早朝高血圧と降圧療法

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はじめに

近年，家庭自己血圧測定(HBP)や携帯型血圧測定装置による24時間自由行動下血圧測定(ABPM)の普及により，外来血圧だけでは評価が困難であった夜間血圧や早朝血圧の把握が可能になり，さらに米国合同委員会第7次報告(JNC-VII)[1)]や日本高血圧学会による高血圧治療ガイドライン(JSH2000)[2)]などの各種ガイドラインでその利用が推奨されるなど，臨床面での応用が期待されている。特に早朝高血圧[3~5)]，白衣高血圧[6)]，仮面高血圧[7,8)]などの診断と治療においては，HBPやABPMの利用が不可欠であり，そのうち早朝高血圧は，心筋梗塞，脳卒中などの脳心血管系事故の発生が起床後から数時間内に多発する[9~13)]ことから，臨床的意義が注目されている。

早朝高血圧の成因については，覚醒，起床に伴う交感神経系やレニン-アンジオテンシン系の賦活化や，圧受容体反射感受性の低下，加齢などに伴う動脈硬化，飲酒をはじめとする生活習慣などの関与が示唆されているが，一方，降圧薬による治療中の患者では，その降圧効果が十分持続しているか否かも重要な問題である。

そこで今回，われわれは家庭血圧を用いてカルシウム拮抗薬(以下，CCB)で治療中の本態性高血圧症患者を対象に，血中濃度半減期の異なるCCBについて，その早朝の血圧上昇度に及ぼす影響を分析し，降圧効果について検討した。さらに，短時間型CCBを長時間型のニルバジピン(ニバジール®)に変更し，その前後での血圧上昇度の変化についても検討した。

I 方 法

本調査は，1999年3月から2002年3月までの間にわれわれの施設に通院した高血圧症外来患者1689名のうち，家庭血圧を2ヵ月以上測定し，早朝の血圧変動の再現性を確認し得た本態性高血圧症患者84例を対象にした。**表1**に示す短時間作用型(血中濃度半減期が短いか，比較的長くても1日投与回数1回の薬剤)CCB(ニフェジピン徐放剤，マニジピンなど)で治療されている群(以下，短時間CCB群)，長時間作用型(血中濃度半減期が長いか，比較的短くても1日投与回数2回の薬剤)CCB(アムロジピン，ニルバジピン)で治療されている群(以下，長時間CCB群)，血圧以外のリスクが低く生活習慣修正のみによる治療をされている群(以下，非薬剤群)の3群間での早朝の血圧上昇度を比較検討した。家庭血圧については患者が起床時(起床直後，排尿後，食事・降圧薬服薬の前)，昼間(午前10時～午後4時)，就寝前(午後9時～午後12時)に測定し，記録した高血圧日誌を基に集計した。降圧療法については調査期間中を通して治療内容を変更しないこととした。

さらに短時間CCB群で短時間作用型CCBを

Key words：家庭血圧，早朝高血圧，Morning surge，カルシウム拮抗薬，ニルバジピン

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表1 Ca拮抗薬の血中濃度半減期と1日投与回数

作用型	一般名	主な薬剤名	血中濃度半減期 (hr)	1日投与回数
長時間	アムロジピン	アムロジン，ノルバスク	33～39	1回
	ニルバジピン	ニバジール	11	2回
短時間	ベニジピン	コニール	1～1.7	1回
	マニジピン	カルスロット	7.3	1回
	ニソルジピン	バイミカード	8.5～9.8	1回
	ニフェジピン徐放剤	アダラートL	3.5～3.7 [8.2]	2回
	ニフェジピン徐放剤	アダラートCR	－ [16]	1回
	シルニジピン	シナロング	2.1～2.5	1回
	ジルチアゼム	ヘルベッサー	約4.5	3回
	ジルチアゼム	ヘルベッサーR	約7	1回

[ ]：平均滞留時間　　(各社添付文書より)

長時間作用型のニルバジピンに変更した時の早朝の血圧上昇度を変更前後で比較検討した。家庭血圧については変更前，変更後ともに2ヵ月以上測定し，記録した高血圧日誌を基に集計した。

結果は平均値±標準偏差 (SD) で表し，検定は多群比較には分散分析を用い，それ以外では対応のあるt検定を用いた。すべての統計解析で$p < 0.05$を有意とした。

II 結　　果

1 3群での比較

1) 患者背景

表2に患者84例の臨床的背景を示す。患者数は，短時間CCB群49例(男性15例，女性34例，平均年齢61.9±8.5歳)，長時間CCB群20例(男性7例，女性13例，平均年齢61.4±11.6歳)，非薬剤群15例(男性4例，女性11例，平均年齢63.4±11.2歳)であった。診察時の血圧および脈拍数は，短時間CCB群で収縮期血圧(以下，SBP)/拡張期血圧 (以下，DBP) が141.6/83.6mmHg，脈拍数66.5/min，長時間CCB群でSBP/DBPが138.4/84.4mmHg，脈拍数64.9/min，非薬剤群でSBP/DBPが150.0/87.6mmHg，脈拍数66.2/minと非薬剤群で有意に血圧が高値であった。また尿中の食塩排泄量はそれぞれ短時間CCB群で9.2g/日，長時間CCB群で9.1g/日，非薬剤群で9.7g/日と非薬剤群で少し多い傾向であったが有意ではなかった。

使用されたCCBの内訳は，短時間CCB群でニフェジピン徐放剤17例，マニジピン15例，ベニジピン7例，ニソルジピン1例，シルニジピン1例，ジルチアゼム8例，長時間CCB群でアムロジピン16例，ニルバジピン4例であった。

併用された降圧薬の内訳は，利尿薬が短時間CCB群1例，長時間CCB群1例，ACE阻害薬がそれぞれ13例，5例，AII受容体拮抗薬がそれぞれ18例，6例，α遮断薬がそれぞれ15例，7例，β遮断薬がそれぞれ16例，5例であった。

合併症の内訳は，糖尿病が短時間CCB群5例，長時間CCB群1例，非薬剤群で0例，高脂血症がそれぞれ8例，5例，2例，心疾患がそれぞれ3例，0例，0例，脳血管障害がそれぞれ4例，4例，3例と非薬剤群で合併症が少なかった。

2) 家庭血圧値の推移

血圧値の日内変動を**表3**と**図1**に示す。短時間CCB群の家庭血圧の平均測定回数は621.2±439.7回(411.8±265.1日)で，その期間中に測定された家庭血圧のうち，起床時のSBP/DBPが147.1/87.7mmHg，昼間のSBP/DBPが135.6/80.6mmHg，就寝前のSBP/DBPが136.8/79.8mmHgであった。長時間CCB群の家庭血圧の平均測定回数は518.9±387.0回(327.2±230.2日)で，その期間中に測定された家庭血圧のうち，起床時のSBP/DBPが143.5/86.4mmHg，昼間のSBP/DBPが135.6/81.3mmHg，就寝前のSBP/DBPが133.9/79.8mmHgであった。非薬剤群の家庭血圧の平均測定回数は502.3±389.3回

表2　患者背景（群別）

		短時間 CCB 群	長時間 CCB 群	非薬剤群
患者数（男 / 女）（人）		49 (15/34)	20 (7/13)	15 (4/11)
年齢（歳）		61.9 ± 8.5	61.4 ± 11.6	63.4 ± 11.2
診察時収縮期血圧（mmHg）		141.6 ± 7.8	138.4 ± 10.4	150.0 ± 7.7 *
診察時拡張期血圧（mmHg）		83.6 ± 6.2	84.4 ± 4.9	87.6 ± 5.7 *
診察時脈拍（/min）		66.5 ± 4.1	64.9 ± 4.1	66.2 ± 3.2
尿中食塩排泄量（g/ 日）		9.2 ± 3.9	9.1 ± 3.2	9.7 ± 4.6
CCB 使用薬剤		ニフェジピン 17 マニジピン 15 ベニジピン 7 ニソルジピン 1 シルニジピン 1 ジルチアゼム 8	アムロジピン 16 ニルバジピン 4	
併用降圧薬	利尿薬	1 (2%)	1 (5%)	
	ACE 阻害薬	13 (27%)	5 (25%)	
	AII 受容体拮抗薬	18 (37%)	6 (30%)	
	α遮断薬	15 (31%)	7 (35%)	
	β遮断薬	16 (33%)	5 (25%)	
合併症	糖尿病	5 (10%)	1 (5%)	0
	高脂血症	8 (16%)	5 (25%)	2 (13%)
	心疾患	3 (6%)	0	0
	脳血管障害	4 (8%)	4 (20%)	3 (20%)
	その他		腎機能障害 1	

短時間 CCB 群との比較：ANOVA　*：$p < 0.05$

表3　家庭血圧値の日内変動

		短時間 CCB 群	長時間 CCB 群	非薬剤群
家庭血圧平均測定回数（回）		621.2 ± 439.7	518.9 ± 387.0	502.3 ± 389.3
家庭血圧平均測定日数（日）		411.8 ± 265.1	327.2 ± 230.2	403.2 ± 259.3
起床時血圧（mmHg）	SBP	147.1 ± 13.6 †	143.5 ± 10.2 *†	138.1 ± 10.3 *
	DBP	87.7 ± 10.2	86.4 ± 8.7	81.3 ± 7.5
昼間血圧（mmHg）	SBP	135.6 ± 10.4	135.6 ± 10.1	135.1 ± 8.9
	DBP	80.6 ± 10.1	81.3 ± 8.7	78.6 ± 7.7
就寝前血圧（mmHg）	SBP	136.8 ± 12.9	133.9 ± 7.8	133.7 ± 7.1
	DBP	79.8 ± 10.0	79.8 ± 9.1	75.4 ± 6.0

