2　身体診察

1) 主に坐位で行う診察

① 視診

a. 全身

姿勢

起坐呼吸の有無．息苦しくて仰臥位になることができないので，坐位のままでいることを好む．

体格

Marfan 症候群では，背は高く四肢や指はクモのように長い．自分の手首を対側の手でつかむと指の長さが長いために余ってしまう．

b. 頭部

顔色不良

顔色をうかがうというわけではないが，はじめて会う患者の様子を知るうえでは重要である．

蒼白では貧血や血圧低下を疑う．赤みがある場合は血圧上昇や興奮状態を考える．チアノーゼで口唇や粘膜が青紫色になる．還元ヘモグロビン量が増加した状態で，先天性心疾患や末梢循環不全などを疑う．

貧血

眼瞼結膜は正常では赤いが，貧血になると白くなる．

発汗

動悸が持続して発汗がいちじるしいときは甲状腺機能亢進症を疑う．冷や汗がでていて四肢が冷たい場合は心原性ショックを疑い，直ちに救急救命処置の用意をする必要がある．

舌下静脈怒張

右心不全により中心静脈圧が上昇すると，舌の下の静脈が太く浮き上がる様子を確認できる．

ミュッセ（Musset）徴候

大動脈弁閉鎖不全症の患者の症状の１つで，頭を前後に小刻みに揺するような運動をする．

c. 胸部

動き

呼吸にともなう胸壁の動きが左右同じであるか．気胸などでは左右の動きが異なる場合がある．

皮疹

帯状疱疹が胸痛の原因であることもある．神経にそって帯状に水泡を交えた赤い発疹を認めることがある．

頸静脈怒張

右心不全の徴候で，頸静脈が坐位でも怒張していることがある．肺の悪性腫瘍で，上大静脈が圧迫されて頸静脈が怒張することもある．

② 打診

a. 心濁音界

心臓拡大の有無を知る１つの方法である．胸骨左縁を第２肋間から下方に打診して大動脈弓の拡大の有無を，胸骨右縁第４－５肋間を右に打診すると右縁から１横指越えれば右室拡大を，胸骨左縁から左に打診して左鎖骨中線より１横指外側よりも左なら左室拡大を疑う．

b. 胸水

一側の肺に胸水が貯留すると，肺の下縁で鼓音が濁音に変わる高さが左右で異なるようになる．

(3) 聴診

a 心音

循環器の診察で最も重要なものが心音の聴取である（図3-12）．心臓の周期をよく理解して，音を聴き分ける必要がある．聴診器で患者の胸に当てる部分のチェストピースは，ベル型と膜型の2つの部分でできている．チェストピースの膜型の膜はやや厚く，心音の低音より高音の音がよく聞こえるようになっている．ベル型では低音がよりよく聴こえる．ベル型のチェストピースを胸壁に強く押しつけると皮膚の緊張によって，あたかも膜型と同じようになり，低音が聴きにくくなるので，ベル型で心音を聴くときは強く当てないようにするのがコツである．耳に入れる部分はイヤーピースとよび，少し前方に向けて，外耳道に後ろからやや前に向けて差し込むようにする．耳にぴったりとはまるようにすると音がよく聴こえる．

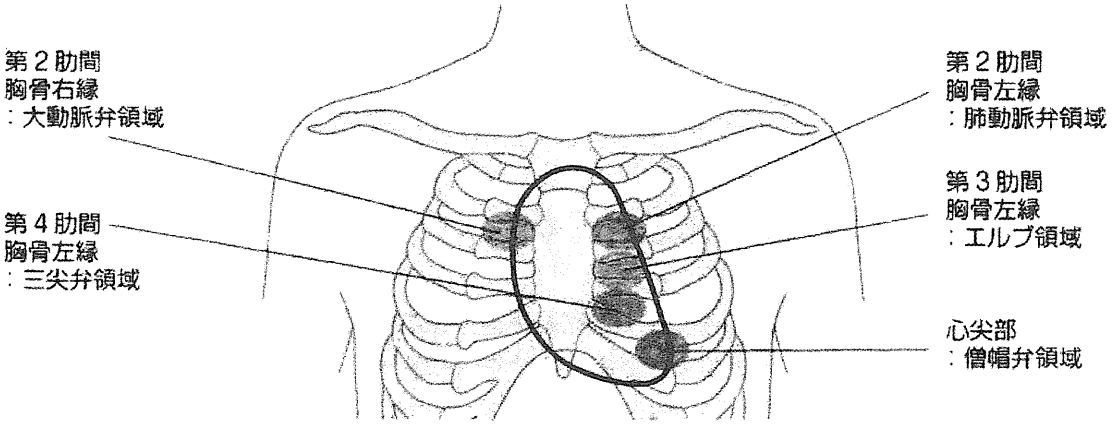

図3-12　心音を聴診する部位

①心周期

心室が血液を送りだす収縮期と，肺や体からもどる血液を心房を介して受け取る拡張期の2つからなり立っている（図3-3参照）．

②Ⅰ音とⅡ音

心室が収縮して大動脈に血液を送りだすときには，ある時期で心房の圧を超えて上昇する．このときに左室側では僧帽弁が，右室側では三尖弁が閉鎖するために第Ⅰ音が生じる．一方，左心室から血液を大動脈へ送りだした後に，左心室の圧が大動脈の圧より下がると大動脈弁が閉じ，右心室圧が肺動脈圧より下がると肺動脈弁が閉じるので第Ⅱ音が生じる．大動脈弁が閉じる音をⅡa，肺動脈弁が閉じる音をⅡpと表現する．通常は大動脈の圧が肺動脈の圧より高いので，大動脈弁が肺動脈弁より先に閉じるのでⅡaⅡpの順序になる．

③Ⅱ音の分裂

Ⅱ音はⅡaとⅡpの2つの成分に聴こえるのが一般的であるが，その間隔は変動する．最も一般的なのが呼吸変動である．呼気の終わりに比べて吸気の終わりにはⅡaとⅡpの間隔は広くなる．吸気時には胸郭が大きくなり右心室へもどる血液量が増加し，右心室は増えた血液を送りだすのに時間がかかるので，Ⅱpが遅くなると考えられている[1]．心房中隔欠損症では右心室の血液量が常に増加した状態なので，Ⅱ音は呼吸で変化しない．これを固定性分裂と表現する．

④Ⅲ音とⅣ音

Ⅲ音は健常な成人や小児で聴取するときがあるが，一般的には心不全のときにⅣ音と合わせて

することが多い．Ⅲ音とⅣ音が出現すると，Ⅰ音とⅡ音と合わせて4つの音が続くので奔馬調（ギャロップリズム）ともよばれ，馬が走るときのトットロットのように聴こえる．Ⅲ音は拡張期のはじめごろで左房から左心室に血液が流入するときに出現し，Ⅳ音は心不全などで左心室が膨らみ過ぎているときに，さらに左房の収縮で血液が送り込まれることで生じる．Ⅳ音は左房の収縮にともなうものなので，心電図のP波の直後に出現する．一方，心房細動になると心房の収縮が十分でなくなるので，Ⅳ音は消失する．

Ⅰ音減弱

心音は通常心尖部でⅠ音が大きく，心基部である胸骨右縁第2肋間あたりではⅡ音が大きい．Ⅰ音とⅡ音の音の大きさは胸骨右縁第2肋間ではⅠ音＜Ⅱ音，心尖部ではⅠ音＞Ⅱ音となるが，心筋梗塞などで左心室収縮能が低下すると心尖部でⅠ音が聴こえにくくなる．この様子をⅠ音減弱とよぶ．

心雑音

弁の接合不全，硬化，変形，心室や心房の中隔に欠損がある場合，さらに心膜の炎症などの異常にともない心雑音（cardiac murmur）が出現する．

収縮期雑音

大動脈弁が動脈硬化や先天性二尖弁の石灰化のために狭窄を起こすと，胸骨右縁第2肋間で最強となる駆出性の収縮期雑音を聴取する．貧血などで体が要求する酸素を補うために，心臓が送りだす血液量の増加にともない，機能的な収縮期雑音が生じることもある．肺動脈弁狭窄では，胸骨左縁第2肋間で収縮期雑音を聴取する．心尖部では僧帽弁の閉鎖不全があると，逆流による全収縮期雑音を聴くことがある．僧帽弁逸脱症候群では，逆流が始まるときにクリック音が聴こえる．心室中隔欠損があると，収縮期に胸骨左縁第3～4肋間で全収縮期雑音が聴かれる．

拡張期雑音

心室が拡張するときに出現する．大動脈弁閉鎖不全では，胸骨左縁第3肋間あたりで高調なピューッというような音を聴くことがある．運動後や患者に少し前屈みになってもらうと聴取しやすい．肺動脈弁閉鎖不全でも，拡張期に胸骨左縁第3～4肋間近傍で聴取する．僧帽弁狭窄症では，心尖部で拡張期ランブルとよばれるゴロゴロとした音が，拡張早期に出現する僧帽弁開放音であるオープニングスナップ（opening snap；OS）とよばれるパチッという音に引き続き出現する．

