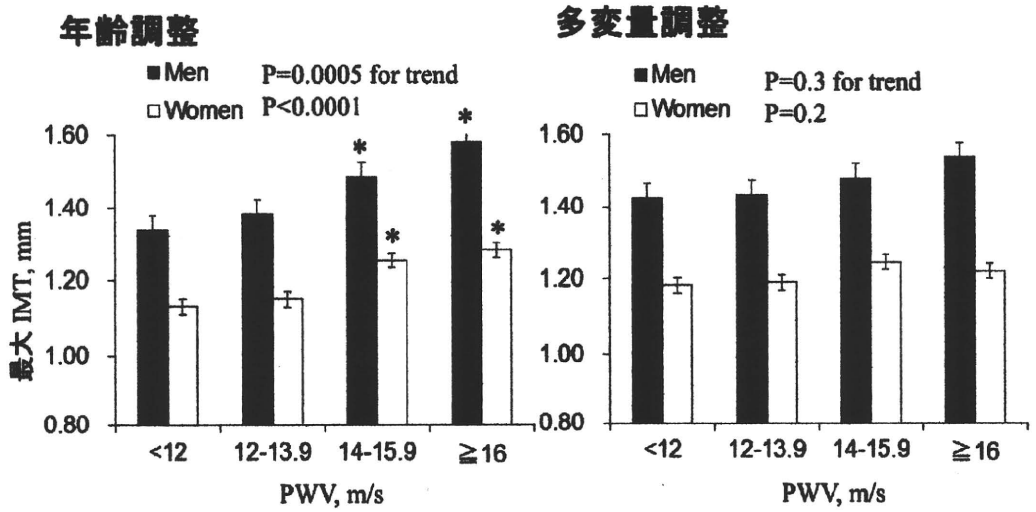
図4．男女別脈波伝搬速度カテゴリー別による頸動脈エコー検査の年齢調整および多変量調整最大 IMT 値



*: P＜0.05, PWV<12m/s 群と比して
多変量調整は、BMI,喫煙、飲酒、血圧カテゴリーIFG, DM, 総コレステロール、HDLコレステロールを行った。

表 3. 脈波伝搬速度カテゴリー別によるプラーク有所見、25%以上狭窄のオッズ比

プラーク有所見のオッズ比

PWV	男性	女性
<12	1	1
12-13.9	1.4 (0.9-2.4)	1.5 (1.0-2.1)
14-15.9	2.0 (1.2-3.3)	2.8 (1.9-4.0)
≧16	2.2 (1.2-4.0)	3.1 (2.0-4.9)

25%以上狭窄率のオッズ比

PWV	男性	女性
<12	1	1
12-13.9	1.8 (0.7-4.9)	1.1 (0.4-3.2)
14-15.9	2.5 (0.9-6.5)	2.5 (0.9-6.5)
≧16	3.2 (1.2-8.4)	2.3 (0.8-6.4)

16m/s 以上の群において年齢調整の平均 IMT が男女とも有意に高い値であった。BMI、喫煙、飲酒、JSH2009 血圧カテゴリー、糖尿病（IFG, DM)、総コレステロール・HDL コレステロールにて調整した平均 IMT 値は、PWV≧14m/s の女性で有意に高い値であった。最大 IMT 値は、平均 IMT 値と年齢調整による結果はほぼ同じような

結果であったが、多変量調整すると統計的に有意差は見られなかった（図 4)。

表 3 は、脈波伝搬速度カテゴリー別にプラーク有所見、25%以上狭窄のオッズ比を示したものである。PWV <12m/s を基準としたときに、頚動脈プラーク有の多変量調整オッズ比（95%信頼区間）は、PWV 12m/s 以上 14m/s 未満、14m/s 以上 16m/s 未満、16m/s 以上の群において、それぞれ 1.3 (0.9-1.7)、1.7 (1.2-2.4)、1.6 (1.1-2.5)であった。さらに、PWV <12m/s を基準としたときに、頚動脈 25%以上狭窄有の年齢調整オッズ比（95%信頼区間）は、PWV 14m/s 以上 16m/s 未満の群で 2.6 (1.3-5.1)、16m/s 以上の群で 3.0 (1.5-6.0)であった。