短時間 CCB 群との比較：ANOVA　*：$p < 0.05$
昼間血圧との比較：paired t-test　†：$p < 0.05$

（403.2 ± 259.3日）で，その期間中に測定された家庭血圧のうち，起床時のSBP/DBPが138.1/81.3mmHg，昼間のSBP/DBPが135.1/78.6mmHg，就寝前のSBP/DBPが133.7/75.4mmHgであった。起床時の血圧は短時間CCB群で他群に比して有意に高値であった。また短時間および長時間CCB群では起床時血圧は，昼間血圧に比して有意に高値であったが，非薬物群では差は認められなかった。

表4に早朝の血圧上昇度を，起床時と昼間と

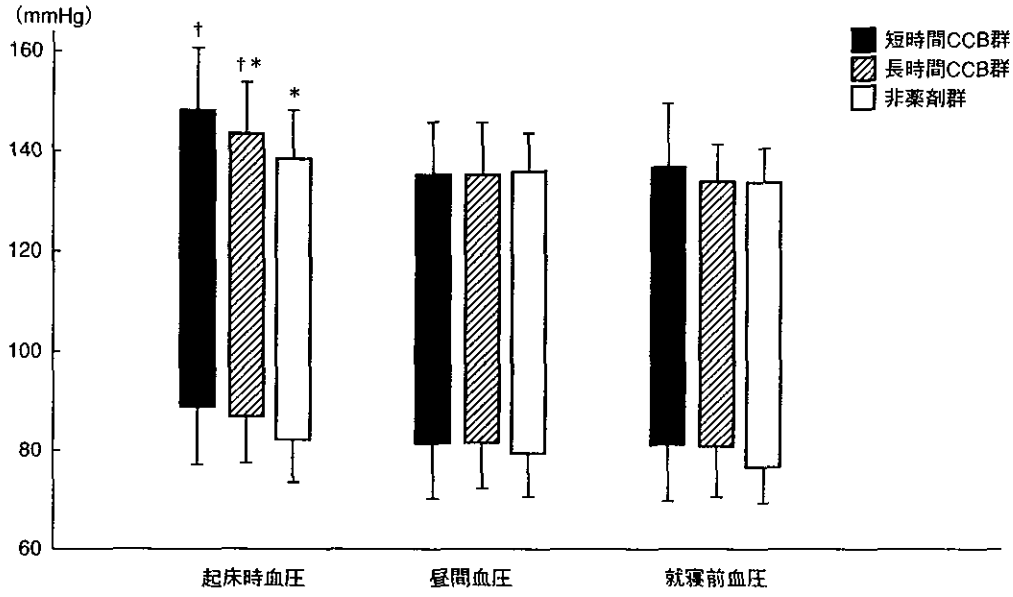

図1 家庭血圧値の推移（平均値±SD）
短時間CCB群との比較：ANOVA　*：$p < 0.05$
昼間血圧との比較：paired t-test　†：$p < 0.05$

表4 早朝の血圧上昇度

		短時間CCB群	長時間CCB群	非薬剤群
Δ起床時血圧－昼間血圧	SBP (mmHg)	12.7 ± 10.5	7.9 ± 11.6 *	2.4 ± 6.0 *
	DBP (mmHg)	7.9 ± 6.5	4.6 ± 5.9 *	2.8 ± 2.7 *
Δ起床時血圧－就寝前血圧	SBP (mmHg)	10.8 ± 10.5	8.2 ± 11.4	4.8 ± 4.8
	DBP (mmHg)	7.9 ± 6.3	5.9 ± 5.5	5.6 ± 3.2

短時間CCB群との比較：ANOVA　*：$p < 0.05$

の差で比較したものと就寝前との差で比較したものを示す。起床時と昼間との差での比較は，短時間CCB群でSBP/DBPが12.7±10.5/7.9±6.5mmHg，長時間CCB群でSBP/DBPが7.9±11.6/4.6±5.9mmHg，非薬剤群でSBP/DBPが2.4±6.0/2.8±2.7mmHgで，短時間CCB群のSBPおよびDBPの血圧上昇度は，他の2群に比し有意に大きかった。また起床時と就寝前との差での比較は，短時間CCB群でSBP/DBPが10.8±10.5/7.9±6.3mmHg，長時間CCB群でSBP/DBPが8.2±11.4/5.9±5.5mmHg，非薬剤群でSBP/DBPが4.8±4.8/5.6±3.2mmHgで，昼間との差と同様の傾向であったが，有意差は認められなかった。

2　短時間CCBからニルバジピンへの切り換え

1）患者背景

表5に登録患者22例の臨床的背景を示す。性別は男性10例（45.5%），女性12例（54.5%）であり，平均年齢は62.2±6.4歳であった。

使用されたCCBの内訳は，ニフェジピン徐放剤9例，マニジピン7例，ベニジピン3例，ニソルジピン1例，ジルチアゼム2例であった。

併用された降圧薬の内訳は，利尿薬は使用されず，ACE阻害薬が7例，AII受容体拮抗薬が8例，α遮断薬が6例，β遮断薬が7例であった。

合併症の内訳は，糖尿病が1例，高脂血症が3例，心疾患が1例，脳血管障害が2例であった。

表5　患者背景（Ca拮抗薬変更）

患者数（男／女）（人）	22（10/12）
年齢（歳）	62.2 ± 6.4
CCB使用薬剤	ニフェジピン 9
	マニジピン 7
	ベニジピン 3
	ニソルジピン 1
	ジルチアゼム 2
併用降圧薬	
利尿薬	0 (0%)
ACE阻害薬	7 (32%)
AII受容体拮抗薬	8 (36%)
α遮断薬	6 (27%)
β遮断薬	7 (32%)
合併症	
糖尿病	1 (5%)
高脂血症	3 (14%)
心疾患	1 (5%)
脳血管障害	2 (9%)
その他	0

表6　Ca拮抗薬変更による血圧の変化

		切り換え前	切り換え後
診察時収縮期血圧（mmHg）		141.7 ± 7.9	139.1 ± 9.7
診察時拡張期血圧（mmHg）		84.0 ± 5.8	82.6 ± 6.9
家庭血圧平均測定回数（回）		373.8 ± 344.8	302.8 ± 207.9
家庭血圧平均測定日数（日）		259.3 ± 236.4	182.1 ± 95.5
起床時血圧（mmHg）	SBP	148.9 ± 15.7	143.7 ± 11.1 *
	DBP	92.2 ± 11.0	89.3 ± 8.7 *
昼間血圧（mmHg）	SBP	133.4 ± 9.6	133.0 ± 8.9
	DBP	82.4 ± 9.3	81.3 ± 7.8
就寝前血圧（mmHg）	SBP	136.8 ± 15.5	135.4 ± 9.7
	DBP	82.3± 9.8	81.2 ± 7.7

切り換え前との比較：paired t-test　*：$p < 0.05$

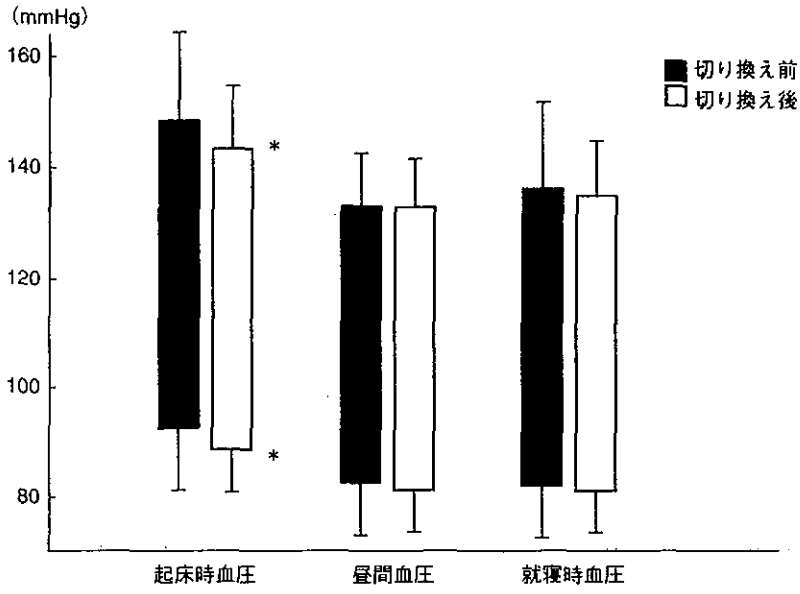

図2　Ca拮抗薬変更による血圧の変化（平均値± SD）
切り換え前との比較：paired t-test　*：$p < 0.05$

2）家庭血圧値の推移

血圧値の変化を**表6**と**図2**に示す。ニルバジピンに切り換え前の家庭血圧の平均測定回数は373.8 ± 344.8回（259.3 ± 236.4日）で，その期間中に測定された家庭血圧のうち，起床時のSBP/DBPが148.9/92.2mmHg，昼間のSBP/DBPが133.4/82.4mmHg，就寝前のSBP/DBPが136.8/82.3mmHgであった。ニルバジピンに切り換え

