として使用．
• 各患者の年齢，性別に加え，心疾患危険因子（高脂血症，肥満，耐糖能異常），標的臓器障害，心血管病などの病態に合わせ降圧薬の副作用，薬価，QOL，性機能への影響を考慮し，最も適するものを選択．
• 主要降圧薬はCa拮抗薬，アンギオテンシンⅡ受容体拮抗薬（ARB），アンギオテンシン変換酵素（ACE）阻害薬，利尿薬，β遮断薬，α遮断薬．
• 他の主要降圧薬に比較し，α遮断薬のエビデンスは少ない．
• 病態に合わせてこれらの薬剤のいずれかを用い，降圧目標に達しない場合は，増量するか，他薬に変更するか，併用投与とする．

降圧薬治療においては，通常は単剤で少量から開始し，血圧値や副作用に注意しながら増やしていく．単一の薬剤の大量投与より作用機序の異なる薬剤の併用が，降圧効果や副作用の点で望ましい．また24時間にわたる血圧コントロールが重要であり，長時間作用性の薬剤が好ましい．降圧治療中でも仮面高血圧や早朝高血圧を呈する者は少なくなく，そのかなりが降圧薬の薬効減弱によることに注意を要する．

おわりに

高血圧は無症状のことが多いが，心血管系に重大な悪影響を及ぼし，有病率の高さとあいまって循環器疾患の最大の危険因子となっている．したがって，高血圧を未病の一つとして認識して管理する必要があり，その予防もまた大事である．高血圧であっても，診断されていない者，治療を受けていない者，コントロールされていない者は少なくない．生活習慣の修正と薬物療法は，高血圧治療においてともに重要であるが，前者は予防にも有用であり広く実践されることが望まれる．

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（河野雄平）

Uric Acid, Left Ventricular Mass Index, and Risk of Cardiovascular Disease in Essential Hypertension

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Abstract—Elevated serum uric acid (UA) is frequently encountered in individuals with hypertension, but whether the relationship between UA and cardiovascular events is circumstantial or causal remains to be answered. We examined the association between serum UA and left ventricular mass index (LVMI) and investigated prospectively whether the combination of UA and LVMI can predict the incidence of cardiovascular disease (CVD) in asymptomatic subjects with essential hypertension. A total of 619 subjects (mean age, 61 years; 52% female) free of prior CVD were included in this study. A significant association between UA and LVMI was also confirmed in multiple regression analysis (male: $F=4.29$, $P<0.04$; female: $F=4.24$, $P<0.05$). During follow-up (mean, 34 months), 28 subjects (14 female) developed CVD including myocardial infarction, angina pectoris, congestive heart failure, cerebral infarction, and transient cerebral ischemia. Sex-specific median values were used to separate the higher group from the lower group of UA and LVMI. Kaplan–Meier curves showed a significantly poorer survival rate in the group with higher UA and LVMI (LVMI, male: >126.9, female: >112.0 g/m^2; UA, male: >374.7, female: >303.3 μmol/L; log-rank $\chi^2=13.18$; $P<0.01$). Multivariate Cox regression analysis showed that the combination of higher UA and LVMI was an independent predictor for CVD events (hazard ratio, 2.38; $P<0.03$). Our findings demonstrate that UA is independently associated with LVMI and suggest that the combination of hyperuricemia combined with left ventricular hypertrophy is an independent and powerful predictor for CVD. The association between UA and CVD events may be introduced in part because of a direct association of UA with LVMI. (***Hypertension.* 2006;47:195-202.**)

Key Words: uric acid ■ cardiovascular diseases ■ hypertrophy ■ risk factors

Effective prevention of cardiovascular disease (CVD) requires the early detection and correction of predisposing conditions and risk factors in susceptible patients. Hypertension is a common risk factor for CVD, and the cardiovascular prognosis in patients with hypertension depends not only on the level of blood pressure (BP), but also on the presence of associated risk factors. Hyperuricemia is frequently encountered in hypertensive patients.[1] Several large epidemiologic studies have identified an association between increased serum uric acid (UA) and cardiovascular risk in the general population[2–6] and among patients with hypertension.[7,8] Other recent reports have also confirmed these associations by angiographic procedure.[9,10] Some studies have claimed that UA is an independent risk factor for CVD, whereas others have failed to identify UA as a significant and independent risk factor.[11–13] Thus, the status of UA as an independent risk marker remains controversial, and whether the relationship between UA level and cardiovascular events is circumstantial or causal remains to be answered.[2] On the other hand, the level of serum UA is affected by or linked to many factors, such as obesity, insulin resistance, dyslipidemia, and hypertension, all of which are also associated with left ventricular hypertrophy (LVH). In a recent report, in female subjects, UA level was independently associated with the presence of LVH detected by echocardiography.[14] These results suggest that UA level may be related to left ventricular mass index (LVMI).