D. 考察

年齢と血圧の PWV への相対寄与率が男女とも 9 割みられ、PWV の評価には年齢と血圧を考慮することが重要であることが分かった。また、正常高値血圧の相対寄与率が 8～9%みられることから、正常高値血圧の段階から生活習慣改善が必要であることが分かった。また、脈波伝搬速度と頚動脈エコー所見のとの間に、特に平均 IMT との間に関連が認められた。多変量調整にすると脈波伝搬速度と頚動脈エコー所見との関連が弱くなるのは、血圧による影響が強いからと考えられる。脈波伝搬速度により動脈硬化の使用としてみるためには、年齢と血圧を調整した評価が必要である、そのためには偏りの少ない多くのデータが必要で、都市部一般住民を無作為抽出した吹田研究を用いて検討する意義は大きい。多くの地域コホート研究は、健診に受診しに来られたものを対象としているので、どうしても男性が少ないのが現状でありのに対して、吹田研究は性年齢階層別に無作為に抽出している点に偏りが少なくなる。

脳卒中の予測指標として脈波伝搬速度と頚部エコー検査がどの程度妥当なのかについては、さらにそれぞれの脳卒中発症または死亡との関連について検討する必要があり、次年度以降で検討する予定である。

E. 結論

年齢と血圧の PWV への相対寄与率が男女とも 9 割みられ、PWV の評価には年齢と血圧を考慮することが重要であることが分かった。また、正常高値血圧の相対寄与率が 8～9%みられることから、正常高値血圧の段階から生活習慣改善が必要であることが分かった。

都市部一般住民を対象に脈波伝播速度と頚動脈硬化症との間にはよい関連性が見られた。

F. 健康危険情報

特になし

G 研究発表

1．論文発表：

Kokubo Y, Toyoda K, Watanabe M, Higashiyama A, Ono Y, Nagatsuka K, Okamura T. Prediction of Stroke and Ischemic Heart Disease by Carotid Intima-Media Thickness in Japanese Urban Cohort: The Suita Study. Stroke. 2011;42;e271-272.

2．学会発表：

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2. 小久保喜弘、岡村智教、渡邊至、東山綾、小野優、長束 一行、豊田 一則、神出計、河野雄平. 都市部一般住民を対象とした循環器病危険因子の脈波伝播速度への相対寄与率：吹田研究. 第 10 回臨床脈波研究会. 2010 年 5 月 22 日，東京.

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H. 知的財産権の出願・登録状況

なし

10. 資　　料

「細動脈硬化の評価指標に関する多施設共同前向き研究」
研究計画書

1)協力の任意性と撤回の自由

この調査は強制的なものではなく、したがってこの調査への参加を断っても患者への不利益が生じることはない。またいったんこの調査に参加したあと、途中でやめることも自由である。

2)研究の目的

脳卒中の基盤となる動脈硬化は、主として粥状硬化と細動脈硬化に大別される。粥状硬化は画像検査が進歩し、早期から詳細な診断が可能で、治療効果に対するエビデンスも多い。一方、細動脈硬化は、血管径が細いため従来の画像診断技術では評価が困難であり、治療介入の効果に関するエビデンスも乏しい。日本をはじめとするアジア諸国の脳卒中病型は未だに細動脈硬化をもとにしたラクナ梗塞や脳出血が欧米よりも頻度が高いため、細動脈硬化にも注意を払った診断や治療法を確立してゆく必要がある。

本研究の目的は、アテローム血栓性脳梗塞、ラクナ梗塞、脳出血症例を対象に、頸動脈エコーのみで得られる指標（内中膜厚、プラークスコア、総頸動脈および内頸動脈の pulsatility index）、脈波伝播速度、脳血管反応性を多施設で前向きに調査・集計し、各病型との関連性について解析し、細動脈硬化を特異的に評価可能な指標を探索することである。粥状硬化の指標としては、頸動脈の内中膜厚、プラークスコアがこれまでの研究でも頻繁に用いられている。細動脈硬化の指標としては、末梢血管抵抗を表す pulsatility index、脳血管反応性を選択した。さらに脈波伝播速度は大血管の硬さを表す指標であるが、ラクナ梗塞やアルブミン尿との関連があることから、脳や腎臓の細動脈効果を反映すると考えられている。また１年後に再検査が可能な症例は１年後に同様の項目について再検し、１年間の治療による影響や再現性を解析する。