後の家庭血圧の平均測定回数は302.8±207.9回(182.1±95.5日)で，その期間中に測定された家庭血圧のうち，起床時のSBP/DBPが143.7/89.3mmHg，昼間のSBP/DBPが133.0/81.3mmHg，就寝前のSBP/DBPが135.4/81.2mmHgで，切り換え前に比べ起床時のSBP，DBPが有意に低下した。昼間血圧および就寝前血圧は，切り換え前後で変化しなかった。

III 考　　察

HBPやABPMの普及により，外来血圧は正常であるが，日常生活において高血圧を認めるケースが問題になっている。特に心筋梗塞[10]，狭心症[11]，突然死[12]，脳卒中[13]などの脳心血管系事故が早朝覚醒時から午前中にかけて多発するとの報告が多く，その原因の一つに早朝高血圧との関連が指摘されている。

早朝高血圧とは主として覚醒，起床などの一連の行動に伴って上昇した血圧が病的レベルに達した病態を示すが，睡眠中の血圧は正常でありながら起床に伴う急峻な血圧上昇(morning surge)のため高血圧を呈するタイプ(surge-type)と，夜間睡眠中からの高血圧が起床後にも持続するタイプ(sustained-type)が存在する。

早朝高血圧の診断に関してはいまだ一定の見解が得られておらず，測定法や報告によって異なっているのが現状である。

早朝高血圧の臨床的意義として，臓器障害との関連が示唆されており，桑島ら[14]はABPMを用いた検討で起床後の血圧上昇と左室壁厚，左室心筋重量係数等が有意に正の相関を示すことを報告している。今井ら[15]は一般地域住民を対象とした大迫研究において，朝夕の家庭血圧の差が10mmHg以上になると，心血管疾患のリスクが高くなることを明らかにしている。また苅尾ら[16]は高齢高血圧症患者519例を対象にABPMを用いて早朝高血圧と脳卒中との関連について検討を行い，起床後2時間のSBPの平均値と夜間最低SBPの前後1時間平均値の差が55mmHg以上をmorning surge群とした場合，morning surgeのない群と比較しmorning surge群で2.7倍脳卒中発生率が高くなること，また無症候性脳梗塞の頻度も有意に高いことを報告している。

早朝高血圧の成因として，起床に伴い交感神経系の緊張亢進とレニン-アンジオテンシン系の賦活化が行われ，カテコラミンおよびアンジオテンシンIIの血中濃度が上昇し，最終的に細胞内のfree Ca濃度が上昇することにより，心拍出量の増大と末梢血管の収縮が生じること，また起床すると心臓が相対的に高い位置となるため脳血流量を保つために血圧が上昇すると考えられている。さらに高齢者や高血圧症患者では，圧受容体機能の低下や大動脈のコンプライアンスの低下などにより血圧の短期変動性が増加しているために，血圧の上昇はより急峻となると考えられている。一方，降圧薬の治療中の患者では，降圧薬の効果が翌朝まで持続しないために朝の血圧が高くなっている可能性も考えられる。

大迫研究[17]によると，朝の家庭血圧が同時期に捉えられた昼間のABPMの平均値にくらべて10mmHg以上高い相対的早朝高血圧の頻度を調べると，このような対象は，無治療正常血圧者の5.6%に，無治療高血圧者の2.9%に認められている。ところが現在治療中の高血圧症患者では，その頻度は25.8%であった。また現在治療中の40歳以上の高血圧症患者で，朝の家庭血圧が135/85mmHg以上を呈するものは，49%と極めて高率であった[18]。またRedonら[19]によると，降圧薬服用中の高血圧症患者の外来血圧が良好にコントロールされている例でも約半数が早朝血圧のコントロールが不良であり，外来血圧のコントロールが不良な例では早朝血圧のコントロールが不良な例は70%以上あった。

今回，われわれはCCBの血中濃度半減期の違いが早朝の血圧にどのように影響するのかに注目し，まず家庭血圧を用いて本態性高血圧症患者を対象に，短時間CCB群，長時間CCB群，非薬剤群の3群間での起床時，昼間，就寝前の血圧較差を検討し，さらに短時間型のCCBから長時間型のCCBに変更し，起床時，昼間，就寝前の家庭血圧の変化を比較検討した。短時間型CCBからの切り換え時に使用した薬剤はニルバ

ジピンで，血中濃度半減期が比較的長く，また1日2回投与型であるため，ほぼ24時間均等に降圧を図れること，服薬後急速に降圧するのでなくゆっくりと降圧すること，薬理学的に血管選択性が高く，特に脳および冠動脈に対する作用が強く，また組織親和性も高いという特徴を有すること[20]から選択した。

本調査の結果，短時間CCB群では長時間CCB群，非薬剤群に比べて早朝血圧上昇(Δ起床時－昼間血圧)が有意に大きかった。また短時間CCB群のCCBをニルバジピンに切り換えると，昼間，就寝前の血圧は全く変化せず，起床時の血圧が有意に下降し，早朝血圧上昇が有意に減少した。この結果から早朝高血圧には降圧薬の薬物動態に起因する例があることが確認された。また非薬剤群で早朝血圧上昇が小さかったことは大迫研究[16]の報告を裏付けた。

日常診療においては，いまだ外来血圧のみで経過を観察しているケースは多い。実際その測定時間が朝服用した降圧薬の効果のピークである可能性もあり，24時間の血圧の推移を検討する必要がある。近年，早朝高血圧と同様に仮面高血圧（外来血圧140/90mmHg未満，ABPM 135/85mmHg以上）が予後増悪因子であるとの報告がある。Bjorklundら[21]は，「持続性高血圧(外来血圧140/90mmHg以上，ABPM 135/85mmHg以上)」「仮面高血圧」「正常血圧」の3群を平均5年追跡し，正常血圧群の心血管系事故発生率と比較したところ，持続性高血圧群と仮面高血圧群はいずれも有意に増加していたと報告している。またPickeringら[22]は，「正常血圧」「持続性高血圧」「白衣高血圧」「仮面高血圧」の4群を平均8.5年追跡し，正常血圧群と比較した心血管系事故の発生相対リスクは，白衣高血圧群では増加せず，持続性高血圧群では2.7と増加傾向にあり，仮面高血圧群では3.6と著明かつ有意に増加していたと報告している。

仮面高血圧や早朝高血圧を考える場合，降圧治療による血圧管理には注意が必要である。現在，ほとんどの降圧薬の投与回数は「1日1回型」であるが，実際には次の投与時間まで十分効果が持続しない場合がある。CCBを例にとってみても，**表1**に示すように同じ1日1回型でも実際の血中濃度半減期には差があり，また降圧薬の作用持続性には個人差もあるため，半減期の長い薬剤を使用しても朝の血圧がコントロールできない症例もある。

今回の結果で短期間CCB群が他の群に比べ早朝血圧の上昇が大きく認められたのは，短時間型のCCBが十分に作用を持続することができなかったためと考えられる。またそのことは今回のニルバジピンへの切り換えにより早朝血圧が下がったことでも裏付けられよう。すなわちHBPやABPMにより降圧薬の作用時間が足りないと判断される場合には，血中濃度半減期の長さや1日投与回数を考慮して降圧薬の種類や投与法を変更することで，24時間均等に降圧を図ることが望ましいと考えられる。また，降圧作用が緩徐に発現する薬剤を選択する必要があり，短時間型による急速な降圧は夜間の過降圧や心拍数を増加させるため，心保護の観点からも避けるべきである。

早朝高血圧の治療には，α遮断薬のように交感神経系を抑制する薬剤の有用性も指摘されているが[23]，組織反応の最終段階にかかわるCaイオン動態の異常を是正し得るCCBも極めて有用である。CCBは高い血圧には降圧効果を示すが，夜間など血圧が低く保たれている場合には降圧作用を示さない特徴を有しており[24,25]，早朝高血圧の治療に適した薬剤と考えられる。さらに，今回の成績のように薬物動態に留意した降圧薬や投与方法の選択を行うことにより，無症候性脳梗塞も含めた脳心血管系事故の発生減少につながれば降圧薬の有用性がさらに高まると考えられる。今後大規模な研究によりevidenceの集積が行われることを期待したい。

ま と め

カルシウム拮抗薬(以下，CCB)で治療中の本態性高血圧症患者のうち，家庭血圧を起床時，昼間，就寝前に測定している外来患者を対象に，CCBの血中濃度半減期の違いが早朝の血圧上昇度に及ぼす影響を分析した。さらに短時間型のCCBを長時間型のニルバジピン(ニバジール®)