In hypertension, LVH is initially a compensatory process against abnormal loading conditions, but it is also the first step toward the development of overt clinical disease, such as CVD.[15] In essential hypertension, the risk of future CVD complications is higher in patients with LVH on echocardiography than in those with normal left ventricular (LV) mass.[15,16] Thus, assessment of LV mass by echocardiography is a well-established procedure to estimate the risk of CVD in hypertensives.

The hypothesis that the combination of serum UA level and LVMI may be a strong predictor of CVD has never been examined. In this study, we investigated the relationship between UA level and LVMI in essential hypertensive subjects. Furthermore, we also examined prospectively the relations of UA level, LVMI, and their combination to the incidence of CVD during follow-up in asymptomatic hypertensive subjects.

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Methods

Study Subjects

A total of 619 hypertensive subjects who had good-quality echocardiographic recordings were enrolled and monitored for 33.5±0.8 months in this study. All of the subjects were selected from patients who were admitted and underwent medical investigation at the National Cardiovascular Center in Osaka, Japan. Hypertension was defined as a systolic BP of ≥140 mm Hg and/or a diastolic BP of ≥90 mm Hg on repeated measurements or receiving antihypertensive treatment. Diabetes mellitus was defined according to the American Diabetes Association criteria.[17] Smoking was defined as current smoking or having a history of habitual smoking. Ischemic heart disease was defined as a ≥75% organic stenosis of ≥1 major coronary artery as confirmed by coronary angiography or a history of myocardial infarction or percutaneous transluminal coronary angioplasty. Renal insufficiency was defined as a serum creatinine concentration >176.8 μmol/L. All of the subjects enrolled in this study had essential hypertension. Exclusion criteria included ischemic heart disease, acute coronary syndrome, congestive heart failure (CHF; New York Heart Association class II or greater), chronic renal insufficiency, valvular heart disease, old cerebral infarction, and history of transient ischemic attack. Participants with moderate or severe aortic or mitral regurgitation or a heart rate >100 bpm were also excluded. The study protocol was approved by the ethics committee of our institution. All of the subjects enrolled in this study were Japanese, and all of the subjects gave informed consent to participate in this study.

Baseline Clinical Characteristics

After fasting overnight, BP was measured with an appropriate arm cuff and a mercury column sphygmomanometer on the left arm after a resting period of ≥10 minutes in the supine position. After BP measurements, venous blood sampling from all of the subjects was performed. Height and body weight were measured, and body mass index (BMI) was calculated. Insulin sensitivity was estimated using the homeostatic model assessment index; that is, plasma glucose level×(plasma insulin level/22.5). Urine samples were collected for 24 hours and used to evaluate creatinine clearance (Ccr). The following parameters were also determined: total cholesterol (T-chol), triglycerides (TG), high-density lipoprotein cholesterol (HDL-chol), serum UA, serum creatinine, and C-reactive protein (CRP) levels. Serum UA levels were determined by the uricase-peroxidase method.[18]

Echocardiographic Methods and Calculation of Derived Variables

Imaging and Doppler echocardiography were performed in all of the participants in this study. Studies were performed with phased-array echocardiography with M-mode, 2D, pulsed, and color-flow Doppler capabilities. LV internal dimension and septal and posterior wall thickness were measured at end-diastole and end-systole according to the American Society of Echocardiography recommendations.[19,20] Color-flow Doppler recordings were used to check for aortic and mitral regurgitation, as described previously.[21] End-diastolic dimensions were used to calculate LV mass by a previously reported formula.[22] LV mass was considered an unadjusted variable and was normalized by body surface area and expressed as LVMI.

The LV diastolic filling pattern was recorded from the apical transducer position with subjects in the left lateral decubitus position, with the sample volume situated between the mitral leaflet tips. The leading edge of the transmitral Doppler flow pattern was traced to derive the peak of early diastolic and atrial phase LV filling (E-velocity and A-velocity, respectively), their ratio (E/A ratio), and the deceleration time of early diastolic LV filling (DcT). All of the measurements were performed by a trained investigator who was blinded to the clinical data of the subjects.

Clinical End Points

For survival analysis, observation began on the date of echocardiography, with verified dates updated through March 2004. All of the subjects were followed at the National Cardiovascular Center in Osaka and treated by implementation of standard lifestyle and pharmacological measures. All of the subjects were periodically referred to our institution for BP control and other diagnostic procedures. CVD events of interest in this study were myocardial infarction and angina pectoris confirmed by electrocardiographic changes, coronary angiography and/or myocardial scintigraphy findings, stroke and transient cerebral ischemia confirmed by clinical symptoms, computed tomography and magnetic resonance angiography and/or cerebrovascular angiography findings, and CHF requiring hospitalization. CHF was diagnosed from clinical symptoms and findings (paroxysmal nocturnal dyspnea or cough, pulmonary rales because of pulmonary congestion, distended jugular veins, neck vein distension, enlarging heart size, pleural effusion and/or acute pulmonary edema on chest radiography, hepatojugular reflux, bilateral ankle edema, shortness of breath on ordinary exertion, and/or heart rate of ≥120 bpm). The cause of death was classified as CVD if there was sudden death from CVD by an independent review panel of physicians who were unaware of the echocardiographic and clinical findings. Events that were more equivocal, such as unrecognized myocardial infarction, angina pectoris, and transient cerebral ischemia, were not included as CVD for this analysis. Furthermore, patients with clinical evidence of pneumonia or uremia were excluded. For patients who experienced multiple nonfatal episodes of CVD, the analysis included only the first event.