心膜摩擦音

心膜炎により壁側と臓側の心膜に炎症が起き，平滑でなくなった心膜が擦れて摩擦音が生じる．座位でやや前屈みになると，胸骨左縁の第3か第4肋間で聴こえやすくなる．

呼吸音

呼吸音（狭義）と呼吸音以外に聴こえる音である副雑音に分類される．副雑音にはラ音と胸膜摩擦音がある．ラ音は断続性ラ音と連続性ラ音に分類される．

断続性ラ音

細かい断続音は血圧計のマンシェットのベルクロを剝がすときのようなバリバリとした音で肺線維症や肺水腫などで聴取する．細かい断続音は捻髪音ともいわれ，髪の毛を指でもみ合わせたときのようなバリバリとした音のことで，間質性肺炎などで聴かれる．

連続性ラ音

笛音といびき音に分類される．笛音は笛を吹いたときのようにヒューヒューという音が，気管支喘息や気管支が腫瘍で圧迫されたときなどに聴取される．いびき音はゼロゼロとした低音で，炎症や腫瘍で聴かれることがある．

d　血管雑音

頸動脈，大動脈，腎動脈などの狭窄があると収縮期に一致して雑音を聴取することがある．

(4) 触診

a　心尖拍動（左側臥位で診察する方がよい）

心尖拍動は心臓が収縮したときに心尖部が胸壁に当たって生じる拍動であり，通常は鎖骨中線外側1 cmあたりまでの第5肋間で触れる．示指から薬指をそろえて肋間にそわせるように当て指先を鎖骨中線あたりに置くと心臓の拍動にともない，指先に下から突き上げるような拍動を触る．左室肥大があると，鎖骨中線より前腋窩線あたりに拍動部位は移動する．坐位よりはやや前した方が，仰臥位より左側臥位の方が触れやすい．肥満していたり，肺気腫や心拍出低下があると触れにくくなる．

b　脈拍

①測定部位（大腿動脈，膝窩動脈，足背動脈は臥位で行われる）

橈骨動脈：母指のつけ根の橈骨側

総頸動脈：甲状軟骨の側方

大腿動脈：鼠径部

膝窩動脈：膝関節の裏側の中央

足背動脈または内顆動脈：足背または内顆の後方

②測定方法

3本の指（示指，中指，薬指）を動脈にそって並べて置いて脈をはかる．

③脈拍の診断

・脈の強弱

脈が触れにくい：血圧が下がっていて触れにくいのか，脈拍が速くて触れにくいのかを見極める必要がある．

脈動が強い：鋭脈は脈が鋭く立ち上がり，すぐに下がる．大動脈弁閉鎖不全症の際に心拍出量が多いために出現するが，弁の逆流があるために立ち上がった脈は長続きせずに低下する．

・脈拍数

頻脈：1分間に100回以上

徐脈：1分間に50回未満

不整の有無：何回かに1回抜ける場合は，期外収縮を考える．まったく不規則な場合は絶対性不整脈として心房細動を疑う．

・左右差

脈拍に左右差が生じる場合は，血圧にも左右差が生じているはずである．原因には大動脈炎症候群や解離性大動脈瘤などがある．

c　血圧測定

①血圧の測定場所

上腕：肘関節の1～2 cm肩関節よりにマンシェットを巻く（図3-116）．

大腿：膝関節の後面で聴診する．マンシェットは大腿用の幅の広いものを用いる．

足首：上腕用に用いるものと同じものを足首に巻き，足背動脈の血流を超音波ドプラ法で調べる

臥位で行う診察

視診

内頸静脈拍動（半坐位）：右心不全の確認に，半坐位（背中をベッドから45度起こしたとき）で内頸静脈の上縁の拍動をみる．正常例の内頸静脈拍動は胸骨角から垂直に測定して4.5 cm以内の高さであるが，それ以上の高さになる場合は右心不全があると判断する．外頸静脈の怒張を認めることもあるが，静脈弁があるので誤差が生ずることがある．上腹部を圧迫すると，正常例では下大静脈から右房に流入する血液が減少して，みえていた内頸静脈が消失するようにみえるが，右心不全があると圧迫による消失はなく，むしろ内頸静脈上縁が上方に変位する（肝頸静脈逆流：hepatojugular reflux）．

触診

肝腫大

右心不全のときに肝臓が腫れる．

前脛骨部の浮腫

脛骨の前面に浮腫があるか否かを右心不全時に調べる．

足背動脈触知

下肢の動脈に動脈硬化などで狭窄や閉塞があると，足背動脈は触れにくくなる．糖尿病性の血管障害の際にも動脈硬化が進展して触れにくくなる．

脈拍の左右差

大動脈や下肢の動脈に動脈硬化が進展したものを閉塞性動脈硬化症とよび，足背動脈を触知しにくくなることがある．

[引用文献]

Constant, J. 著，井上博監訳（2002）Bedside Cardiology：診断のエキスパートを目指して．pp.77-86，総合医学社．

検査の方法

心電図

概要

心電図（electrocardiogram；ECG, EKG）は，心筋の収縮に際して発生する電気現象を身体表面の電極（electrode）でとらえて経時的に記録したものである．操作が比較的簡単で，有用な情報を提供してくれるため，医療現場では広く用いられている．

心電図検査は虚血性心疾患や不整脈などの疾患の診断にたいへん有用であり，胸部X線写真やエコー図検査とともに日常診療で必須の検査となっている．しかし，精度は必ずしも高くなく，心電図のみで診断を下すことはできない病態や疾患も多い．医療面接，身体所見，心エコー図やX線所見などと合わせて判断する必要がある．また，1回の心電図記録では判断しにくいこともある．そのような場合は，心電図を経時的に何回か記録し比較して変化を把握することも大切である．

心電図は，特に心筋の虚血，調律異常，伝導異常，心室肥大の発見や評価に有用で，狭心症，心筋梗塞，各種不整脈の診断に必須のツールとなる．また，症候の面からは胸痛，動悸，失神などの診断を進めるうえできわめて重要な検査となる．

第2章 頸部編

12 Stiffness parameter β について

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βの計測法

Stiffness parameter β（以下 β とする）は血圧に依存しない血管弾性の指標として林紘三郎教授により考案された[1]．大動脈や総頸動脈などの弾性血管では，動脈硬化の進行により血管外膜間径の拡張が起こり，血管壁の拍動は減少する．血管弾性を測定する指標には pressure strain elastic modulus（Ep）などがあるが，Ep＝（ΔP/Δd）×D で計算されるように測定時の血圧に計測値は依存する（ΔP：脈圧＝Ps－Pd，Δd：血管拍動幅＝Ds－Dd）．一方で β は，測定時の血圧に依存することが少ない指標であることが特徴である．このことは同一の個人の血管弾性を経時的に観察するときに重要である．

Stiffness parameter $\beta = |\log_e Ps/Pd| \times Dd/(Ds-Dd)$
Ps：収縮期血圧，Pd：拡張期血圧，Dd：拡張期血管内径，Ds：収縮期血管内径．

βの計測のコツ

現在，β を直接計測できる機器は，eTRACKING（早期動脈硬化評価パッケージ）として日立アロカメディカル社製の prosound F75，prosound α7 である．他には，血管拍動を M モード法で計測し，血管径と拍動幅をマニュアルで計測して β を算出しているものもある．計測は仰臥位で行い，左右の総頸動脈を測定する（**図1**）．eTRACKING では，画面の左側に総頸動脈長軸像を描出し，内中膜の淡いエコーと外膜の高輝度エコーの境界からやや外膜側にトラッキングゲートを掛ける（**図2**）．トラッキングゲートは，組織からの反射エコーの RF 信号で，その波形の基線より上方にある面積（**図2** の A1 と B1）と，下方の面積（**図2** の A2 と B2）が同じようになるようにして追従する．血管の拍動が良好に計測されるようになると，計測画面（**図2**）右側に示す M モード像の外膜に一致した部位にトレースしている波形が近位側と遠位側に表示される．併せて拍動波形が心電図とともに表示される（**図3**, Web）．良好に壁の拍動が計測されていることを確認して波形をフリーズする．良好な波形を選び，4～5 心拍の加算波形