に切り換え，その前後での血圧上昇度の変化についても検討し，以下の成績を得た。

1)早朝の血圧上昇度を起床時と昼間との差として比較すると，短時間型（血中濃度半減期が短いか，比較的長くても1日投与回数1回の薬剤)CCBで治療されている群(以下，短時間CCB群）でSBP/DBPが12.7±10.5/7.9±6.5mmHg，長時間型（血中濃度半減期が長いか，比較的短くても1日投与回数2回の薬剤)CCBで治療されている群(以下，長時間CCB群）でSBP/DBPが7.9±11.6/4.6±5.9mmHg，血圧以外のリスクが低く生活習慣修正のみによる治療をされている群(以下，非薬剤群）でSBP/DBPが2.4±6.0/2.8±2.7mmHgで，短時間CCB群のSBP，DBPの血圧上昇度は，各群に比し有意に大きかった。

また早朝の血圧上昇度を起床時と就寝前との差で比較すると，短時間CCB群でSBP/DBPが10.8±10.5/7.9±6.3mmHg，長時間CCB群でSBP/DBPが8.2±11.4/5.9±5.5mmHg，非薬剤群でSBP/DBPが4.8±4.8/5.6±3.2mmHgで，昼間との差と同様に短時間CCB群の血圧上昇度は，各群に比し大きかった。

2)ニルバジピンに切り換え前に測定された家庭血圧は，起床時のSBP/DBPが148.9/92.2mmHg，昼間のSBP/DBPが133.4/82.4mmHg，就寝前のSBP/DBPが136.8/82.3mmHgであった。ニルバジピンに切り換え後に測定された家庭血圧は，起床時のSBP/DBPが143.7/89.3mmHg，昼間のSBP/DBPが133.0/81.3mmHg，就寝前のSBP/DBPが135.4/81.2mmHgで，切り換え前に比べ，昼間や就寝前の血圧は変化しなかったが，起床時の血圧はSBP，DBPともに有意に低下した。

以上の結果より，早朝の血圧上昇には降圧薬の薬物動態に起因する例があることが示され，薬物動態に留意した降圧薬や投与方法の選択を行うことが重要であると思われた。

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Morning Hypertension and Antihypertensive Therapy

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We studied how a difference in plasma half-life of calcium channel blockers (CCBs) affects the elevation of blood pressure in the early morning. In this study, we analyzed the data of outpatients under treatment of essential hypertension with CCB, who measured their blood pressures at home at wake–up time, during the day and before going to bed. In those who received a CCB with short–lasting actions, we changed it to nilvadipine (Nivadil®) , a CCB with long–lasting actions to evaluate changes in blood pressure elevation before and after the change. Results are shown below.

Blood pressure elevation in the early morning was evaluated by comparing the blood pressure values at wake–up time and those during the day. In the evaluation, we categorized the subjects into the following three groups: short–lasting CCB group; those treated

with a CCB with a short plasma half-life or a CCB with a once-daily regimen at longest; long-lasting CCB group; the subjects treated with a CCB with a long plasma half-life or a CCB with a twice-daily regimen at shortest; and non-medication group; those with no serious health risks other than blood pressure and treated only by lifestyle modification. As a result of the evaluation, SBP/DBP in the short-lasting CCB group was 12.7±10.5/7.9±6.5 mmHg, SBP/DBP in the long-lasting CCB group was 7.9 ± 11.6/4.6 ± 5.9 mmHg, and SBP/DBP in the non-medication group was 2.4 ± 6.0/2.8 ± 2.7 mmHg. The blood pressure elevation of SBP and DBP in the short-lasting CCB group was significantly greater than that in the other groups.

We also evaluated blood pressure elevation in the early morning by comparing the blood pressure values at wake-up time and those before going to bed. As a result, SBP/DBP in the short-lasting CCB group was 10.8 ± 10.5/7.9 ± 6.3 mmHg, SBP/DBP in the long-lasting CCB group was 8.2 ± 11.4/5.9 ± 5.5 mmHg, and SBP/DBP in the non-medication group was 4.8±4.8/5.6±3.2 mmHg. As can be seen in the differences between the wake-up time and daytime, the blood pressure elevation in the short-lasting CCB group was greater than that in the other two groups.

The blood pressure values measured at home before a change into nilvadipine were as follows: SBP/DBP at wake-up time was 148.9/92.2 mmHg, SBP/DBP during the day was 133.4/82.4 mmHg, and SBP/DBP before going to bed was 136.8/82.3 mmHg. Those after the change were as follows: SBP/DBP at wake-up time was 143.7/89.3 mmHg, SBP/DBP during the day was 133.0/81.3 mmHg, and SBP/DBP before going to bed was 135.4/81.2 mmHg. Although no changes were observed in the blood pressures during the day and before going to bed, both SBP and DBP at wake-up time were lowered significantly.

The results stated above indicate that blood pressure elevation in the early morning is, in some cases, caused by pharmacokinetics of an antihypertensive drug. We have therefore concluded that it is important to take pharmacokinetics into consideration in selecting an antihypertensive drug and administration method.

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Pulse Pressure Is an Independent Predictor for the Progression of Aortic Wall Calcification in Patients With Controlled Hyperlipidemia

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Abstract—Recent epidemiological studies suggested that calcifications of the aorta and the coronary arteries are important predictors for cardiovascular morbidity and mortality. However, the relation between blood pressure components and the progression of vascular wall calcification has remained unclear. We quantified calcium deposits in the abdominal aorta as the percentage of aortic calcification volume (%ACV) using computed tomography in patients with hyperlipidemia. Those who had aortic calcification were treated with lipid-lowering agents and followed-up for >2 years (6.3±3.2 years). The relationship between the components of blood pressure and the increase in %ACV per year (Δ%ACV/year) was assessed in subjects in whom serum lipid levels were well controlled during the follow-up periods. An age- and sex-adjusted correlation analysis showed that Δ%ACV/year was significantly correlated to body mass index (r=0.229, P=0.015), systolic blood pressure (r=0.244, P=0.009), and pulse pressure (r=0.359, P<0.001). A multivariate regression analysis revealed that pulse pressure is an independent and the most sensitive predictor for Δ%ACV/year (β=0.389, P<0.001) among the blood pressure components. These results suggested that increase in pulse pressure promotes the progression of vascular calcification. (***Hypertension.* 2004;43:536-540.**)

Key Words: hypertension ■ calcium ■ aorta ■ pulse ■ imaging ■ risk factors

Calcification in the aorta and coronary arteries is a strong predictor for cardiovascular morbidity and mortality.[1,2] Previous studies have shown the close relationships between arterial wall calcification and abnormal serum lipid levels. Arterial wall calcification is common in patients with familial hypercholesterolemia, a genetic disorder of cholesterol metabolism.[3-5] Several studies have identified the relationship between the serum level of low-density lipoprotein cholesterol (LDL-C) and arterial wall calcification; moreover, lipid-lowering therapy using 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors has been reported to inhibit the progression of arterial wall calcification.[6,7] In patients receiving long-term hemodialysis, elevated serum triglyceride (TG) levels and reduced high-density lipoprotein cholesterol (HDL-C) levels are risk factors for coronary artery calcification.[8] These studies suggested that abnormal serum lipid levels promote calcium deposition in the arterial wall.

Several studies have examined the influence of hypertension on the progression of arterial wall calcification. In these studies, antihypertensive therapy has been shown to inhibit the formation of calcified lesions, suggesting that hypertension promotes calcium deposition in the arterial wall.[9-11] However, it remains undetermined which blood pressure (BP) component, ie, systolic BP (SBP), diastolic BP (DBP), mean BP (MBP), or pulse pressure (PP) is responsible for the accelerated formation of calcification, probably because the abnormal serum lipid levels may have made it difficult to assess the effect of BP alone on the formation of calcified lesions.

Computed tomography (CT) is a useful tool to evaluate the level of arterial wall calcification. Most of the previous studies used the "calcium score" determined by CT as a semiquantitative index of calcification of the aorta or coronary arteries.[3-7] However, the calcium score may not accurately reflect subtle changes in calcium deposit levels. To accurately quantify the degree of calcium deposition, we developed an image color analysis software program that can automatically determine the percentages of calcified volume against whole vascular volume (%ACV) using plain CT.[9] We previously reported a strong correlation between %ACV and aortic calcification dimension in aortas of autopsy specimens, the latter of which was determined using soft X-ray photographs.[12]

In the present study, using our method, we studied the relationship between the BP components and the progression of aortic wall calcification. To exclude interference by serum lipid levels, only subjects whose lipid levels were well controlled during the follow-up periods were analyzed.