TABLE 1. Baseline Clinical Characteristics of Study Subjects

Variables	Male	Female
n	296	323
Age, y	60.2±0.7	62.5±0.7*
BMI, kg/m²	24.6±0.2	24.2±0.2
Duration of hypertension, y	14.7±0.6	14.8±0.6
Smoking, %	72.0	18.7†
Systolic BP, mm Hg	142.5±0.9	144.6±0.8
Diastolic BP, mm Hg	83.2±0.6	80.8±0.6†
Pulse pressure, mm Hg	59.3±0.8	63.8±0.7†
Heart rate, bpm	66.4±0.5	67.4±0.5
Diabetes, %	26.7	18.9*
T-chol, mmol/L	5.16±0.04	5.37±0.04†
TG, mmol/L	1.69±0.06	1.29±0.06†
HDL-chol, mmol/L	1.24±0.02	1.43±0.02†
UA, μmol/L	378.5±4.8	313.2±4.6†
Ccr, Ml/min	101.6±2.3	94.2±2.2*
HOMA-index	1.79±0.10	1.63±0.10
CRP, mg/L	2.1±0.4	1.5±0.4
Septal wall thickness, mm	11.2±0.1	10.2±0.1†
Posterior wall thickness, mm	11.1±0.1	10.2±0.1†
LV internal diameter, mm	47.1±0.2	43.8±0.2†
LVMI, g/m²	130.5±1.7	116.0±1.7†
Peak E-velocity, m/s	0.68±0.01	0.72±0.01†
Peak A-velocity, m/s	0.77±0.01	0.86±0.01†
DcT, ms	229.3±2.8	230.1±2.6
E/A ratio	0.92±0.02	0.87±0.02*

HOMA indicates homeostatic model assessment. Data are mean±SE.
*$P<0.05$ and †$P<0.01$ vs male subjects.

Statistical Analysis

Parametric data are presented as mean±SE. The relations between LVMI or serum UA and various parameters were assessed using univariate linear regression analysis and Pearson's correlation coefficient. Multiple linear regression analysis was applied to identify independent determinants of LVMI after adjustment for potential confounding factors affecting LVMI.

Serum UA level and LVMI were stratified into 4 groups according to median values of baseline serum UA level and LVMI by each sex. One-way ANOVA with Dunnett multiple comparison posttest was used to analyze data among 4 groups. Event-free survival analysis was performed with the Kaplan–Meier method to plot the cumulative incidence of CVD, and the groups were compared by the Mantel log rank test. Cox proportional hazard analysis was used to examine the association between variables and the cumulative incidence of CVD. With respect to serum UA and LVMI, the cumulative incidence of CVD was calculated using the group with lower UA and LVMI as a reference for each other. These effects were measured by hazard ratios (HRs) and their 95% CIs based on Cox regression models. We used multivariable Cox proportional hazards regression models to examine the relations of serum UA and LVMI to CVD events, after accounting for relevant variables using a P value of <0.05 as the selection criterion. A P value <0.05 was considered statistically significant. All of the calculations were performed using a standard statistical package (JMP 4.0, SAS Institute).

Results

Association Between UA and LVMI

The baseline clinical and biochemical characteristics of the study subjects, analyzed on the basis of sex, are shown in Table 1. UA level and LVMI were significantly higher in men than in women. At baseline, 78.5% of the study patients were taking antihypertensive drugs, and 21.5% were complying with lifestyle measures only. Diuretics, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and calcium-channel blockers were used alone or in various combinations in 11.3%, 26.7%, 33.9%, and 62.8% of the study patients, respectively. In addition, 9.0% of the study subjects were taking urate-lowering medication (allopurinol and probenecid).

We first examined the simple correlations between serum UA and clinical variables after dividing the subjects into 2 groups according to sex (Table 2). In both male and female subjects, UA level was significantly associated with BMI, TG, HDL-chol, Ccr, and LVMI. In addition, only in female subjects, there was a significant association between UA level and CRP, smoking, taking diuretics, and taking urate-lowering medication.