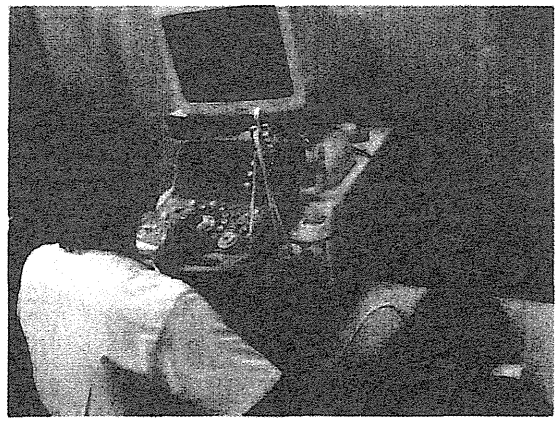


図1 計測風景

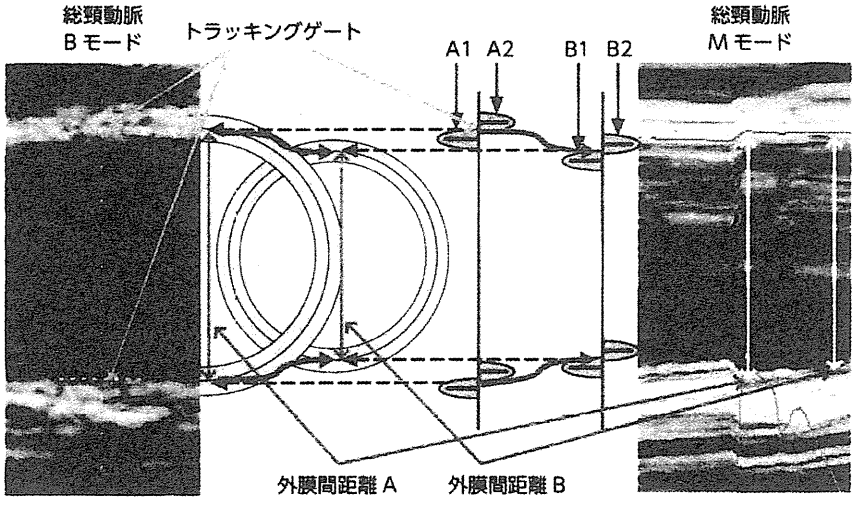


図2　β計測時のトラッキングゲートとその動きの模式図

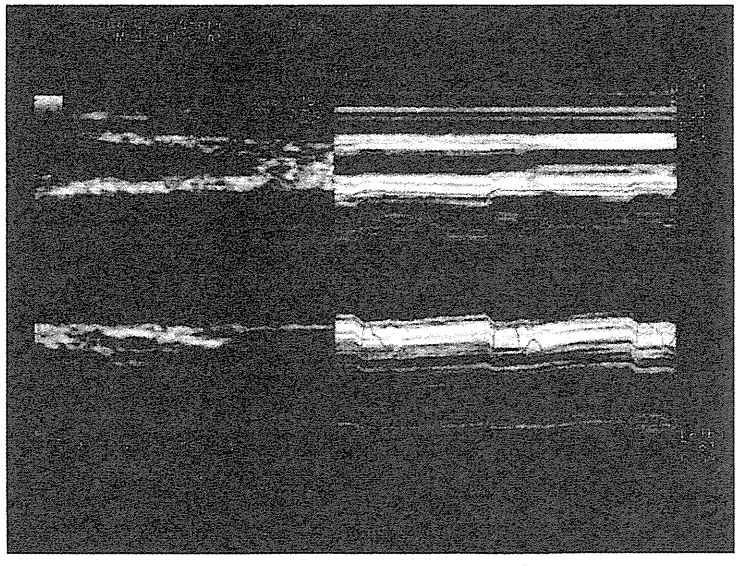


図3　β計測モニタ波形（20歳代）（Web）

が表示され，上腕血圧値を入力するとβが算出される（**図4**）．

βは，血管径，血管の拍動幅および血圧で算出される．特に血管径を計測する際に，血管外膜間距離を測定する（**図2**）．外膜間距離は，血管のリモデリングにより年齢とともに拡張する．一方，内膜間距離は，加齢とともに徐々に拡張するが，内膜に動脈硬化病変が生じると狭窄に転じる可能性が高い．βの再現性を高めるには血管径の計測精度が重要である．そのために，計測部位は内外頸動脈血流分岐部から15 mm心臓側の総頸動脈と決めて，血管径がほぼ一様な部分で行うこと

程度でほぼ同じである（Fujishiro, 1982）[2]．実測例での50歳代のモニタ波形では，Mモード法での血管拍動幅はかなり少なくなり，キャリパーで測定する場合の誤差が大きくなる可能性がある．eTRACKING法では，壁拍動を目測よりも高い精度で計測可能である（**図5**）．βは血管径を拍動幅で除して求めるので，血管径が細く拍動幅が大きい若年代で値が小さい．高年齢になると大きな血管径を小さな拍動幅で除すために値は大きくなる．さらに，若い頃の拍動幅は大きいが50歳以上で一定になるので，若い頃のβは加齢で大きく変動するが，高齢者ではβの加齢変化が少なくなる．

βの臨床的意義

βは加齢で増加

実測例（**図4**）では，20歳代のβは7.0で，50歳代のβは10.3であった．Wadaら（1991）は，βは20歳代で5.5が60歳代で11.8と加齢で増加するとしている．Hiraiら（1989）は40～80歳で$\beta = 0.11 \times$年齢$+2.8$としている．血管外膜間径は20歳代で6.9 mmが70歳代で7.9 mmと加齢でほぼ一律に拡大する．一方で血管拍動幅は20歳代から40歳代までに0.64 mmから0.35 mmまで減じ，以後50歳代から70歳代まで0.30 mm

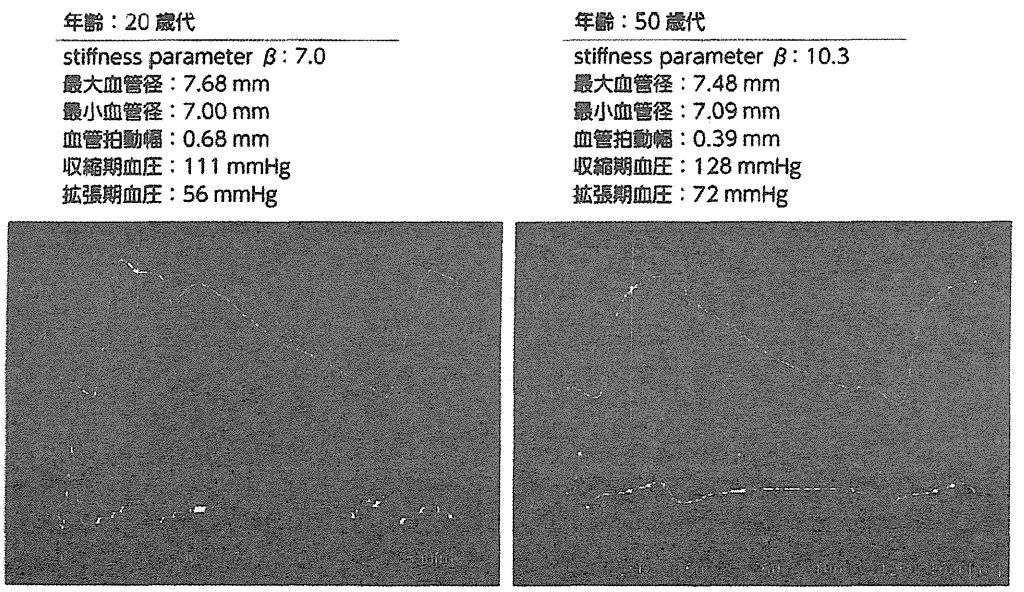


図4 計測結果

描出・読影のコツ 長軸でIMTと外膜が2～3 cmの長さで明瞭に描出することが，外膜間径を良好に測定するために必要である．

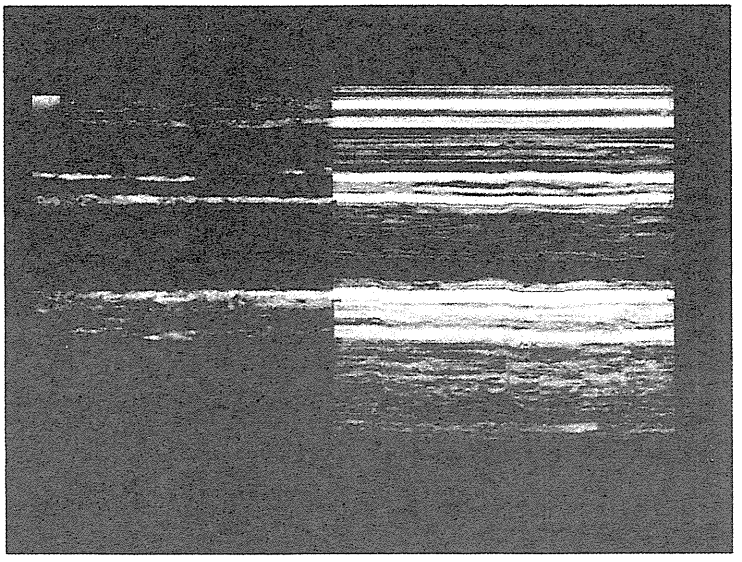
βの基準値[2]

Wadaら（1994）[3]は生前にβを測定し，剖検し得た例で総頸動脈断面の病理所見を分析した．動脈硬化度の重症度で2群に分けて累積発現率で検討すると，動脈硬化なしの群と動脈硬化ありの群のβの境界は13であった．Kawasakiら（2005）[4]は，健常例と強皮症の症例の総頸動脈後壁の中膜の超音波integrated backscatter（IB）値，βおよび内膜中膜複合体厚（IMT）の関係を検討している．IBとβとは健常例に強皮症の症例を加えても高い相関を示す（r＝0.8）．IMTとβとは健常例で相関度が高い（r＝0.72）が，強皮症の症例を含めると相関度は下がるとしている．強皮症では血管壁硬化が進んでIBが上昇してもIMTは肥厚せずβが上昇する．すなわちβは血管壁中膜の硬化による質の変化を表す指標であることを示している．また，β値の平均は強皮症で20.6±5.6であり，年齢と性をマッチさせた健常例では11.5±4.5であり，前出の正常値上限13に合う結果と考えられた．