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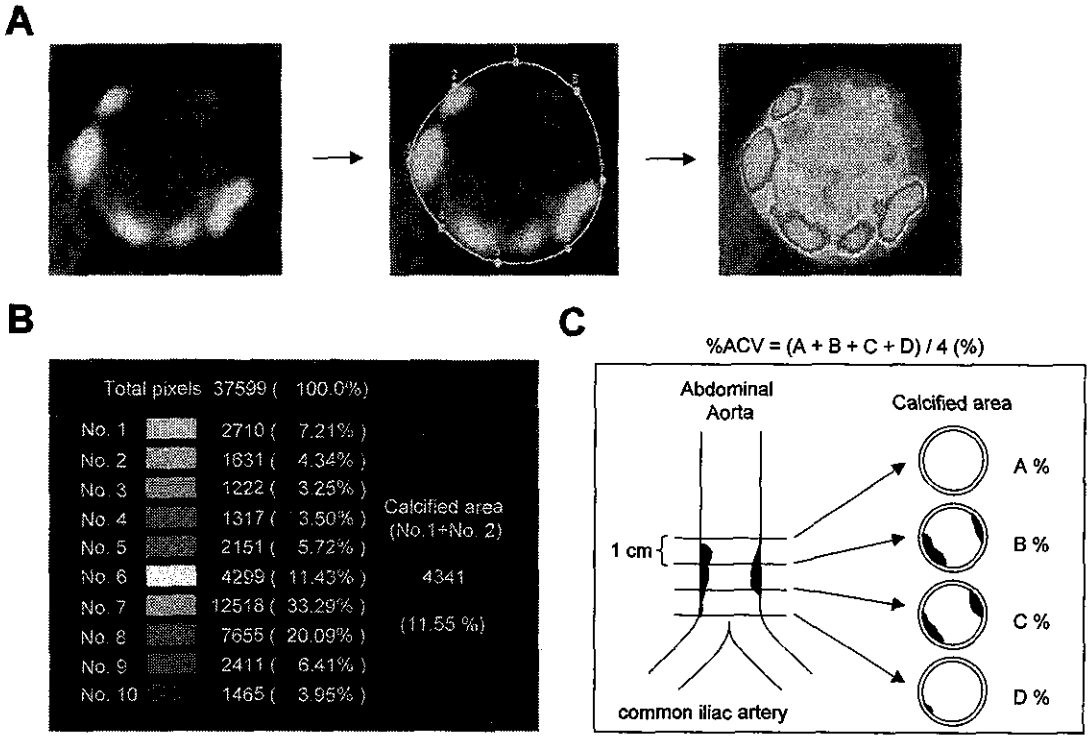

Figure 1. The method to determine %ACV. A, When an observer circles the abdominal aorta, the software program (TES-100 image color analysis software program) transforms the monochrome contrast image into a color image. B, The software automatically calculates the percentage of calcified area from pixel numbers. C, %ACV was calculated as an average value of 4 slices just above the bifurcation.

Methods

Subjects

This prospective cohort study was started in April 1988 at the National Cardiovascular Center (Suita, Japan). Recruitment of the subjects was closed in March 1999 and the follow-up ended in April 2001. We obtained informed consent to join this study from asymptomatic patients with untreated hyperlipidemia (serum total cholesterol [TC] levels >5.72 mmol/L or serum TG levels >1.70 mmol/L). Patients with severe hyperlipidemia (TC >9.10 mmol/L or TG >5.65 mmol/L), genetic disorders in lipid metabolism such as familial hypercholesterolemia, severe diabetes mellitus (HbA1c >7.0%), secondary hypertension, renal insufficiency, and abdominal aortic aneurysm were excluded from the analysis. Those using warfarin were also excluded. They were subjected to lipid-lowering therapy and followed until 2001. Simultaneously, we started antihypertensive therapy in all subjects with untreated hypertension. To subjects already using antihypertensive agents, we re-administered the drugs after a washout period of at least 1 month.

Four hundred eight patients agreed to join the study. They were subjected to a plain CT examination, and aortic wall calcification was found in 204 subjects. During the study, 2 subjects died of cerebral infarction, 16 subjects chose to discontinue their participation in the study, and serum lipid levels could not be well controlled in 70 subjects. Finally, 116 subjects (74 men and 42 women) who achieved optimal serum lipid levels (whose average TC and TG concentrations through the follow-up periods were <5.72 and 1.70 mmol/L, respectively) entered into the present study.

Calculation of %ACV and Δ%ACV/Year

We conducted plain CT at the first examination and every 6 months thereafter during follow-up periods for >2 years. The lower abdominal aortas of subjects in the supine position were scanned for 9.6 seconds at 120 kV and 200 to 250 mA at 10-mm intervals using a CT/T 2-8800 (GE Company, Milwaukee, Wisc). The percentages of calcified areas against the whole vascular area were calculated from images of 4 consecutive slices just above the bifurcation of common iliac arteries using the TES-100 image color analysis software program as described.

As shown in Figure 1A, when an observer traced the edge of the aorta after placing CT images into the computer system, this software transformed the monochrome CT image into a color image indicating the levels of density with 10 different colors. We considered the areas with 2 yellow colors (Figure 1B, No.1 and No. 2) to be calcified. The percentage of the sum of these areas against the whole area was automatically calculated by the software program; %ACV was determined by averaging the values of the 4 slices (Figure 1C).

To assess the reproducibility of %ACV measurements, paired examinations were performed by a single observer on 2 different occasions (intraobserver reproducibility) and by two observers on the same occasion (interobserver reproducibility) in a group of 50 subjects. The intraobserver and interobserver coefficients of variation were 4.4% and 5.1%, respectively.

Two independent masked observers determined the level of %ACV. The rate of progression of %ACV was represented by Δ%ACV/year calculated with the following formula: (%ACV at the end of follow-up−%ACV at the baseline)/follow-up period (year).

Clinical Parameters

We evaluated several clinical parameters at the first examination and every 6 months thereafter during follow-up periods for more than 2 years. In each examination, we measured BP, fasting serum lipid levels (TC, LDL-C, HDL-C, and TG), fasting plasma glucose (FPG), and %ACV. The measurements were performed in the morning after an overnight fast. BP was measured after 15 minutes of quiet rest in the supported right arm of the seated subjects with a mercury sphygmomanometer cuff-size adjusted for arm circumferences. Phases I and V of the Korotkoff sounds were considered SBP and DBP, respectively. PP and MBP were calculated with the following formula: PP=SBP−DBP and MBP=DBP+PP/3. Three measure-

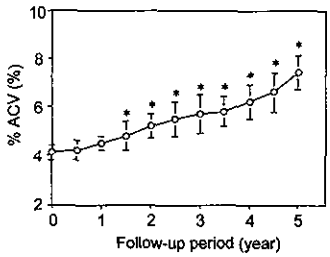

Figure 2. In 50 randomly selected subjects, %ACV values determined every 6 months were plotted. Error bars indicate the standard deviations. *$P<0.05$ against the baseline (time 0).

ments performed with intervals for more than 2 minutes were averaged. Hypertension was defined as: (1) current use of antihypertensive agents and/or a history of hypertension; (2) SBP≥140 mm Hg; or (3) DBP≥90 mm Hg. During follow-up periods for more than 2 years, we examined BP, lipid levels, and FPG every 6 months. TC, HDL-C, and TG levels were enzymatically determined using an autoanalyzer. The levels of LDL-C were calculated using Friedewald equation. The concentration of FPG was measured by the glucose oxidase method.

Statistical Analyses

In the present study, we used the values of clinical parameters obtained at the first examination after starting treatment as baseline values. To compare the mean values of %ACV, analysis of covariance was used. When a significant difference was obtained by analysis of variance, the differences among groups were assessed by Scheffe test. In a simple regression analysis, Pearson correlation coefficients were used for continuous variables and Spearman correlation coefficients were used for categorical variables. Age- and, sex-adjusted, and multivariate-adjusted correlations were analyzed by multiple regression models. In a multivariate-adjusted analysis, age, sex, BMI, HDL-C, LDL-C, TG, FPG, habitual smoking (yes=1, no= 0), antihypertensive treatment (yes=1, no=0), and follow-up period were entered into the model. Values were represented as means±SD; $P<0.05$ was considered statistically significant. Statistical analyses were performed with Stat View Version 5.0 (SAS Institute Inc, Cary, NC).

Results

First, to confirm that our method is able to evaluate the progression of aortic calcification, we analyzed the change of %ACV during follow-up for 5 years in 50 randomly selected subjects. As shown in Figure 2, %ACV significantly increased at 1.5 or more years after the baseline examination. The increase in %ACV was almost linear. Therefore, we considered Δ%ACV/year as a marker of the progression of calcification in subjects whom we could follow-up for >2 years in the present study.

Table 1 shows the characteristics of the subjects at the baseline (first examination after the beginning of the treatment). Their ages ranged from 43 to 75 years. The mean value of basal %ACV was 5.0%. The mean follow-up period was 6.3 years. %ACV decreased in 12 subjects and increased in 103 subjects when the study was completed.

To determine clinical parameters that influence the progression of aortic wall calcification, we analyzed the relationships between the conventional risk factors for atherosclerosis and Δ%ACV/year. In a simple correlation analysis, Δ%ACV/year was significantly correlated with age, BMI, SBP, and PP (Table 2). The lipid levels, FPG, habitual smoking, and the use of HMG-CoA reductase inhibitors showed no significant relationships with Δ%ACV/year. In an age- and sex-adjusted correlation analysis, BMI, SBP, and PP showed significant correlations with Δ%ACV/year. When the subjects were divided into 3 groups according to the levels of PP, age-adjusted and sex-adjusted Δ%ACV/year was significantly elevated in the high PP (≥60 mm Hg) group compared with the moderate PP (50≤PP<60 mm Hg) and low PP (<50 mm Hg) groups (Figure 3). Furthermore, by a multivariate regression analysis including age, sex, BMI, HDL-C, LDL-C, TG, FPG, habitual smoking, antihypertensive treatment, and follow-up period, PP was revealed to be the strongest risk factor for the progression of aortic wall calcification, whereas DBP and MBP were not detected as a predictive factor (Table 3).