The simple correlations between LVMI and clinical variables were also examined (Table 2). In male subjects, LVMI was significantly correlated with duration of hypertension, systolic BP, pulse pressure, heart rate, T-chol, UA, and CRP and was significantly higher in smokers and those taking urate-lowering medication. In female subjects, LVMI was significantly correlated with age, BMI, duration of hyperten-

TABLE 2. Simple Correlation Among Serum UA, LVMI, and Clinical Characteristics

	UA, μmol/L		LVMI, g/m²	
Characteristics	Male	Female	Male	Female
Age	0.10	0.04	0.10	0.16†
BMI	0.13*	0.17†	0.10	0.18†
Duration of hypertension	0.10	0.09	0.13*	0.13*
Smoking, yes vs no	381.0±5.7 vs 369.0±9.1	332.6±10.5 vs 309.2±5.1*	133.3±2.1 vs 123.5±3.4*	119.7±3.8 vs 115.2±1.8
Systolic BP	0.01	0.05	0.14*	0.26†
Diastolic BP	0.01	0.06	0.01	0.04
Pulse pressure	0.03	0.01	0.17†	0.26†
Heart rate	0.03	0.01	−0.21†	−0.12*
Diabetes, yes vs no	381.0±5.7 vs 368.5±9.3	322.0±10.5 vs 311.1±5.1	131.0±3.5 vs 130.4±2.1	128.5±3.7 vs 113.1±1.8†
T-chol	0.03	0.02	0.12*	0.01
TG	0.25†	0.32†	0.08	0.19†
HDL-chol	−0.19†	−0.27†	−0.10	−0.15†
Ccr	−0.14*	−0.19†	−0.11	−0.01
HOMA-index	0.11	0.11	0.04	0.18†
CRP	0.03	0.15†	0.13*	0.08
LVMI	0.15†	0.16†		
Taking diuretics, yes vs no	397.1±15.3 vs 375.5±5.1	353.3±12.7 vs 307.5±4.8†	132.0±5.7 vs 130.4±1.9	123.7±4.6 vs 114.8±1.7
Taking urate-lowering medication, yes vs no	385.9±12.5 vs 376.2±5.3	431.7±22.6 vs 308.6±4.5†	140.2±4.6 vs 128.9±1.9*	121.2±8.5 vs 115.8±1.7
Peak E-velocity	−0.04	−0.01		
Peak A-velocity	0.01	0.06		
DcT	0.08*	0.12*		
E/A ratio	−0.02	−0.05		

HOMA indicates homeostatic model assessment. Data indicate correlation coefficients and mean±SE.
*$P<0.05$.
†$P<0.01$.

sion, systolic BP, pulse pressure, heart rate, TG, HDL-chol, homeostatic model assessment index, and UA and was significantly higher in diabetics.

Multiple linear regression analysis was performed including age, duration of hypertension, BMI, systolic and diastolic BP, heart rate, T-chol, TG, HDL-chol, Ccr, CRP, smoking, and diabetes and revealed that UA was independently associated with LVMI in male and female subjects (Table 3). In addition, even after adjustment for taking diuretics and taking urate-lowering medication, UA was still independently associated with LVMI (male, F=4.831, P=0.0290; female, F=4.591, P=0.0330).

To exclude the effect of drugs on UA level, we next examined the association between UA and LVMI after excluding subjects receiving diuretics and urate-lowering medication (male; n=232, female; n=273). Even after excluding these subjects, a significant association between UA and LVMI was observed (male: r=0.16, female: r=0.17, P<0.01 respectively).

LVH was considered to be present when LVMI was >125 for men and >110 g/m^2 for women.[23] UA level was significantly higher in subjects with LVH (male, 383.4±6.2 versus 363.5±6.6; female, 323.5±6.2 versus 303.0±6.5 μmol/L, P<0.03 respectively). A significant association between UA and LVH was also confirmed in multiple regression analysis including age, duration of hypertension, BMI, systolic and diastolic BP, heart rate, T-chol, TG, HDL-chol, Ccr, CRP, smoking, and diabetes (male, 384.5±7.6 versus 363.7±8.0, F=4.3, P<0.04; female, 329.7±9.1 versus 302.0±10.5 μmol/L, F=5.8, P<0.02).

The association between LV diastolic function and UA level was examined, and a significant association between UA and DcT was observed (Table 2). On the other hand, UA was not significantly associated with E-velocity, A-velocity, and E/A ratio. It is well described that early diastolic relaxation decreases with increasing age.[24] In the present study, we also found that DcT had a significant positive relationship with age (male: r=0.36, female: r=0.30, P<0.01 respectively), but not heart rate (male: r=−0.05, female: r=−0.01) and body surface area (male: r=0.07, female: r=0.05). Even after adjustment for age, DcT was significantly related to UA level (male: F=4.34, P<0.04; female: F=3.99, P<0.05).