疾患特異性

虚血性心疾患とβ

Hiraiら（1989）[5]は，正常例19例と心筋梗塞例49例（42～76歳）でphase-locked echo-tracking



■5　β計測モニタ波形（50歳代）

20歳代に比べて血管壁拍動を目視しにくいほどに拍動の減少が認められる．

よくある間違い・注意点

長軸で総頸動脈を描出すると，総頸動脈より浅い部分に内頸静脈が描出されることがある．内頸静脈にトラッキングゲートを掛けてしまう間違いがときどきある．これを防ぐには心電図を同時に記録することと，短軸で総頸動脈の確認が必要である．

system を搭載したβ測定専用機を用いて比較している．冠動脈病変数0枝，1枝，2枝，3枝のそれぞれのβは9.17，9.42，10.54，11.44，13.17であり，2から3枝病変例で正常例に比べβが有意に高値であったとしている．Lee ら（2009）は，日本人439名の平均年齢56歳の非糖尿病患者と1,528名の平均10年の治療歴がある平均年齢61歳の2型糖尿病患者で冠動脈疾患の有するものと冠動脈疾患のない患者について13 MHz リニアプローブとeTRACKINGを用いて調べている．βは非糖尿病患者の平均が11.6±5.4，冠動脈疾患のない2型糖尿病患者で14.8±6.2，冠動脈疾患のある2型糖尿病患者で17.3±7.3である．それぞれのIMT（mm）は，0.79±0.40，1.06±0.53，1.36±0.75である．IMTが1.3 mm以上であり，なおβが20以上の場合は冠動脈疾患のオッズ比が3.1と高値であり，IMTとβを組み合わせると冠動脈硬化を判別する良い指標になるとしている．

Leone ら（2008）は，フランスで65歳以上の3,337例を5～10 MHz のリニアプローブで総頸動脈を計測し，Mモード法で血管径を計測して血管拍動幅を求め頸動脈壁進展度やβを測定している．33カ月経過観察し，冠動脈疾患は128例に発症し，総頸動脈の血管拍動分を拡張期の血管径で除した壁進展度の増加はリスクになったが，βは関連しなかったとしている．

運動とβ

Heffernan ら（2009）によると，59歳から78歳の地元のマラソンチームなどに所属している6名ずつの男女12名と，対照として主に座業をしていて，週に15分以上の脈拍数が上がるような運動をしていない年齢をマッチさせた12名を比較している．両者の血圧やIMTに差はなかったが，eTRACKING法で計測した頸動脈のβは持久性の運動をしている人で7.3±0.8に対し，座業の多い人では9.9±0.6とで明らかに前者が低かった．

Aizawa と Petrella（2008）によると，座業が主の平均年齢68歳の9名（2名は男性で7名は女性）の高血圧患者を対象に20週間の有酸素運動を行い，その前後でβを測定している．βは10 MHz のリニアプローブで血管断面を計測し，VHS テープに記録後に収縮期と拡張期で血管径を計測して求めている．結果，最大酸素摂取量の70％に達する運動を行ってもβは改善しなかった．

Aizawa ら（2008）によると，正常高値血圧と耐糖能異常および空腹時高血糖の境界型糖尿病がある63例を対象に，さらにメタボリックシンドロームの有無で2群に分けて食事療法と有酸素運動を24週行い，24週継続できたメタボリックシンドロームのない6例と有する8例を比較すると，メタボリックシンドロームを有する群でβは12.5から9.8に有意に低下した．

薬物によるβの改善

Mizuguchi ら（2008）は，30例の脂質異常症患者に高コレステロール改善薬であるピタバスタチンをランダムに投与し，12カ月観察した．βは頸動脈を7.5 MHz のリニアプローブで計測し，Mモードから計測し算出した結果，5.6から4.1に低下したが，IMTの変化はなかった．

Okura ら（2008）は，バルサルタンを24カ月内服した高血圧患者では，血圧が低下し，IMT

覚え方のコツ βは，血管径が大きいほど，血管の拍動が少ないほど大きくなる

は変化なかったが，βが低下したとしている．

頸動脈以外での stiffness parameter β計測

Xu ら（1997）は，大動脈縮窄症の5～16.5歳，平均年齢7歳の13例に血管内超音波診断装置を用いてβを計測している．対照は大動脈二尖弁の患者などで，対照の大動脈のβは1.67±0.77のところ，大動脈縮窄症の縮窄部位のβは6.19±5.68と高値を示した．Lau ら（2012）は，肺動脈高血圧症の平均年齢66歳の患者の肺動脈のβを，血管内超音波診断装置を用いて測定している．対照の平均年齢67歳の例のβは11.0±0.7に対して15.0±1.4と高値であった．Gurses ら（2012）は，大動脈二尖弁の平均年齢10歳の小児の腹部大動脈で stiffness parameter βを計測したところ，正常弁の例の0.84に比べ1.1と有意に高値を示したとしている．頸動脈以外でのβは，計測する血管径が異なるので，当然ながら基準値が異なる．

まとめ

βは頸動脈での動脈硬化指標のみならず，肺動脈，大動脈などの計測も行われるようになってきた．現時点では，冠動脈疾患の項で示した Hirai ら，Lee らの横断的研究では，冠動脈疾患とβに関連性を認めるものがあるが，Leone らのコホート研究ではβの有用性は示されなかった．ESH/ESC2007高血圧管理ガイドラインでは，動脈硬化の指標として頸動脈のある1カ所の測定であるβよりも，長い血管全体の血管硬化を知る脈波速度の方が有用であるとも記載されている．前2者のβの計測はeTRACKING法で行われているが，Leone らはMモード法でβを計測している．eTRACKING法を搭載した機器は高価であり，多くの研究報告が出にくいのが現状である．しかしMモード法でβを測定するよりもeTRACKING法でβを計測する方が精度は高いと考えられるので，今後はe-TRACKING法を用いた縦断研究報告が出てくることを期待したい．

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first hours of the day. The only therapy is the application of CPAP (Continuous Positive Airway Pressure) when the patient go to bedside. Some other studies have demonstrated a relation between CPAP and cerebral flux expecially about variations of velocity but nobody have valuated it with transcranial echocolordoppler. We observed one obese woman , affected by OSAS, that applys , before sleeping, the CPAP device. We have measured IR (resistance index) before and immediately after use of the device. We found a significative decrease of IR after CPAP than its value before sleeping. (from 0.58 to 0.47). These data show that correcting the nocturnal desaturations permits a better cerebral perfusion. It will be interesting to confirm these findings studing a larger crew of patients. when the patient go to bedside.

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P48

Intima-media thickness in rheumatoid arthritis patients

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Background: Intima-media thickness (IMT) of the carotid arteries in patients with RA is potential maker of inflamation and subclinical atherosclerosis. **Methods**: IMT was measured ultrasonographicaly in 42 non-diabetic, normotensive, female RA patients and 32 matched healthy controls (age 45.3 ±10.0 vs 45.2 ±9.8 years) at common carotid arteries (CCAs), carotid bifurcation (BF) and internal carotid arteries (ICAs), bilaterally. Mean IMTs were calculated from three measurements at each site. Clinical work-up included laboratory analyses, determination of the disease activity and evaluation of treatment. **Results**: RA patients had increased IMT (mm) in comparison with controls: CCA: 0.671 ±0.119 vs 0.621 ±0.085; bifurcation: 0.889 ±0.168 vs 0.804 ±0.124; ; ICA: 0.577 ±0.101 vs 0.535 ±0.076. Parameters associated with IMT in RA patients were: age, BMI, smoking, RF concentration, sedimentation rate. Duration of MTX + chloroquine therapy were in inverse correlation. Multivariate regression analysis revealed that RA is an independent risk factor for increased IMT. Factors correlating with IMT in the controls were: age, BMI, total cholesterol, low-density lipoprotein cholesterol, total/high-density lipoprotein cholesterol, triglycerides and glycaemia. **Conclusion**: Female RA patients had significantly enlarged carotid IMT than controls. RA itself was an independent risk factor for increased IMT. Impact of chronic inflammation on atherosclerosis was confirmed by negative correlation of IMT and duration of anti-inflammatory treatment.

P49

Multilayer image in the intima-media complex in a patient with giant cell arteritis

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Background: Giant cell arteritis (GCA) is a challenging diagnosis in many patients due to great variability of the clinical presentation and limitations of the diagnostic tests available. Although the biopsy of the temporal artery is the gold standard test, it has some disadvantages: is an invasive and sometimes a delayed procedure with several false negatives which could promote a delay in treatment onset. Duplex of the temporal and other cervical and cranial arteries is an useful, fast and reliable tool for GCA diagnosis. The hypoechoic image around the lumen of temporal (and others) arteries is very characteristic of the disease (halo sign). We present a new echographic finding in the common carotid artery (CCA) related to GCA. **Material and methods:** In all patients in whom GCA was suspected a cervical and cranial duplex study was performed within 48 hours. We studied carotid, vertebral, occipital, temporal and orbital arteries, searching for vasculitis data (smooth concentric narrowing due to an hypo/anechoic area in the artery). **Results:** Between 2008-2011 we studied 73 patients with symptoms suggesting GCA. 22(30%) showed echographic signs of GCA. One of them showed a thickening and split in the three layers of the intima media complex on both CCAs presenting it a multilayer image (5 layers, alternating hyper and hypoechogenic ones). In this patient, temporal biopsy confirmed the diagnosis of GCA. A cervical CT and PET showed thickening and inflammatory activity in both CCAs. After corticoid treatment, the echographic image disappeared in 4 weeks. **Discussion:** We found a new echographic sign for vasculitis in GCA, a multilayer image of the intima media complex on CCA. This image might correspond to a break of the internal elastic lamina of CCA, as has been described in severe GCA. Recognize this sign can help in ecographic study of patients with GCA suspiction.