TABLE 1. Baseline Characteristics of the Subjects

N (men/women)	116 (74/42)
Age (years)	57.4±8.3
BMI (kg/m^2)	24.0±2.2
SBP (mm Hg)	132.1±14.4
DBP (mm Hg)	77.4±9.1
MBP (mm Hg)	95.6±10.3
PP (mm Hg)	54.8±9.3
TC (mmol/L)	5.44±0.28
HDL-C (mmol/L)	1.26±0.36
LDL-C (mmol/L)	3.52±0.47
TG (mmol/L)	1.41±0.40
FPG (mmol/L)	5.48±0.74
%ACV (%)	5.0±4.4
Habitual smoking (%)	44.8
Hypertension (%)	62.9
Lipid-lowering drug	
HMG-CoA reductase inhibitors (%)	79.3
Probucol (%)	31.9
Fibrates (%)	21.6
Antihypertensive drug	
ACEIs (%)	14.7
CCBs (%)	35.3
BBs (%)	17.2
Others (%)	5.2
N of antihypertensive drug	
0 (%)	37.1
1 (%)	55.2
2 (%)	6.0
≥3 (%)	1.7

Values are the mean±SD or frequencies.

Discussion

To our knowledge, this is the first prospective study revealing that PP is an independent risk factor for the progression of arterial wall calcification in patients with controlled hyperlipidemia to exclude the influence of abnormal lipid levels.

In general, SBP progressively increases while DBP decreases in humans older than 50 years, resulting in the

TABLE 2. Correlation Coefficients Relating to Δ%ACV/year

	Simple Correlation		Age- and Sex-Adjusted Correlation	
Risk Factors	*r*	*P* Value	β	*P* Value
Age	0.206	0.026	...	...
Sex	0.117	0.209	...	...
BMI	0.196	0.035	0.229	0.015
SBP	0.274	0.003	0.244	0.009
DBP	0.032	0.736	0.044	0.640
MBP	0.147	0.116	0.136	0.144
PP	0.392	<0.001	0.359	<0.001
TC	0.040	0.673	0.004	0.969
HDL-C	−0.022	0.812	−0.084	0.387
LDL-C	0.010	0.913	0.031	0.737
TG	0.080	0.394	0.103	0.303
FPG	0.024	0.803	0.047	0.619
Smoking habit (yes/no)	−0.075	0.425	−0.024	0.806
HMG-CoA reductase inhibitor (yes/no)	−0.045	0.633	−0.042	0.648

increase in PP. This change is thought to be caused by the remodeling of arterial walls resulting from the decrease in wall elasticity, for which vascular calcification is one of the major factors. In the present follow-up study, the multivariate regression analysis showed that PP was the strongest risk factor for the increase in %ACV/year. To take into account the interim measures every 6 months during the follow-up periods, we also assessed predictors for the increase in %ACV by the pooling of repeated observation method.[13,14] By using this method, PP was again detected as the strongest predictor for %ACV increase (data not shown). These results suggest that the increase in PP on its own promotes arterial calcification.

Previous studies reported a difference between genders in the frequency of vascular calcification. In a cohort study in a large population of >100 000, the prevalence of aortic calcification detected with a chest x-ray examination did not

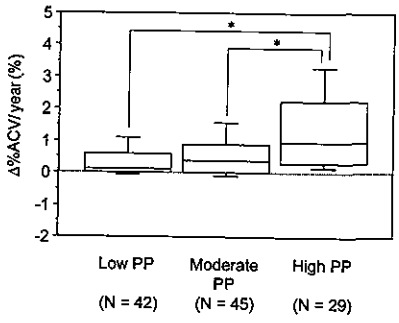

Figure 3. The levels of Δ%ACV/year in the 3 groups divided by PP. Low PP group indicates PP<50 mm Hg; moderate PP group, 50 mm Hg≤PP<60 mm Hg; high PP, PP≥60 mm Hg. The central line represents the distribution median, and the boxes span from the 25th to 75th percentile. Error bars indicate the 95% confidence interval. Statistical significances between the groups were evaluated by age-adjusted and sex-adjusted analysis of variance. *$P<0.01$.

TABLE 3. Multivariate Regression Coefficients Relating to Δ%ACV/year

	r	β	*P* Value
SBP	0.381	0.293	0.008
DBP	0.295	0.059	0.577
MBP	0.324	0.166	0.124
PP	0.436	0.389	<0.001

Multivariate regression analysis including age, sex, BMI, HDL-C, LDL-C, TG, FPG, habitual smoking, antihypertensive treatment, and follow-up period.

differ between men and women before middle age. However, in subjects older than 65 years, the frequency was significantly larger in women than in men.[15] One of the reasons for this difference was considered to be the change in hormone levels after menopause in women. The decrease in estrogen concentrations is associated with the increase in LDL-C levels and induces vascular calcification; furthermore, hormone replacement therapy suppresses the progression of aortic calcification in women after menopause.[16–18] However, in our population, there was no significant gender difference in Δ%ACV/year (Table 2), probably because most of our subjects were middle-aged and the lipid profiles were controlled.

The calcified lesions we analyzed in the present study were only atherosclerosis-related. There are 2 distinct forms of arterial wall calcification.[19] One is an intimal calcification that develops as part of an atherosclerotic plaque, and the other is a medial calcification formed with aging and in patients with diabetes, end-stage renal disease, neuropathy, and a number of rare genetic disorders. Most previous studies did not discriminate between them, although the volume of vascular calcification has been reported to be proportional to that of whole atheromatous plaques including calcification.[20,21] However, we excluded patients who had diseases that would promote the medial calcification, and almost all of the calcium deposits found with CT were located in the intima in our subjects. Therefore, our results may be inapplicable to the medial calcification.

Our study has several limitations. First, although ≈80% of the subjects were administered HMG-CoA reductase inhibitors, the other classes of lipid-lowering drugs such as probucol and fibrates were also used. HMG-CoA reductase inhibitors[22] and probucol[23,24] have been reported to have pleiotropic effects besides cholesterol-lowering effects in recent studies. In our subjects, however, this lack of uniformity may not have affected the analysis because there was no significant difference in Δ%ACV/year among lipid-lowering agents in a simple correlation analysis (Table 2). Second, BP was measured only in the office. Therefore, other factors such as the white-coat effect may have influenced the BP.

In conclusion, we demonstrated that PP is an independent predictor for the progression of atherosclerotic calcification in lipid-controlled subjects. Our results suggested that an increase in PP is not only a result of vascular wall stiffening but also an accelerator of vascular calcification. These results support, in part, the strong correlation between PP and cardiovascular morbidity and mortality.

Acknowledgments

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Original Article

Effects of Repeated Alcohol Intake on Blood Pressure and Sodium Balance in Japanese Males with Hypertension

Yuhei KAWANO, Hitoshi ABE, Shunichi KOJIMA, Shuichi TAKISHITA, and Hiroaki MATSUOKA

Alcohol consumption causes biphasic changes in blood pressure (BP) in Asians. The aim of the present study was to investigate the effects of repeated alcohol intake on BP and sodium metabolism. Fourteen Japanese males with hypertension (37–67 years old) were examined under standardized conditions (Na intake 120 mmol/day). After 1 week of alcohol restriction, the patients consumed a control drink with dinner for 3 days, 1 ml/kg of alcohol for the next 7 days, then the control drink for 3 days. Supine BP and heart rate were measured 5 times daily, and urinary excretion of water and sodium was determined throughout the study period. Average BP decreased initially, then returned to the baseline level during the alcohol period. Evening BP decreased significantly throughout the alcohol period, although the reduction was attenuated during the late phase. Morning and afternoon BP did not change significantly, but tended to be elevated during the late phase. Heart rate increased both in the morning and evening during the alcohol period. Urine volume did not change during the early phase, but increased significantly during the late phase. Urinary sodium excretion decreased initially, but increased during the middle phase of the alcohol period. In conclusion, BP decreases initially with sodium retention, then returns to the baseline level with restoration of sodium balance during repeated alcohol intake in Japanese males with hypertension. Sodium retention during the early phase appears to be the consequence of BP reduction and may contribute to the subsequent changes in BP. (*Hypertens Res* 2004; 27: 167–172)

***Key Words*: alcohol, hypertension, blood pressure, sodium, natriuresis**

Introduction

The relation between alcohol consumption and hypertension is well known (*1*, *2*), and restriction of alcohol intake is recommended in the management of hypertension (*3*). Although the pressor effect of alcohol has been well documented (*1*, *2*, *4–6*), ethanol has both vasoconstrictive and vasodilatory actions, and a metabolite of ethanol acetaldehyde dilates blood vessels (*7*). We reported previously that a single intake of alcohol lowers blood pressure (BP) for several hours, while repeated alcohol consumption causes biphasic changes in the BP of Japanese males with hypertension (*8–10*). It is also known that cessation of drinking sometimes causes alcohol withdrawal syndrome, which includes transient BP elevation and tachycardia (*11*). These effects of alcohol appear to be dependent on the duration and amount of consumption, the time from the last drinking, and the presence or absence of alcohol flush, which is common in Asians (*12*, *13*). However, the time-related changes in BP caused by alcohol consumption and its withdrawal have not been clarified precisely.