TABLE 3. Independent Determinants of LVMI by Each Sex in Multiple Linear Regression Analysis

	Male		Female	
Variables	F	*P* Value	F	*P* Value
Age	0.068	0.7946	9.410	0.0024
BMI	4.718	0.0309	1.903	0.1689
Duration of hypertension	1.489	0.2236	0.026	0.8711
Smoking	3.935	0.0485	0.204	0.6516
Systolic BP	6.362	0.0124	20.479	0.0001
Diastolic BP	0.086	0.7702	0.011	0.9150
Heart rate	8.872	0.0032	5.859	0.0162
Diabetes	0.007	0.9357	9.837	0.0019
T-chol	2.826	0.0942	3.071	0.0808
TG	1.182	0.2781	6.239	0.0131
HDL-chol	0.294	0.5881	0.498	0.4812
UA	4.285	0.0396	4.244	0.0403
Ccr	1.886	0.1710	5.516	0.0196
CRP	0.246	0.6206	0.468	0.4944
	R^2=0.162; F=3.095; P=0.0002		R^2=0.249; F=6.344; P<0.0001	

Predictive Value of Serum UA and LVMI for CVD

Because of the sex difference in serum UA levels and LVMI values, different median values for men and women were used to separate the higher group from the lower group in each variable. Demographic and hemodynamic data of the subjects grouped according to the median value of serum UA (male: 374.7; female: 303.3 μmol/L) and LVMI (male: 126.9; female: 112.0 g/m^2) in each sex. As a result, the total subjects were divided into 4 groups as follows; lower LVMI and UA, lower LVMI and higher UA, higher LVMI and lower UA, and higher LVMI and UA. The baseline clinical and biochemical characteristics of the study subjects are shown in Table 4. There was a trend toward higher age, longer duration of hypertension, higher systolic BP, higher pulse pressure, and lower heart rate with increasing LVMI. On the other hand, the groups with higher UA showed higher BMI and lower Ccr. In addition, the group with higher LVMI and UA showed significantly lower HDL-chol and Ccr than that with higher LVMI and lower UA. At the follow-up contact, the proportions of subjects treated with diuretics, alone or combined with other agents, during follow-up were 6.8%, 11.9%, 9.6%, and 16.6% (P<0.05 versus lower LVMI and UA), respectively, in the 4 groups. The proportions of subjects treated with urate-lowering medication were 3.7%, 9.8%, 13.2% (P<0.05 versus lower LVMI and UA), and 10.7%, respectively.

During the follow-up period, 28 patients (4.5%; 14 female) developed CVD. There were 11 subjects with CHF, 1 with myocardial infarction, 8 with angina pectoris, 7 with cerebral infarction, and 1 with transient cerebral ischemia. Serum UA level and LVMI were significantly higher in patients who developed CVD during the follow-up period than in event-free subjects (UA: 385.3±16.8 versus 341.8±3.6 μmol/L, LVMI: 139.5±5.8 versus 122.1±1.3 g/m^2, P<0.01, respectively). Life table analyses of CVD throughout the follow-up period according to the 4 groups of baseline serum UA and LVMI are plotted in Figure 1. These curves illustrate significantly poorer survival in the group with higher UA and LVMI.

We next performed Cox regression analysis to examine whether the influence of higher UA and LVMI on CVD events was independent of other risk factors. As shown in Table 5, the risk for CVD was significantly higher in the group with higher UA and LVMI compared with that with lower UA and LVMI (HR, 2.70). In addition, age, duration of hypertension, pulse pressure, and Ccr were also significantly associated with the incidence of CVD. In multivariate Cox regression analysis, the combination of serum UA level and LVMI was an independent predictor for CVD (HR, 2.38).

TABLE 4. Baseline Clinical Characteristics of Study Subjects

	Lower LVMI		Higher LVMI	
Variables	Lower UA	Higher UA	Lower UA	Higher UA
N	166	145	138	170
Male, %	50.6	45.1	50.0	45.3
Age, y	59.3±0.9§	59.5±1.0§	63.9±1.0†	62.8±0.9*
BMI, kg/m^2	23.5±0.3‡	24.7±0.3†	24.4±0.3*	25.2±0.3†
Duration of hypertension, y	12.3±0.8§	14.9±0.9	16.0±0.9†	16.3±0.8†
Smokers, %	41.4	42.4	45.6	47.7
Systolic BP, mm Hg	140.8±1.2§	141.4±1.3‡	146.1±1.3†	145.9±1.1†
Diastolic BP, mm Hg	82.0±0.8	82.1±0.9	82.8±0.9	81.1±0.8
Pulse pressure, mm Hg	58.9±1.0‡	59.3±1.1‡	63.3±1.1*	64.9±1.0†
Heart rate, bpm	68.6±0.7§	68.0±0.7‡	65.4±0.8†	65.8±0.7*
Diabetes, %	18.9	18.8	27.2	26.5
T-chol, mmol/L	5.29±0.06	5.37±0.06	5.26±0.06	5.17±0.06
TG, mmol/L	1.28±0.08	1.76±0.09†‡	1.35±0.09	1.56±0.08†
HDL-chol, mmol/L	1.43±0.03	1.33±0.03	1.38±0.03	1.23±0.03†§
UA, μmol/L	280±5	400±5†	287±6	406±5†§
Ccr, mL/min	102.8±3.1	96.8±3.3	102.9±3.4	89.8±3.1†‡
HOMA-index	1.80±0.26	1.93±0.27	1.59±0.27	2.05±0.24
CRP, mg/L	1.42±0.36	1.25±0.37	1.62±0.37	1.83±0.33
Septal wall thickness, mm	9.6±0.1§	9.9±0.1§	11.5±0.1†	11.8±0.1†
Posterior wall thickness, mm	9.8±0.1§	9.9±0.1§	11.3±0.1†	11.5±0.1†
LV internal diameter, mm	43.7±0.3§	43.4±0.3§	46.9±0.3†	47.4±0.3†
LVMI, g/m^2	99.9±1.6§	99.9±1.7§	143.1±1.7†	147.8±1.6†
Peak E-velocity, m/s	0.71±0.01	0.71±0.01	0.69±0.01	0.70±0.01
Peak A-velocity, m/s	0.78±0.01§	0.81±0.02	0.84±0.02†	0.84±0.01†
DcT, ms	223.7±3.7	226.1±3.9	230.0±4.0	237.4±3.6*
E/A ratio	0.95±0.02§	0.92±0.02	0.85±0.02†	0.85±0.02†
No. of CVD events	2	5	5	16