P50

Examination of the utility of intima-media thickness and plaque score in the common carotid artery as the aortic stiffness index to aorta and lower limbs

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Purpose: We investigated associations of indicators of aortic stiffness - carotid-femoral pulse wave velocity (cfPWV) and cardio-ankle vascular index (CAVI) . with an indicator of vascular-wall thickening, ie, intima-media thickness (IMT), in common carotid

arteries. When cfPWV and CAVI of 9 or more are assumed in arteriosclerosis, we examined which carotid index was the most useful. **Methods**: A total of 185 patients (81 women, mean age 62.9 years; 104 men, mean age 61.2 years) were assessed between June 2008 and May 2010. Ultrasonic tomography was used to evaluate the left and right common carotid arteries and the root of the internal carotid artery. Mean IMT (calculated from measurements obtained at the 3 locations), maximum IMT and plaque score were measured. The measurement of cfPWV and CAVI used Vasera1000. cfPWV was corrected in diastolic blood pressure 80mmHg. **Results**: cfPWV values ranged from 5.7 to 12.0 m/s; CAVI ranged from 6.3 to 11.2. The area under the curve in ROC of mean IMT, maximum IMT and plaque score when we assumed cfPWV>=9 arteriosclerosis was 0.682, 0.692, and 0.686 each. The area under the curve in ROC of mean IMT, maximum IMT and plaque score when we assumed CAVI>=9 arteriosclerosis was 0.650, 0.649, and 0.656 each. **Conclusions**: From a result of cfPWV, it was thought that maximum IMT was useful for an index of aortic stiffness, and plaque score was useful for the arterial stiffness indexes from the aorta to lower limbs. However, the differences of each value are very few, and it is necessary to examine in large cases.

P51

Ultrasonographic evaluation of acute ischemic stroke patients with radiation-induced carotid artery atherosclerosis

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Background and Purpose: Radiation therapy (RT) for the patients with head and neck malignancies is often associated with atherosclerotic change in cervical portion of the carotid artery, which is risk of stroke. To investigate the characteristics of atherosclerotic change induced by RT, we evaluated ultrasonographic findings of carotid artery in the patients with acute ischemic stroke caused by radiation-induced carotid artery atherosclerosis. **Methods**: The subjects were the patients with acute ischemic stroke who had past history of RT for head and neck malignancies. We evaluated ultrasonographic characteristics of carotid artery as mention bellow; the distribution and properties of plaque, the grade of stenosis and occlusion of vessels. **Results**: Six patients were included in this study (6 male, mean age; 73.3±7.8y.o.). They performed RT with 8±4.5 years before AIS. Three paitents had laryngeal carcinoma, two patients had pharyngeal carcinoma and one patient had pharyngeal and tongue carcinoma. All patients had no stenosis of intracranial arteries on MRA. Severe stenosis (over 70%) of infarction side's internal carotid artery (ICA) was two patients and occlusion of infarction side's ICA was four patients. In all patients, intima media thickness of common carotid artery (CCA) was thickening in all circumferences and there were multiple low and iso intensity plaque or ulcerative plaque. On the other hand, atherosclerotic change of carotid bulb was not so severe compared to CCA and ICA. **Conclusion**: Radiation-induced carotid artery atherosclerosis is more severe in CCA and ICA than in carotid bulb evaluated by ultrasound. This result shows that pathology of radiation-induced carotid artery atherosclerosis is presumably different from that found in common atherosclerotic disease.

P52

Role of carotid plaque morphology in ischemic stroke

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Background: Carotid Plaque morphology it is been consider important for the risk of ischemic stroke. **Method :** Data was retrieved and analysed from carotid ultrasound studies of 352 patients using Siemens Acuson machine. The atherosclerotic carotid plaque was classified as heterogeneous, hyperdense and hypoechogenic using gray appearance view ,color flow and Doppler wave form characteristics. Patients were defined as having an ischemic stroke by clinical diagnosis and imaging CT and /or MRI. **Results:** Hipoechogen plaque has 66% more risk to cause ischemic stroke (OD=1.66, CI95%: (1.01-2.66) while male patients have 49 % more risk than females to have ischemic stroke from hipoechogenic plaque (OD=0.49, CI95%: (0.26-0.97). **Conclusion:** Hipoechogen plaque has significant risk to cause stroke. Male patients with hipoechogen plaque are at the highest risk of having ischemic stroke. This fact justifies more aggressive treatment for such patients.

P53

Reproducibility of shear wave elastography measurements of carotid plaque stiffness: *in-vivo* and *in-vitro* studies

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Background: Measures of stroke risk may be improved by assessing the physical elastic properties of plaque. A new ultrasound imaging modality, shear wave elastography (SWE) quantifies tissue stiffness and studies suggest clinical value in assessing relatively static tissues such as breast, liver and thyroid. **Aim**: To assess the feasibility and reproducibility of SWE measurements of tissue stiffness (Young's Modulus) in vascular applications assessing carotid artery plaque tissue. **Methods**: A Supersonic Imagine Aixplorer ultrasound scanner with L15-4 probe was used to acquire 7 seconds of SWE cine-loop data from longitudinal sections of 24 carotid plaques in 21 patients presenting with atherosclerotic disease (stenosis diameter reduction ranged 10%-90%, mean 40%). SWE data were also acquired from a 70% symmetrical stenosis vessel flow phantom made of PVA cryogel of similar stiffness to carotid arterial tissue. A blood

AP-3 東京都城南地区の病診連携共同研究―城南地区血圧調査（TOHO-JOINT 研究）―における降圧目標達成率の経年変化

○正林　浩高[1]、盛田　俊介[2]、山崎　純一[3]、池田　隆徳[3]、並木　温[3]、中野　元[3]、南條　修二[3]、山科　昌平[3]、酒井　謙[4]、藤代　健太郎[5]

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【目的】東京都城南地区において大学病院と地域医療機関との共同で、血圧管理状況の季節変動および経年変化を、外来血圧、家庭血圧の起床時と就寝時について降圧目標達成率で検討した。【方法】城南地区の医療機関と東邦大学医療センター大森病院の医師の参加で、外来通院中の高血圧患者を対象とした。調査期間は第1回（春）2009年4月～5月、第2回（冬）2010年1月～2月、第3回（春）2010年4月～5月、第4回（冬）2011年1月～2月、第5回（春）2011年4月～5月の計5回。各医療機関で同意の得られた外来患者30から50例を連続登録した。外来血圧は2回の平均、家庭血圧は血圧計を保有する患者について記録した。【結果】協力医療機関はのべ131施設、登録症例は合計5888例。降圧剤の処方割合はCCBとRAS抑制薬がともに約7割であった。配合剤の処方割合は第1回5.2%から第5回17.5%へ、処方剤数が1剤の割合は37.1%から43.9%へと増加。J-HOME研究の単剤投与49%比べると、多剤併用療法が積極的に行われていた。一方、配合剤の使用により処方剤数は減少傾向がみられた。降圧目標達成率はそれぞれ、外来血圧（59.4%、55.7%、55.9%、58.7%、59.2%）、起床時（54.7%、40.1%、55.5%、33.9%、38.4%）、就寝時（66.0%、61.2%、70.0%、56.5%、60.9%）。合併症別の外来血圧の達成率は、心筋梗塞既往（61.5%、36.7%、38.3%、58.3%、59.5%）、糖尿病（35.7%、27.1%、28.0%、42.3%、35.4%）、CKD（38.8%、34.7%、35.3%、42.7%、37.2%）、脳血管障害（55.9%、49.3%、51.5%、63.1%、64.6%）であった。J-GAP研究などの従来の報告と比べ、外来血圧の降圧目標達成率は良好であった。【総括】家庭血圧・起床時や糖尿病・CKD患者では降圧目標達成率が悪く、冬に実施した第2回と第4回調査では達成率の低下がみられた。血圧の日内変動・季節変動を考慮した治療が今後の検討課題である。

Association Between Interleukin-6 Levels and First-Ever Cerebrovascular Events in Patients With Vascular Risk Factors

Kaori Miwa, Makiko Tanaka, Shuhei Okazaki, Shigetaka Furukado, Manabu Sakaguchi, Hideki Mochizuki, Kazuo Kitagawa

Objective—The objective of this study was to examine the association of inflammatory markers with risk of first-ever cerebrovascular events (CVEs), while simultaneously evaluating subclinical vascular disease.