It has been reported that alcohol has effects on water and electrolyte metabolism, such as diuresis due to the suppres-

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sion of vasopressin release and increases in urinary excretion of magnesium and calcium (*14–16*). We observed previously that ingestion of alcohol decreased the serum potassium level and intracellular sodium concentration in hypertensive subjects (*17*). It has also been reported that alcohol acutely reduces urinary sodium excretion (*14*, *18*, *19*). This effect of alcohol may be involved in alcohol-induced hypertension, since sodium balance plays an important role in BP regulation and hypertension. However, there have been no studies investigating the effects of repeated alcohol consumption on sodium balance with reference to changes in BP.

In the present study, we examined the effects of repeated intake of alcohol and its withdrawal on BP and sodium and water metabolism in Japanese males with essential hypertension. To investigate the effects of alcohol on BP in detail, BP was measured 5 times per day from early morning to late evening throughout the study period under standardized conditions.

Methods

Subjects

Fourteen Japanese males with essential hypertension and drinking habits were studied. Their ages were 37–68 years old (54±2 years, mean±SEM), and average height and weight were 168±1 cm and 67±1 kg, respectively. The amount of their usual alcohol intake ranged from 30–105 ml/day (67±5 ml/day). All patients were diagnosed as having mild to moderate essential hypertension and none of them had serious cardiovascular, hepatic, or renal disorders. Two patients were never treated, and the other 12 patients were treated with antihypertensive drugs before the present study.

Protocol

The study protocol was approved by the Ethics Committee of the National Cardiovascular Center, and informed consent was obtained from each subject. All subjects abstained from alcoholic drinks and stopped antihypertensive medications for at least 1 week before the study. Subjects were hospitalized in a ward of the National Cardiovascular Center where they ate a regular hospital diet (Na 120 mmol/day, 1,600 kcal/day). Before entering the protocol, subjects stayed in the ward for several days to minimize the effect of hospitalization on BP during the study protocol.

The study was divided into three consecutive phases: Control phase—a 3-day period during which nonalcoholic drinks having the same number of calories as the alcoholic drinks were added to the dinners (17:00–18:00); Alcohol phase—a 7-day period during which 1 ml/kg of ethanol was administered with dinner, in the form of vodka, lime juice and water; Recovery phase—a 3-day period during which the nonalcoholic drinks were added to dinners. Additional water intake was not restricted throughout the study protocol.

Supine BP was measured using mercury sphygmomanometers at 6:00, 10:00, 14:00, 18:00 and 21:00 by trained nurses throughout the study period. Heart rate was measured manually immediately before the BP measurements. Urine collections for 24 h and measurements of fasting body weight were also carried out each day. Venous blood samplings were performed before dinner (17:00), 60–90 min after dinner (19:00), and before breakfast (8:00) on the morning following the last day of the control period and on Days 1 and 7 of the alcohol period.

Biochemical Measurements

Serum electrolytes and urinary excretion of sodium, potassium and creatinine were determined using a biochemical analysis system (TBA-80S; Toshiba, Tokyo, Japan).

Statistical Analysis

Values are expressed as the mean±1 SEM. Comparisons were made by repeated measures analysis of variance followed by the contrast method. Analyses were performed using Stat View (ver. 5) and Super ANOVA software (Abacus Concept Inc., Berkeley, USA). A p value of less than 0.05

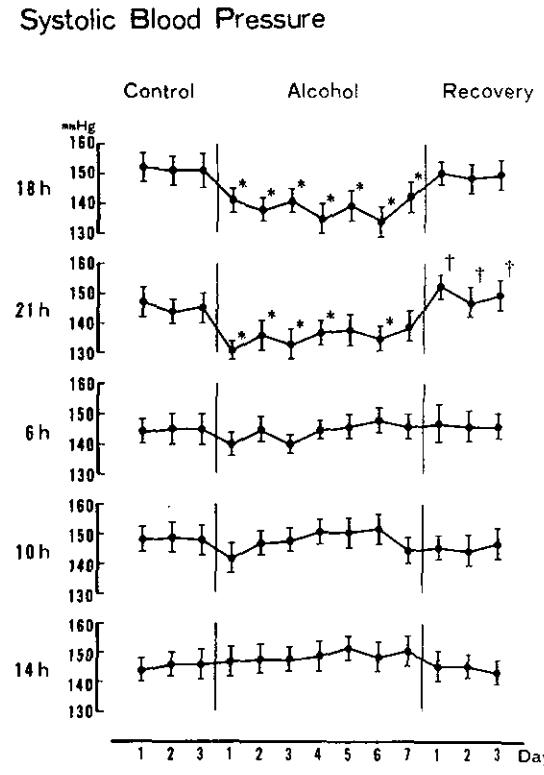

Fig. 1. *Systolic blood pressure at 5 different time points during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

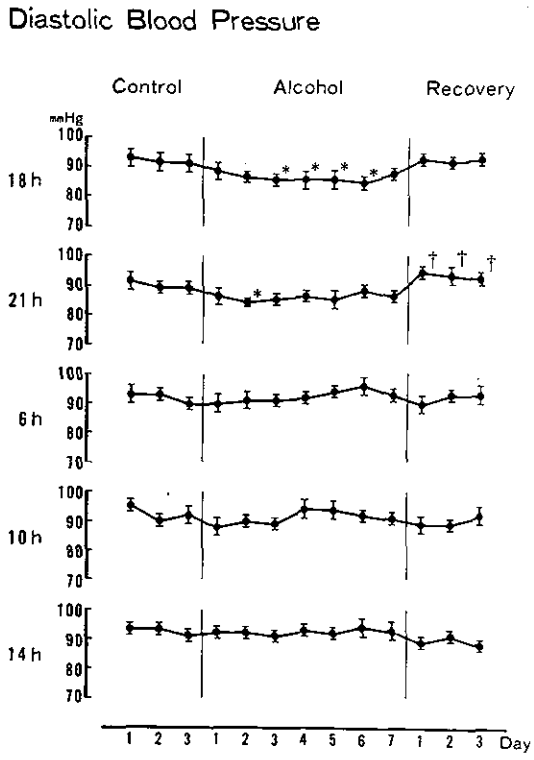

Fig. 2. *Diastolic blood pressure at 5 different time points during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

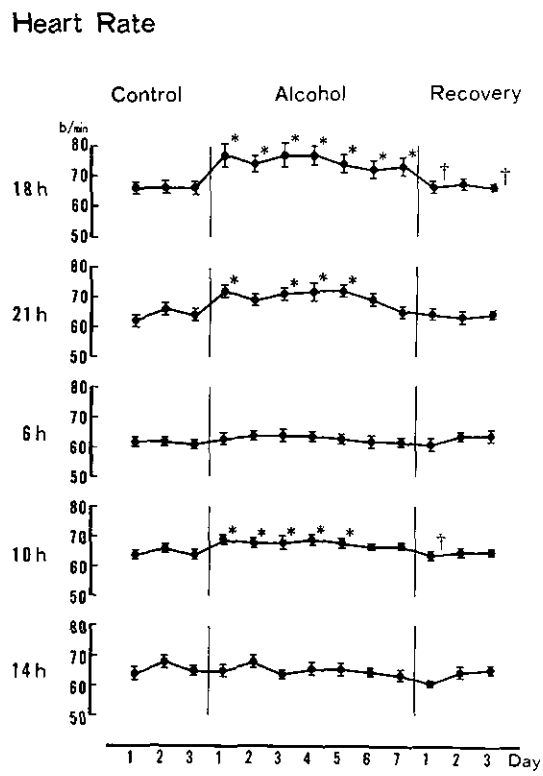

Fig. 3. *Heart rate at 5 different time points during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

was considered statistically significant.

Results

Blood pressure and heart rate at different times of the day during the control, alcohol and recovery periods are shown in Figs. 1–3. Evening BP during the alcohol period was consistently lower than that during the control period (systolic BP at 21:00 was 145.4±4.9 mmHg on the last day of the control period, and 130.7±3.2 mmHg on Day 1 of the alcohol period). Morning and afternoon BPs did not change during the alcohol period, although they tended to increase during the late phase (systolic BP at 14:00 was 146.1±6.2 mmHg on the last day of the control period, and 151.8±4.9 mmHg on Day 7 of the alcohol period). These changes in BP returned to the control level during the recovery period. Heart rate increased significantly both in the morning and evening during the alcohol period, although these changes were attenuated during the late phase. The increases in heart rate returned to baseline during the recovery period.