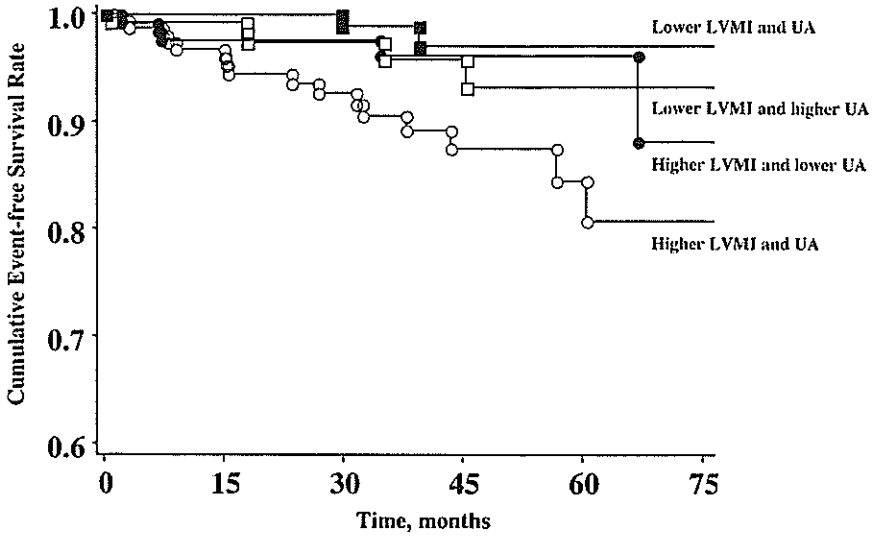
HOMA indicates homeostatic model assessment. Data are mean±E.
*P<0.05 and †P<0.01 vs lower LVMI and lower UA.
‡P<0.05 and §P<0.01 vs higher LVMI and lower UA.

In addition, the influence of the combination of UA and LVMI on CVD events was also examined by dividing the 4 groups according to the normal levels of UA (UA level ≤420 in men and ≤390 μmol/L in women) and with/without LVH; that is, normal UA and without LVH (n=244), hyperuricemia and without LVH (n=53), normal UA and LVH (n=245), and hyperuricemia and LVH (n=77). The independent predictive value of the hyperuricemia and LVH for CVD events was also confirmed by the Kaplan–Meier method (log-rank χ^2=5.58; P=0.0355) and by Cox regression analysis (HR, 1.7; 95% CI, 0.78 to 3.41; P<0.03). In multivariate Cox regression analysis, the combination of hyperuricemia and LVH was an independent predictor for CVD events (HR, 1.8; 95% CI, 0.85 to 3.48; P<0.05).

Discussion

This study documented and validated that serum UA level is associated with LVMI, and the results of multiple linear regression analysis indicated that serum UA is independently associated with LVMI. Compared with the group with lower UA and LVMI, the group with higher UA and LVMI showed a condition of increased risk for cardiovascular and renal morbidity, such as significantly longer duration of hypertension, higher pulse pressure, worse dyslipidemia, and lower Ccr. Even after adjustment for other clinical factors, higher UA level and LVMI and age were independent predictors for CVD.

Our results suggest that serum UA is independently associated with LVMI, whereas an elevation of UA is associated with an actual metabolic disorder, and whether an elevation of serum UA level is the cause or result of LVH is unclear. The association between UA and LVMI might relate to an association of UA with other risk factors, especially including renal dysfunction, oxidative stress, severity of hypertension, and obesity. Renal dysfunction increases serum UA and activates the renin–angiotensin system, and angiotensin II is essential for the development of LVH.[25] UA is the final breakdown product of dietary or endogenous purines and is generated by xanthine oxidase (XO). A net release of urate in coronary heart disease[26] and the presence of XO in the human