3)研究責任者および研究組織

1)研究責任者

長束一行　　（国立循環器病研究センター・脳神経内科部長）

2)研究施設および代表者

国立循環器病研究センター脳神経内科（部長・長束一行）
東京女子医科大学神経内科（教授・内山真一郎）
広島大学神経内科（教授・松本昌泰）
東邦大学医学部医学部教育開発室（教授・藤代健太郎）
大阪大学神経内科（准教授・北川一夫）
獨協医科大学神経内科（講師・竹川英宏）
福井大学神経内科（助教・山村修）
大阪医療センター脳卒中内科（医長・多賀谷昌史）

4)研究の対象および方法

1)対象

アテローム血栓性脳梗塞、ラクナ梗塞、脳出血、無症候性脳梗塞、無症候性脳出血、無症候性脳血管狭窄症のある患者（急性期・慢性期を問わない）で、2011年2月（倫理委員会承諾後）から2012年12月までに当研究の説明を行い同意の得られた症例（文書および口頭説明で同意書は不要であるが、診療録に記載する）。

2)方法

上記対象の診療録より、観察項目として年齢、性別、危険因子、血液検査（脂質、腎機能）、尿蛋白、内服薬、脳卒中病型分類、頭部 MRI、頭部 MRA 所見についてデータ収集する。また対象者

は全例に頸動脈エコー検査、脈波伝播速度の計測を行い、側頭部より経頭蓋ドプラー検査で頭蓋内主要血管の血流波形が得られる症例では、血流波形の **pulsatility** index および、息こらえ法による脳血管反応性を計測する。これらの検査は脳血管障害の評価として日常診療で行われる検査項目であり、保険収載もされている。1年後の再評価が可能な症例は、1年後に同項目の検査を実施する。
1年後の再評価は入外を問わないが、観察項目が11ヶ月後から13ヶ月以内に施行される必要がある。
統計解析に関してはまず脳卒中病型を評価項目として、これらを粥状硬化の指標(頸動脈エコーでの IMT、プラークスコア)および細動脈硬化の指標(頸動脈血流波形の **pulsatility** index、経頭蓋ドップラー方による頭蓋内動脈の **pulsatility** index と脳血管反応性、脈波伝播速度)で区別可能かを判定する。1年後再評価が可能な症例では、急性期例では投薬内容による変化、特に細動脈硬化の指標が改善するかについて注目して解析を行い、慢性期の症例では再現性に注目して解析を行う。
3)研究デザイン
多施設共同前向きコホート研究

5)データ集積
各施設で作製したデータを連結可能匿名化し、国立循環器病研究センター中央事務局で収集し解析を行う。
データの保管は脳神経内科部長室内のパスワードで管理され移動不可能なコンピューターで管理され、データベースの操作も ID、パスワードで保護する。データの管理者は主任研究者の長束で、他施設からのデータの受け渡しは個人情報を消去したデータをCDに記録し、配送の確認が可能な郵送方法で行う。

6)目標症例数
各施設の検査実績についての調査から 400 例程度はデータ収集が可能と考えた。

7)研究期間
2011 年 2 月～2013 年 3 月
2011 年 12 月以降の登録症例は再検査を行わない。

8)研究計画等の開示
研究対象者から要請があれば研究計画を開示する。

9)予測される危険性
診療録からの情報と、経頭蓋ドプラー検査や脈波伝播速度は通常の臨床で行われる非侵襲的な検査であるので危険性はない。

10)被験者の利益及び不利益
本研究により直ちに被験者が得られる利益、不利益はないが、将来この研究で個々の症例について至適な治療法が見つかる可能性がある。

11)費用負担に関する事項
この研究に必要な費用は、平成22年度厚生労働省科学研究費補助金「動脈硬化の多角的評価による脳卒中個別化治療開発に関する研究」(主任研究者：長束一行) から支出される。