Methods and Results—We enrolled 464 outpatients who had vascular risk factors without any preexisting cardiovascular disease. We examined the presence of silent lacunar infarction (SLI) by magnetic resonance imaging; carotid intima-media thickness by ultrasound; and measured high-sensitivity C-reactive protein, interleukin (IL)-6, and IL-18 at baseline, and assessed their associations with CVEs using Cox proportional hazards models of 4.8±2.6 years follow-up. We further calculated measures of reclassification and discrimination. In age- and sex-adjusted analysis, IL-6, but neither high-sensitivity C-reactive protein nor IL-18, was associated with CVEs. The association remained significant after adjustment for conventional risk factors, intima-media thickness, and SLI (hazard ratios: 1.80, per 1-SD increase in log IL-6, P=0.03). Compared with the patients with below median IL-6 without SLI, those with above median IL-6 and SLI had a higher risk of CVEs (hazard ratios: 4.14, P=0.0014). The combination of IL-6 and SLI resulted in the net reclassification improvement of 14.3% (P=0.04), and the integrated discrimination improvement gain of 2.1% (P=0.05).

Conclusion—IL-6 levels were independently associated with CVEs and could improve reclassification in those with SLI.

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Key Words: cerebrovascular disease prevention ■ epidemiology ■ inflammation ■ interleukin (IL)-6 ■ risk factors

Low-grade chronic inflammation has been widely recognized as playing an important role in the process of atherogenesis,[1] and levels of inflammatory markers (eg, high-sensitivity C-reactive protein [hsCRP], interleukin (IL)-6, and IL-18) are associated with risk of cardiovascular disease (CVD).[2-4] However, investigation of inflammatory markers for cerebrovascular events (CVEs) as a principal outcome measure is limited.

With the growing interest in CVD-risk stratification by combining vascular imaging with conventional risk factors, established surrogate markers of subclinical CVD, such as carotid intima-media thickness (IMT),[5] and asymptomatic cerebral small-vessel disease on brain magnetic resonance imaging (MRI), such as silent lacunar infarction (SLI),[6] might more accurately predict risk assessment for clinical CVEs. Such findings make sense because the greater the progression of subclinical atherosclerotic disease, the closer an asymptomatic patient should be to a clinical outcome. Indeed, inflammatory markers are associated with both the severity of IMT[7] and presence of small-vessel disease.[8] Thus, the association between inflammatory markers and CVEs risk could be modified by IMT[9] and SLI.[10] Consequently, to help evaluate complementary information as risk predictors and stratification of more high-risk patients, studies of different sets of markers might be informative, as inflammatory marker measurement alone could provide little improvement in prediction compared with conventional risk factors, as evaluated by C-statistic.[11-13]

Therefore, the objective of this study was to clarify the values of 3 inflammatory markers (hsCRP, IL-6, and IL-18) for predicting CVEs in a cohort of patients with cardiovascular risk factors without prior CVD, while simultaneously evaluating IMT and the presence of SLI.

Materials and Methods

The participants originated from the Osaka Follow-up Study for Carotid Atherosclerosis, Part 2—a prospective cohort study in which physicians control risk factors in high-risk patients for primary and secondary prevention of CVD.[14] Outpatients aged >40 years with >1 cardiovascular risk factor, including hypertension, diabetes mellitus, hyperlipidemia, history of smoking, established arteriosclerosis documented as transient ischemic attack (TIA), stroke, coronary heart disease, or peripheral artery disease, were enrolled. Between January 2001 and December 2009, 811 outpatients who visited the Department of Neurology and Stroke Center at Osaka University Hospital were enrolled. All participants underwent a baseline clinical assessment that included medical history, inquiry into medications and smoking habits, physical and neurological examination, blood

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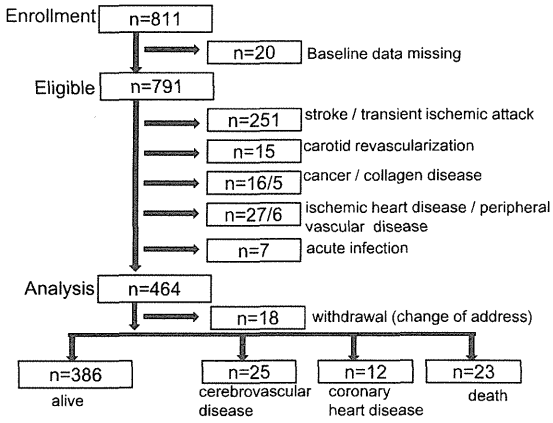

Figure 1. Study population description.

sampling, carotid ultrasound, and brain MRI. MRI was mostly performed to examine lesions in cases of stroke history or suspicious neurological symptoms (eg, headache, vertigo, dizziness, numbness, syncope, or subjective memory impairment). After we excluded participants who did not revisit our hospital because of a refusal of further participation, a change of address, or physical inability, as well as those who had incomplete baseline examinations (n=20), 791 subjects were identified as candidates. Then, individuals with clinical history of CVD and patients with evidence of nonvascular inflammatory disease were excluded. Thus, patients with a history of stroke or TIA (n=251), carotid revascularization (n=15), ischemic heart disease (n=27), peripheral vascular disease (n=6), collagen disease (n=5), or cancer (n=16) were excluded. Patients with a history of acute infections, and those with obvious signs and clinical evidence of acquired infection, were also excluded (n=7). Finally, all analyses were based on 464 patients (Figure 1). This study was approved by the local ethical review board; all patients gave written informed consent.

Risk Factors

Hypertension was defined as blood pressure ≥140/90 mm Hg on measurements taken at least twice, or the use of antihypertensive medications. Diabetes mellitus was defined as fasting plasma glucose level ≥126 mg/dL, HbA1c level ≥6.2%, or the use of antidiabetic therapy. Hyperlipidemia was defined as a low-density lipoprotein cholesterol level ≥140 mg/dL, total cholesterol level ≥220 mg/dL, or triglyceride level ≥150 mg/dL, or the use of cholesterol-lowering therapy. Smoking was classified as current smoking. Habitual alcohol intake was defined as alcohol drinking of ≥20 g/day.

Inflammatory Marker Measurement

After MRI examination, blood was drawn with minimally traumatic venipuncture to measure serum inflammatory markers. Blood was centrifuged at 3000 rpm at 4°C for 15 minutes; aliquots were stored at –80°C. Circulating hsCRP was measured by latex turbidimetric immunoassay with a sensitivity of 0.01 mg/dL (Shionogi Biomedical Laboratory Inc). Serum IL-6 and IL-18 levels were measured by ELISA (High-sensitivity Quantikine Kit, R&D System; Human IL-18 ELISA Kit, MBL Co Ltd, respectively). The detection limits for IL-6 and IL-18 were 0.10 and 12.5 pg/mL, respectively. The intraassay variations for IL-6 and IL-18 were 7.8% and 5.6%, respectively; the corresponding interassay coefficients were 7.2% and 7.6%, respectively.

MRI Protocol and Assessment

MRI protocol scans has been described.[15] MRI assessment was performed by 2 trained observers blinded to the clinical information. SLI was defined as a focal lesion >3 mm and <15 mm with a hypointense lesion and hyperintense rim on FLAIR images when located supratentorially, according to the corresponding hyperintensity and hypointensity on T2- and T1-weighted images, respectively, without stroke history. Briefly, SLI was defined as lacunar infarction on MRI without any history of clinically evident CVD. The degree of white-matter hyperintensities was visually rated on FLAIR using the Fazekas scale.[16] The interrater reliability for the presence of SLI expressed as Cohen κ was 0.80.

We evaluated the degree of intracranial artery stenosis according to MRA, as previously reported.[17] Briefly, assessment of stenosis on MRA was based on comprehensive images, and on the least change of vessel column width in those images. Stenosis was categorized by degree into 5 grades depending on the narrowness of the arteries (normal, mild, moderate, severe, and occluded).[17] We assigned patients with at least 1 stenotic segment with more than moderate stenosis to the intracranial large-artery atherosclerosis group.

Carotid Atherosclerosis Evaluation

We calculated the mean IMT by averaging the thickness at 12 sites: the near and far walls of the right and left distal common carotid arteries, bifurcation, and internal carotid artery.[18]

Follow-Up

Subjects visited outpatient clinic settings to control risk factors (eg, hypertension and hyperlipidemia) every 3 months, 6 months, or 1 year. Follow-up data were collected in June 2011. If subjects did not undergo regular examinations, their health status was checked by telephone annually, and a questionnaire about clinical events was completed upon hospitalization. If a cardiovascular event was reported, original medical records were reviewed to determine the occurrence of CVD. All possible events were audited independently by 3 physicians. Follow-up was terminated when patients withdrew from the study because of death (n=23) or personal reasons (n=18).

The outcomes used in Osaka Follow-up Study for Carotid Atherosclerosis, Part 2 were death as a result of vascular or nonvascular mortality, CVEs, coronary heart diseases, and peripheral artery disease.[14] However, in this study, the primary end point was fatal or nonfatal CVEs. CVEs included stroke, which was defined as an acute disturbance of focal neurological dysfunction with symptoms lasting >24 hours (or resulting in earlier death) and thought to be a result of either cerebral infarction or hemorrhage. We also included surgical or endovascular treatment resulting from of TIA as CVEs. However, we excluded TIA in which the neurologic deficit cleared completely within 24 hours from the onset of symptoms, without imaging evidence of stroke.