Kaplan–Meier plots showing cumulative CVD-free survival in subjects according to 4 groups divided by median values of UA and LVMI (log-rank χ^2=13.18; P=0.0042). Marker groups for LVMI (g/m^2): lower-LVMI, ≤126.9 for men and ≤112.0 for women; higher-LVMI, >126.9 for men and >112.0 for women. Marker groups for UA (μmol/L): lower-UA, ≤374.7 for men and ≤303.3 for women; higher-UA, >374.7 for men and >303.3 for women.

heart has been demonstrated.[27] UA may reflect the generation of superoxide and resultant oxidative stress via the XO system.[28] Furthermore, the independent association between UA and the severity of hypertension is well accepted.[1] On the other hand, there is a possibility that UA itself may induce LVH. Previous reports have shown that UA impaired NO generation and induced endothelial dysfunction and smooth muscle cell proliferation.[29,30] In experimental and in vitro systems, UA appears to have the ability to induce inflammatory mediators, such as tumor necrosis factor α,[31] and potentially stimulates mitogen-activated protein kinases,[32] which are known to induce cardiac hypertrophy.[33,34] These results suggest that cardiac hypertrophy may be, at least in part, attributable to an increase in UA itself, via stimulation of endothelial dysfunction, smooth muscle cell proliferation, and inflammation.

Our results showed that the incidence of CVD in subjects with higher UA and LVMI was ≈2.4-fold higher than that in subjects with lower UA and LVMI, even after adjustment for confounding factors. Thus, our results indicate that hyperten-

TABLE 5. Predictors for CVD Events by Cox Regression Analysis

	Univariate		Multivariate	
Variables, Unit of Increase	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
LVMI and UA	χ^2=12.79	0.0051	χ^2=9.08	0.0282
Lower LVMI and UA	1 (reference)		1 (reference)	
Lower LVMI and higher UA	1.01 (0.43 to 2.17)		1.14 (0.48 to 2.47)	
Higher LVMI and lower UA	1.02 (0.43 to 2.19)		1.01 (0.49 to 2.06)	
Higher LVMI and higher UA	2.70 (1.51 to 5.08)		2.38 (1.31 to 4.55)	
Age, 1 y	1.07 (1.03 to 1.12)	0.0004	1.05 (1.01 to 1.11)	0.0260
Sex, male	1.07 (0.74 to 1.56)	0.7212		
BMI, 1 kg/m^2	1.04 (0.93 to 1.16)	0.4566		
Duration of hypertension, 1 y	1.06 (1.03 to 1.10)	0.0003	1.03 (0.99 to 1.07)	0.0931
Smoking, yes	1.14 (0.78 to 1.66)	0.4844		
Systolic BP, 1 mm Hg	1.01 (0.98 to 1.03)	0.5092		
Diastolic BP, 1 mm Hg	1.03 (0.99 to 1.07)	0.0502		
Pulse pressure, 1 mm Hg	1.03 (1.00 to 1.05)	0.0343	1.01 (0.98 to 1.03)	0.5577
Heart rate, 1 bpm	0.98 (0.94 to 1.02)	0.4500		
Diabetes, yes	1.40 (0.93 to 2.05)	0.1005		
T-chol, 1 mmol/L	0.87 (0.52 to 1.43)	0.5757		
TG, 1 mmol/L	1.07 (0.69 to 1.34)	0.7261		
HDL-chol, 1 mmol/L	0.81 (0.28 to 2.07)	0.6685		
Ccr, 1 mL/min	0.99 (0.98 to 1.00)	0.0439	1.00 (0.99 to 1.01)	0.9661
HOMA-index, 1	1.01 (0.82 to 1.10)	0.8801		
CRP, 1 mg/L	1.00 (0.85 to 1.03)	0.7561		

HOMA indicates homeostatic model assessment.

sive subjects with LVH and hyperuricemia have an increased risk of developing CVD and suggest that the assessments of serum UA level and LVMI by echocardiography are useful and sensitive for predicting the risk for CVD. Many epidemiologic studies have attempt to identify whether hyperuricemia is an independent risk factor for CVD, but the results obtained were controversial after adjusting for other CVD risk factors, especially including LVH determined by electrocardiography.[7,8,13] Although hyperuricemia itself may have the ability to increase the risk of CVD, our results suggest that the association between UA and CVD events may be introduced in part because of a direct association of UA with LVMI. On the other hand, all of the antihypertensive drugs failed to show a cardioprotective effect in this study. Previous epidemiologic studies have also shown that UA level was independently predictive for the development of CVD even after antihypertensive treatment.[7,8,35,36] Furthermore, in the Systolic Hypertension in the Elderly Program trial, a subanalysis showed that the cardioprotection by diuretics was lost in those treated patients in whom UA levels increased.[36]