Daily average BP and heart rate are shown in Fig. 4. Systolic BP decreased significantly during the early phase of the alcohol period (Day 1: 140.2±3.2 mmHg) compared with the control period (147.2±4.7 mmHg); however, the reduction was blunted during the late phase (Day 7: 144.7±

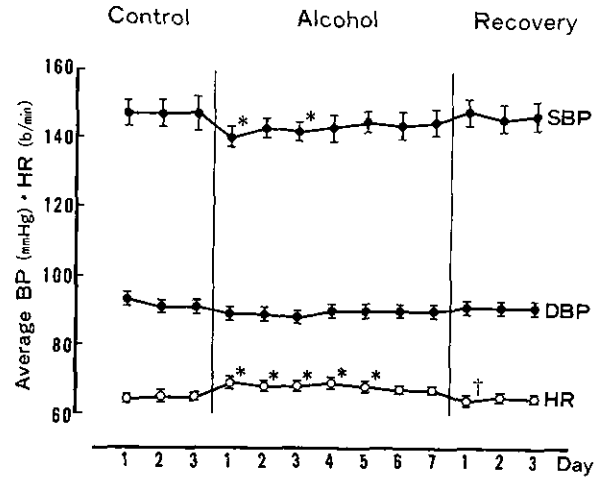

Fig. 4. *Average systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

3.6 mmHg). Diastolic BP showed a similar tendency, although its change was not significant. Average heart rate increased during the alcohol period (Control: 64.0±1.0; Day

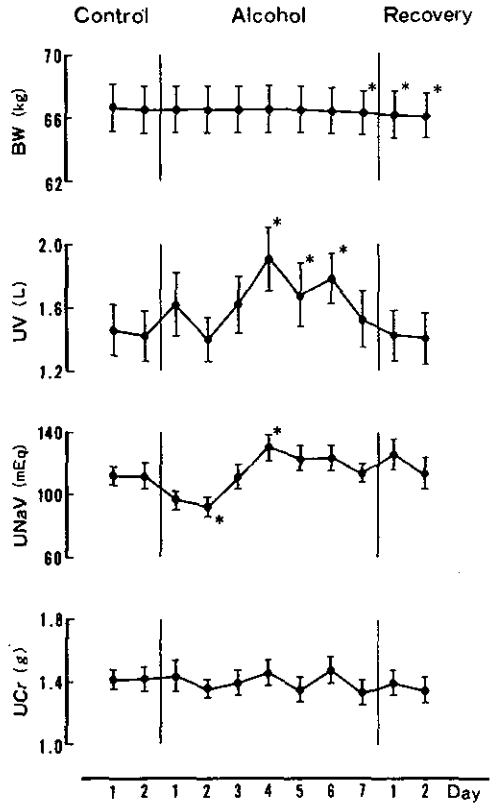

Fig. 5. *Body weight (BW), urine volume (UV), urinary sodium excretion (UNaV), and urinary creatinine excretion (UCr) during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.*

1: 68.7±1.4; Day 7: 66.5±1.1 beats/min), and returned to baseline during the recovery period.

Body weight decreased slightly but significantly during the late phase of the alcohol period and the recovery period (Fig. 5). Urine volume did not change during the early phase of the alcohol period, but increased significantly on Days 4–6. Biphasic changes in urinary Na excretion were observed during the alcohol period. It decreased from 112± 8 mmol/day during the control period to 97±6 mmol/day on Day 2, then increased to 130±8 mmol/day on Day 4. There were no significant changes in urinary excretion of creatinine or K.

Serum Na and K concentrations at 17:00, 19:00 and 8:00 during the control and alcohol periods are shown in Table 1. There were no significant changes in serum Na concentration. Serum K decreased after meals both during the control and alcohol periods; however, the level of serum K after ingestion of alcohol was significantly lower than that during the control period.

The alcohol-induced reductions in BP and urinary sodium excretion were more obvious in two patients who showed marked facial flush after alcohol ingestion than in the rest of subjects. The amount of usual alcohol intake did not relate to the changes in BP or sodium excretion.

Table 1. Serum Concentrations of Sodium and Potassium during the Control and Alcohol Periods

	Control	Alcohol Day 1	Alcohol Day 7
Serum Na (mmol/l)			
17:00	140.1±0.7	140.0±0.5	139.5±0.5
19:00	139.7±0.7	140.0±0.6	139.6±0.6
8:00	140.3±0.7	140.1±0.6	139.6±0.5
Serum K (mmol/l)			
17:00	4.09±0.06	4.06±0.07	3.97±0.05
19:00	3.84±0.05†	3.65±0.05†,*	3.61±0.04†,*
8:00	4.18±0.06	4.16±0.07	4.14±0.06

† $p<0.05$ *vs.* 17:00, * $p<0.05$ *vs.* control period.

Discussion

In the present study, repeated intake of alcohol for 7 days caused significant changes in BP and Na balance in Japanese males with hypertension. The alcohol-induced reduction in evening BP was consistently observed throughout the alcohol intake days, while the decrease in average BP was observed in the early but not the late phase of alcohol consumption. These changes in BP were associated with early sodium retention followed by natriuresis during the alcohol period. The present study demonstrates that repeated alcohol intake causes biphasic changes in BP and sodium metabolism, and suggests these changes may interact with each other.

The changes in BP after repeated alcohol consumption confirm previous observations (*8–10*). The reduction in evening BP was observed throughout the alcohol period in this and our previous studies. This depressor response may be specific to Asian subjects, since alcohol flush syndrome characterized by facial flush and tachycardia is common in Asians but rare in Caucasians and Africans (*8, 20*). The alcohol-induced BP elevation was not apparent in the present study, but morning and afternoon BPs tended to increase in the late phase (*9, 10*). The mechanisms of the hypertensive effect of alcohol have not been completely clarified, although neurohumoral substances, vascular smooth muscle, and endothelium may be involved (*13, 16*). Our studies suggest that the alcohol withdrawal rather than any straightforward action of alcohol itself may play an important role in the BP elevation because BP fell at the time of high blood alcohol level. The average BP measured at 5 different hours decreased during the early phase of the alcohol period, then returned to the baseline level in the present study. These findings suggest that some slow pressor mechanisms may operate in the changes in BP after repeated alcohol intake.

Heart rate increased during the alcohol period in the present study, confirming previous observations (*8–10, 16*). The change in heart rate was most apparent in the evening but was also seen in the morning. The evening tachycardia appears to be due to the direct action of alcohol and to the re-

flex response to BP reduction. Mechanisms related to alcohol withdrawal, such as activation of the sympathetic nervous system, may be involved in the morning rise in heart rate.

Urinary sodium excretion decreased during the early phase but increased during the middle phase of the 7-day alcohol period in the present study. The early reduction in sodium excretion appears to be related to the initial decrease in BP, since BP is a powerful regulator of renal sodium handling and *vise versa* (*21*). This sodium retention may contribute to the subsequent BP change, including the rise in daytime BP. The late natriuresis also appears to follow the change in average BP, which returned to the baseline level after repeated alcohol consumption. The acute reduction in urinary sodium excretion after alcohol consumption was also observed in some earlier studies (*14*, *18*, *19*). In addition to the hemodynamic mechanism, neurohormonal factors might contribute to the alcohol-induced sodium retention, since activation of the sympathetic nervous system and the renin-angiotensin system acts on the kidney to reduce sodium excretion (*22*). In the related previous studies, we observed that both plasma norepinephrine concentration and plasma renin activity increased after a single alcohol ingestion (*8*, *23*). However, those changes were attenuated after repeated intake of alcohol (*9*).

The alcohol-induced changes in BP, heart rate and sodium metabolism may not be restricted to hypertensive patients, but may also be seen in normotensive subjects. Acute reductions in BP and sodium excretion (*19*, *20*) and a chronic increase in BP (*24*) have also been observed in normotensive individuals. However, these effects of alcohol may be more clinically relevant in hypertensives than in normotensives. The effects of alcohol on BP appear to be dose-dependent, since a linear relationship has been observed between the amount of alcohol consumption and the level of BP (*1*, *2*). A similar dose-related effect would be expected regarding sodium metabolism, although have been no studies examining the dose-response relationship in humans.

In the present study, urine volume did not change during the early phase but increased during the middle phase of the alcohol period. It is known that alcohol temporally stimulates water excretion from the kidney. This alcohol-induced diuresis is mediated by the suppression of vasopressin secretion (*18*, *23*). The lack of initial diuresis in our study may be related to the decrease in BP, which acts to reduce renal water excretion. The increase in urine volume was observed in parallel with natriuresis when BP returned to the baseline level. However, a precise assessment of water balance was not possible in the present study, since the amount of daily water intake was not measured.

Several studies have shown that serum sodium concentration increases after alcohol ingestion (*25*, *26*). This change in sodium concentration may be related to the alcohol-induced diuresis. In the present study, the level of serum sodium did not change during the alcohol period. The lack of marked diuresis and the free access to water may explain the stable level of serum sodium. On the other hand, the serum potassium concentration decreased acutely after alcohol intake, confirming earlier observations (*8*, *26*, *27*). This alcohol-induced hypokalemia was not due to kaliuresis, but was mediated by activation of the sympathetic nervous system, since propranolol attenuated the change in serum potassium in our previous study (*27*).

Alcohol consumption may also influence BP through its effects on magnesium and calcium metabolism (*13*). It has been shown that urinary excretion of these minerals increases after ingestion of alcohol (*14*, *15*), although we did not measure urinary magnesium and calcium in the present study. The alcohol-induced deficiency of these minerals may play a role in BP elevation. An experimental study has shown that magnesium supplementation prevents the development of alcohol-induced hypertension in rats (*28*). However, the depressor effect of magnesium and calcium supplementation was not significantly different between drinkers and nondrinkers in our previous studies (*29*, *30*).

In conclusion, the findings of the present study show that average BP decreases during the early phase but returns to the baseline level during the late phase during repeated alcohol intake in Japanese males with hypertension. Urinary sodium excretion decreased initially, then increased during the alcohol period. The early sodium retention appears to be the consequence of alcohol-induced BP reduction and may participate in the subsequent BP elevation.

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