Statistical Analysis

Patients were followed from the date of MRI scan until death, loss to follow-up, or the end of follow-up. Baseline characteristics were compared using Student t test or χ^2 test, as appropriate. Where necessary, continuous variables were transformed logarithmically to give near-normal distributions of data for parametric analysis. The hazard ratio (HR) from Cox proportional hazards model with a stepwise multivariable regression (ie, backward elimination) was used to estimate the risk associated with a 1-SD increase in 3 inflammatory marker levels (hsCRP, IL-6, and IL-18) for CVEs, adjusted for age and sex (Model 1); hypertension, diabetes mellitus, smoking, hyperlipidemia, and variables showing $P<0.10$ on univariate testing (Model 2); and the white-matter hyperintensities -grade, a 1-SD increase in IMT, and the presence of SLI (Model 3). Additionally, we used a global measure of model-fit (the likelihood-ratio test), calibration (Hosmer-Lemeshow χ^2), and discrimination (C-statistics) after addition of the identified marker, individually and in combination, to the base model, including conventional cardiovascular risk factors (age, sex, hypertension, hyperlipidemia, diabetes mellitus, and smoking) and IMT. We further assessed the incremental utility of the identified individual markers in predicting CVEs by calculating the net reclassification improvement (NRI)[19] and the integrated discrimination index (IDI).[19] All analyses were performed with SAS-9.2, with statistical significance inferred as 2-sided values <0.05.

Results

Patient Characteristics

The baseline characteristics are summarized in Table 1. The mean age at the time of the MRI was 68.8±8.6 years. Vascular

risk factors were more prevalent. The correlations between inflammatory markers and conventional risk factors are summarized in Table I in the online-only Data Supplement.

Outcome

During an average duration of 4.8±2.6 years, 25 patients experienced a new onset of CVEs, including 16 ischemic, 5 hemorrhagic, and 4 surgical or endovascular treatments after TIA. We classified 16 patients with ischemic stroke, 5 with large-artery atherosclerosis, 4 with cardioembolism, 2 with lacunar infarction, and 5 with undefined type of infarction.

Stroke Risk

Table 1 shows the clinical characteristics with respect to CVE outcomes. Patients who had development of CVEs showed significantly higher rates of male, SLI, higher IL-6 levels, and IMT. Distributions of conventional risk factors, levels of blood pressure, cholesterol, fasting glucose, HbA1c, white blood cell counts, hsCRP and IL-18, rates of intracranial large-artery atherosclerosis, and the grade of white-matter hyperintensity were not statistically different between CVEs-group and non–CVEs-group. Also, for the association between inflammatory markers and atherothrombotic CVEs (n=11), IL-6 levels showed borderline significance (P=0.054), whereas neither hsCRP (P=0.53) nor IL-18 levels (P=0.196) did. CVEs-free rate curves created using the Kaplan–Meier method, with respect to the presence of SLI and median IL-6 levels are shown in Figure 2A and 2B.

In the stepwise Cox regression model (Table 2), IL-6, but neither hsCRP nor IL-18, was positively associated with risk of CVEs in Model 1. The adjusted HR for IL-6 was virtually unchanged, after adjusting for conventional risk factors in Model 2 (HR: 2.06 [1.18–3.83], P=0.01). After additional adjustment for white-matter hyperintensities grade, IMT, and SLI in Model 3, IL-6 levels remained significant (HR: 1.80 [1.06–3.08], P=0.03).

To test the hypothesis that the proportional risk of CVEs might differ according to above-median IL-6 levels (1.4 pg/mL), and the presence of SLI, both, or neither, patients were categorized into 4 groups on the basis of the median IL-6 level with SLI. Relative to those with low IL-6/SLI (–), there was no significant heterogeneity in the proportional predictive value in low–IL-6/SLI (+) or high–IL-6/SLI (–) groups. However, those with high IL-6/SLI (+) had a significantly increased risk of CVEs (HR: 4.14 [1.31–15.73], P=0.014; Figure 2C).

Table 3 shows that incorporation of the set of markers individually or in combination (ie, SLI, IL-6, SLI+IL-6) into the base model with conventional risk factors and IMT significantly improved the goodness of fit. All models were well calibrated with Hosmer-Lemeshow P values >0.05, suggesting neither model had a significant lack of fit (data not shown). A base model had a C-statistics of 0.673 (95%

Table 1. Baseline Characteristics With Respect to Cerebrovascular Events (CVEs)

		CVEs		*P*
	All, n=464	(–), n=439	(+), n=25	Value
Age	68.8±8.6	70.7±7.5	68.7±8.6	0.27
Sex,% male	49	48	71	0.04
BMI, kg/m^2	23.1±3.1	23.1±3.2	22.5±2.8	0.40
Hypertension, (%)	68	68	71	0.80
Systolic blood pressure, mm Hg	134.9±17	134.8±17.1	137.2±15.9	0.25
Diastolic blood pressure, mm Hg	77.3±11.5	77.5±11.6	73.9±9.0	0.14
Hyperlipidemia, %	53	53	67	0.18
High-density lipoprotein, mg/dL	58.5±16.4	58.6±16.3	56.3±19.4	0.51
Low-density lipoprotein, mg/dL	122.9±30.9	123.4±31.1	111.8±25.2	0.14
Triglyceride, mg/dL	124.0±63.7	125.0±64.4	107.4±47.4	0.19
Diabetes mellitus, %	17	17	17	0.99
Fasting glucose level, mg/dL	105.9±24.9	106.1±24.6	102.7±30.6	0.45
HbA1c, %	5.5±0.7	5.5±0.73	5.6±0.63	0.75
Alcohol, %	17	17	15	0.85
Current smoker, %	15	14	25	0.15
White blood cell	5607 (1448)	5586 (1450)	5990 (1389)	0.17
IMT, mm	1.14±0.61	1.11±0.57	1.69±1.05	0.01
hsCRP, mg/dL	0.05 (0.02–0.11)	0.05 (0.02–0.11)	0.055 (0.033–0.183)	0.06
IL-6, pg/mL	1.40 (0.84–2.31)	1.38 (0.82–2.24)	2.46 (1.14–4.18)	0.006
IL-18, pg/mL	191.8 (135.9–261.6)	171.4 (135.7–259.8)	193.7 (135.8–261.4)	0.80
SLI, %	28	34	58	0.01
PVH	1 (1–2)	1 (1–2)	1 (1–2)	0.28
DWMH	1 (1–2)	1 (1–2)	2 (1–2)	0.32
Intracranial large-artery atherosclerosis (%)	6.3	5.8	10.5	0.43

SLI indicates silent lacunar infarction; IMT, intima-media thickness; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; PVH, periventricular hyperintensities; and DWMH, deep white-matter hyperintensities. Estimates are presented as percentages, mean±SD or median (interquartile-range).

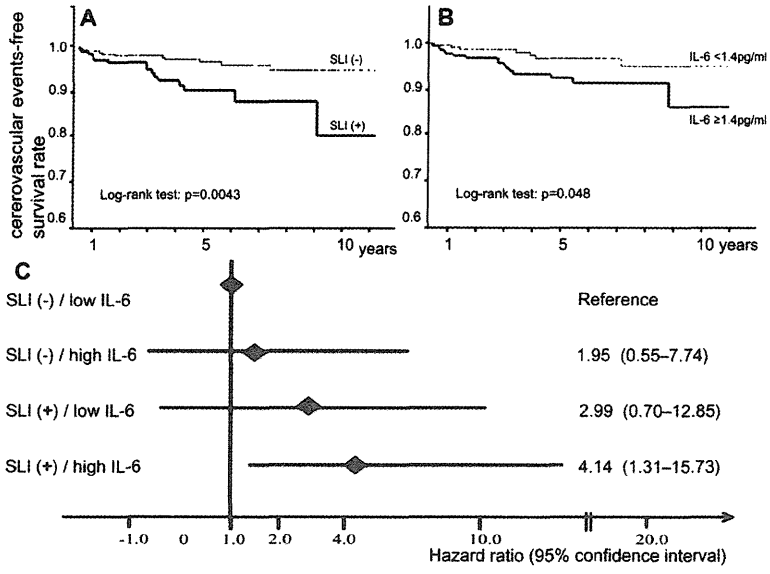

Figure 2. Kaplan–Meier curves of the cerebrovascular event (CVE)-free survival rate stratified by the presence of silent lacunar infarction (SLI; **A**) and median interleukin (IL)-6 levels (**B**). Associations of IL-6 and the presence of SLI with the risk of CVEs by dichotomous cutoff at median IL-6 level with or without SLI relative to the low IL-6 without SLI group (**C**).

CI, 0.637–0.724), and the addition of individual markers resulted in increases in the C-statistics (all changes >0.05), but made less statistically significant (Table 3). When the risk was reclassified into risk categories of <5%, 5% to 15%, or >15% risk of CVEs,[20] reclassification tables of the estimated risk using the models with and without SLI+IL-6 are shown in Table II in the online-only Data Supplement. We observed significant reclassification improvement with NRI of 0.149 (P=0.04) in the base model with SLI+IL-6, and the NRI of 0.259 (P=0.03) in the base model with IL-6, whereas the NRI was nonsignificant for SLI (P=0.44). The IDI was borderline significant improvement for SLI+IL-6 (0.021, P=0.05), IL-6 (0.012, P=0.06), whereas the IDI was nonsignificant for SLI (0.009, P=0.74). We performed additional analyses restricted to intermediate-risk groups (5% to 15% risk of CVEs). The NRI in the base model with SLI+IL-6 was significant (0.423, P=0.01), whereas the NRI was nonsignificant for both IL-6 (0.286, P=0.17) and SLI (0.05, P=0.74; Table 3).