One notable result of this study is that, in the group with higher LVMI, the risk of CVD became higher with increasing UA level. This result may have been introduced because of decreased renal function and HDL-chol level, which are established risk factors for CVD, in subjects with hyperuricemia and LVH. Apart from renal function and lipid metabolism, there are other possible mechanisms by which the risk for CVD became higher with increasing UA levels. Several mechanisms have been proposed to account for the association between hyperuricemia and CVD, including the following: (1) the direct relationship of UA with severity of hypertension,[1] in which the predictive relationship of UA with BP is dose dependent;[37] (2) increased oxidative stress;[38] (3) a subtle reduction in glomerular filtration rate leading to impaired renal UA clearance;[39] (4) impaired NO production,[38] which activates the renin–angiotensin system[40] and induces endothelial dysfunction and smooth muscle cell proliferation;[29,30] (5) impaired platelet adhesiveness, disturbed hemorheology, and aggregation;[38] and (6) synthesis of monocyte chemoattractant protein-1 in vascular smooth muscle cells,[41] which is a chemokine that is importantly involved in CVD.[42] On the other hand, the close association between LVH and CVD events may be explained by decreased myocardial contractility, severe diastolic filling abnormalities, and increased oxygen requirement of the myocardium.[43] Our results showed that more severe relaxation impairment was observed in hyperuricemic subjects with LVH, and this "impaired relaxation" is known to be associated with increased risk of CVD.[44] In addition, a weak but significant association between UA and DcT, a marker of relaxation impairment, was observed in this study, and higher UA levels may contribute to the progression of LV dysfunction. Consequently, we propose the idea that, in subjects with LVH, severe hypertension, activation of oxidative stress and the renin–angiotensin system, stimulation of production of cytokines from leukocytes and chemokines from vascular smooth muscle cells, and more impaired relaxation may occur with increasing UA levels and enhance the risk for CVD.

The limitations of this study include missing baseline data and potentially important characteristics, such as menopause, alcohol intake, and a high-purine diet, which are also associated with a higher serum UA level. Because our data were obtained in subjects with treated essential hypertension at the start of the study, these results could underestimate the involvement of BP itself in the development of LVH and CVD events.

Perspectives

Our results demonstrate that UA is independently associated with LVMI and suggest that the combination of hyperuricemia with LVH is a powerful independent predictor for CVD. The association between UA and CVD events may be introduced in part because of a direct association of UA with LVMI. In hypertensive as well as LVH subjects, assessment of UA levels may help to refine CVD risk stratification. A crucial next step is to investigate whether UA is causally linked to LVH in a longitudinal setting. If so, hypouricemic agents might be used in clinical practice for LVH risk reduction in hypertensive patients. A large prospective population–based study will be important to confirm our preliminary observations.

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高血圧

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【血圧】 血圧とは血管内の圧力で，通常は動脈圧を意味している．心臓の収縮期に最も高く（収縮期血圧），拡張期に最低（拡張期血圧）となる．血圧は心臓や血管，腎臓，神経系や内分泌系などの多くの因子の影響をうけており，また精神，身体活動などにより常に変動している．

【高血圧】 血圧が高い病態で，140/90mmHg以上が診断基準となる．脳卒中やほかの多くの循環器疾患の重要な危険因子となっている．家庭血圧の高血圧診断基準は，135/85mmHg以上となる．

【脈圧】 収縮期血圧と拡張期血圧との差であり，加齢とともに増大する．脈圧の増大は主に大血管の動脈硬化の表れであり，心血管疾患のリスクに関連している．

【収縮期高血圧】 収縮期血圧は高く（140mmHg以上）拡張期血圧は正常（90mmHg未満）な病態で，高齢者に多い．拡張期血圧の低値は，主に大血管の動脈硬化を反映している．心血管疾患のリスクとなり，治療により予後は改善する．

【白衣高血圧】 くり返しの測定でも診察室では高血圧を呈するが，24時間血圧や家庭血圧は正常な病態で，診察室高血圧ともいわれる．臓器障害や予後は持続性高血圧に比べると良好であるが，必ずしも無害とはいえない．

【仮面高血圧】 検診や診察室では正常血圧であるが，24時間血圧や家庭血圧は高い病態で，逆白衣高血圧ともいわれる．心血管リスクが高いことが示されている．

【二次性高血圧】 腎や副腎の疾患などに原因を有する高血圧であり，一部は適切な治療により治癒する．薬剤も原因となることがあり，交感神経系の刺激薬，ステロイドや非ステロイド性抗炎症薬，甘草を含む漢方薬などがあげられる．

【臓器障害】 高血圧による臓器障害には，心肥大，蛋白尿，眼底変化，頸動脈の肥厚やプラーク，無症候性脳血管病変などがある．臓器障害を伴う患者は高リスクとなる．

【生活習慣の修正（非薬物療法）】 食塩制限，野菜や果物の摂取，コレステロールと飽和脂肪の制限，減量，運動，アルコール制限，禁煙などが推奨される．基本的な治療法として，すべての高血圧患者に勧められる．

【降圧薬（薬物治療）】 カルシウム（Ca）拮抗薬，アンジオテンシンⅡ受容体拮抗薬（ARB），アンジオテンシン変換酵素（ACE）阻害薬，利尿薬，β遮断薬，α遮断薬が主要な降圧薬として用いられる．薬物治療により高血圧患者の予後は改善する．