Discussion

Among the 3 inflammatory markers, IL-6 levels is of potential, clinical value to predict future CVEs and to add marginally to the information obtained from determination of conventional risk factors and surrogate markers (ie, IMT, SLI) in individuals without prior CVD, as measured by significant reclassification in both the overall cohorts and in patients categorized as intermediate-risk group.

We confirmed that IL-6 levels are investigated with composite CVD incidence,[3,12,13,21,22] stroke incidence[22–24] and recurrence,[25,26] mortality,[26] or prognosis after stroke.[27] However, the results of only a few clinical studies on initial stroke incidence remain controversial. The Health ABC Study demonstrated that IL-6, but not hsCRP or tumor necrosis factor-α, predict stroke incidence in elderly populations without prior CVD.[23] In contrast, both the PROSPER[24] and Caerphilly[22] studies confirmed that no inflammatory markers, including IL-6,[22,24] hsCRP,[22,24] and IL-18,[24] showed independent associations and discrimination of stroke risk. The significance of inflammation marker in these previous studies has not been consistently shown in terms of discriminatory ability, judged from the C-statistic.[22]

Furthermore, prospective data on the combination of inflammatory markers and SLI for stroke are also limited. Only 1 prospective study reported the predictive value of hsCRP with stroke-risk incorporating SLI; meanwhile, higher hsCRP was no longer a significant predictor without SLI.[10] To our knowledge, this is the first study to examine not only the association of IL-6 with first CVEs, but also the potential predictive ability at the individual levels in calculating the NRI in contrast with previous studies.[12,13] Folsom et al[12] showed IL-6 measurement added only a small increment in the C-statistics in the CVD-risk prediction. They had not applied NRI in statistical approaches. However,

Table 2. Stepwise Cox Proportional Hazards Regression Analysis of Baseline Inflammatory Markers for the Risk of CVEs

	Model 1	Model 2	Model 3
IL-6	1.95 (1.15–3.31) P=0.01	2.06 (1.18–3.83) P=0.01	1.80 (1.06–3.08) P=0.03
hsCRP	1.31 (0.91–1.84) P=0.15	—	—
IL-18	1.47 (0.62–3.55) P=0.38	—	—

IL indicates interleukin; hsCRP, high-sensitivity C-reactive protein; and CVEs, cerebrovascular events.
Hazards ratios are for a 1-SD increase in log inflammatory markers.
Model 1: adjusted age and sex.
Model 2: Model 1+hypertension, hyperlipidemia, diabetes, smoking, and variables showing P<0.10 on univariate testing.
Model 3: Model 2+white-matter hyperintensity grade, IMT, or SLI.

Table 3. Measures of Model-Fit, Discrimination, and Reclassification of Risk Models Without and With IL-6 in the Prediction of CVEs

	Likelihood-Ratio Test (P^a)	C-Statistics (95% CI)	P^a Value
Base model		0.681 (0.637–0.724)	
+SLI	0.09	0.723 (0.680–0.764)	0.59
+IL-6	0.02	0.748 (0.706–0.787)	0.38
+SLI+IL-6	0.01	0.766 (0.725–0.804)	0.26

SLI indicates silent lacunar infarction; IL, interleukin; and CVEs, cerebrovascular events.

	NRI	P^a Value	IDI	P^a Value	NRI (Intermediate-Risk Group)	P^a Value
Base model						
+SLI	0.07	0.44	0.009	0.74	0.05	0.75
+IL-6	0.259	0.03	0.012	0.06	0.286	0.17
+SLI+IL-6	0.149	0.04	0.021	0.05	0.423	0.01

SLI indicates silent lacunar infarction; IL, interleukin; NRI, net reclassification improvement; and IDI, integrated discrimination index. P^a value compared with the base model (cardiovascular risk factors [age, sex, hypertension, hyperlipidemia, diabetes mellitus, and smoking]) and IMT.

recent epidemiologic statistics has proposed that C-statistic should not be the sole determinant of clinical utility.[28,29] Briefly, when examining the usefulness of a marker in improving the overall risk prediction, important parameters to consider include improvement in the C-statistic, as well as the model performance and the calibration.[19] Reclassification is also a practical approach to gauging the effects of adding new risk factors to the conventional risk factors, when differences in the C-statistic are marginal.[19,28,29] Therefore, it is important to note that our results show a consistent pattern for IL-6 levels across statistical methods.

Neither hsCRP nor IL-18 was predictive of stroke incidence in this study. However, a recent meta-analysis suggests hsCRP is associated with the prediction for ischemic stroke, but not with hemorrhagic stroke.[2] In this study, the lack of association between hsCRP and CVEs is possible because the end point—any CVEs including hemorrhagic stroke—could underestimate the strength of their association. Furthermore, a small number of end points precluded a separate analysis for CVEs subtype. Several prospective studies have similarly failed to confirm an association between hsCRP and stroke risk in elderly populations, or those with more vascular risk factors.[23,30] Furthermore, Mendelian randomization studies have reported a lack of concordance between the associations among CRP genotypes, CRP concentrations, and CVD, which has been interpreted as an argument against causality.[31,32] However, 2 recent genetic meta-analyses lend support for the causality of a lifelong genetic predisposition to high levels of IL-6 pathway (ie, upstream of CRP) in determining a proportionally increased risk of CVD, raising expectations for anti-inflammatory strategies for risk reduction.[33,34]

IL-18, specific alternative pathways as the interferon-γ–dependent atherogenesis, predicts CVD, because both clinical and experimental studies have supported its role in atherosclerotic plaque progression and destabilization, as well as predominantly coronary endpoints.[35,36] However, significance of IL-18 for risk of stroke remains unclear. The lack of association between IL-18 and stroke in our study is concordant with recent studies that IL-18 was not associated with an increased risk of stroke incidence[24] or recurrence.[25]

Furthermore, hsCRP, IL-6, and IL-18 levels have all been in positive correlation with IMT, body mass index, and triglycerides, but only IL-6 had predictive value for CVEs (Table I in the online-only Data Supplement). Recent genetic analysis, as discussed above, shows that IL6-receptor genotype is associated with the risk of CVD, but it is not related to conventional risk factors.[33] The effect of Asp358Ala on IL6-receptor for CVD-risk is unlikely to be mediated by conventional risk factors.[33] Taken together, elevated IL-6 level may reflect a response to atherosclerosis and genetic causality, so IL-6 might be of potential clinical value.

We acknowledge several limitations. First, it includes the low incidence of CVEs in this cohort. Thus, although we can speculate that inflammation marker levels are related to atherothrombotic CVEs, we cannot draw any conclusion about the value of inflammatory markers in each stroke subtype from this study. The prevalence of vascular risk factors was relatively high at baseline, but our participants in the ambulatory setting of cardiovascular prevention clinics may have had more intensive risk factor modification in lifestyle and by drug therapy during follow-up, thereby reducing the number of events and decreasing the statistical power. Nonetheless, the association between only IL-6 levels and atherothrombotic CVEs has shown borderline significance. Second, the blood sampling by a single measure could not be corrected for within-person variability.[3] Third, the present study is limited to the cohort of Japanese elderly individuals with vascular risk factors, without known CVD. Consequently, the predictive values of IL-6 may be specific to this population, not generalizable to other races and cohorts. Fourth, we observed a significant improvement in model prediction using the likelihood-ratio test and calibration; however, the improvement in C-statistics was not statistically significant, although this highlights the deficiencies of C-statistics, which are insensitive to small changes in predictive accuracy.[19] We assessed the incremental prognostic value of IL-6 and SLI in combination in using the NRI and IDI, but we recognize that changing the boundaries used to define risk categories would influence the NRI computed,[19] and there is no widely agreed on definition of clinically important boundaries for the prediction of CVEs. Furthermore, direct comparisons with studies evaluating the NRI with other markers should be made with caution because the number of risk categories used, definition of the outcome, and length of follow-up often differ between studies. The lack of consensus in this particular area needs to be addressed. Furthermore, we also calculated the IDI, a newer method for evaluating improvement in risk discrimination, which was marginally significant but was of small magnitude. Therefore, despite a consistent pattern for IL-6 levels across statistical methods, our study does not seem to bring major advances in risk stratification. Thus, given the characteristics of our cohort, our results suggest IL-6 measurement should not routinely be performed in the general population because the overall added value may be small and unlikely to be a clinical importance at the moment. We concluded that determining a patient's stroke risk on the basis of IL-6 level may be clinically challenging, if IL-6 is used in low-risk populations. We assume that further studies are needed to better define the target population.

In conclusion, IL-6 level was independently associated with the incidence of CVEs in patients with vascular risk factors, but without prior CVD. However, whether to use screening based on IL-6 levels as a more routine test for risk prediction requires full consideration. Further, large investigation or randomized controlled trial will be needed to assess whether risk refinements measuring IL-6 levels lead to a meaningful change in clinical outcome.

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Disclosures

None.

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