12)知的所有権に関する事項
この研究の結果として特許権等が生じた場合、その権利は国、共同研究機関及び研究遂行者などに属し、協力患者には属さない。またその特許権等に関して生じうる経済的利益についても協力

患者には権利はない。

13)倫理的配慮

この研究は、国立循環器病研究センター倫理委員会で研究計画書の内容及び実施の適否等について、科学的及び倫理的な側面が審議される。また研究計画の変更、実施方法の変更が生じる場合には適宜審査を受け、安全性と人権に最大の配慮を行う。

調査結果は、個人名が特定できない形で集計し、本研究の目的のみに使用する。この調査に参加することによって患者の個人情報が外部へ漏れたりプライバシーが侵害されたりすることが無いように留意する。

「細動脈硬化の評価指標に関する多施設共同前向き研究」への参加ついてのお願い

1．研究への協力の任意性と撤回の自由

この研究へ参加するかどうかはあなたの自由意思で決めてください。強制はいたしません。参加したくない場合は、遠慮なくお断りください。また、研究に参加しなくても、今後のあなたの治療において不利益になるようなことはありません。

また、一度同意した場合でも、途中でやめたい場合は、いつでも同意を取り消すことができ、診療記録などもそれ以降は研究目的に用いられることはありません。

ただし、同意を取り消した時すでに研究結果が論文などで公表されていた場合などのように、調査結果などを廃棄することができない場合があります。

2．研究調査の目的及び内容

【目的】

脳卒中は多くの場合、動脈硬化が原因で発症しますが、動脈硬化にも種類があり太い血管が主に障害される粥状硬化と、細い血管が主に障害される細動脈硬化に分かれます。粥状硬化は太い血管ですので評価する方法がたくさんありますが、細動脈硬化は0.1-0.2㎜程度の血管が対象ですので直接検査で見ることが困難で、まだ確立した評価法がありません。この研究では、粥状硬化と細動脈硬化を評価できる可能性のある検査を複数行い、両者を区別できるかどうかについて研究します。

【内容】

（1）対象

登録期間中に脳卒中で入院された患者さんが対象です。過去の脳卒中や無症候の患者さんも含まれます。

（2）調査方法

1）初回検査

検査項目は通常脳卒中の診断のため行われている検査で、採血（一般、生化学）、尿検査、頭部MR検査、脈波伝播速度、頸動脈エコー検査、経頭蓋ドプラ検査です。全て一般的に動脈硬化の診断のために行われている検査で危険性はありません。経頭蓋ドプラ検査は頭の中の太い血管の血流速度を測る検査です。うまく取れない方もいますので、全員にしていただくわけではありませんが、途中で出来るだけ長く（少なくとも２０秒以上）息を止めていただく必要がありますので、ご協力宜しくお願いいたします。

2）再検査

１年後再検査が可能な方は、同様の検査を外来か短期間の入院で行っていただき、１年間の変化をみます。

3）研究責任者および研究組織

・研究責任者　長束一行（国立循環器病研究センター・脳神経内科部長）

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大阪大学神経内科
獨協医科大学神経内科
福井大学神経内科
大阪医療センター脳卒中内科

登録期間は平成23年2月から平成24年12月までです。

3．研究計画等の開示
あなたが希望される場合、この研究計画の内容を見ることができます。

4．予想される危険性及びその対応
この研究では通常一般的に行われている侵襲のない検査を行うだけですので、特に予想される危険性はありません。

5．参加者にもたらされる利益及び不利益
調査に協力することにより起こりうる不利益は特に考えられません。

6．個人情報の保護
この調査にご協力いただいた場合、疫学研究に関する倫理指針に基づきプライバシーは固く守ります。研究調査のデータ及び結果は、目的以外には使用することはありません。また調査結果を論文やその他の方法で公表する際、匿名性を厳守いたします。データの保管はデータ管理者のパスワードで管理され移動不可能なコンピューターで管理され、データベースの操作もID、パスワードで保護いたします。他施設からのデータの受け渡しは個人情報を消去したデータをCDに記録し、配送の確認が可能な郵送方法で行います。

7．研究調査結果の公表
調査結果は、学会発表や、雑誌などで公表されることがありますが、その際には匿名化により個人の特定はできなくなります。

8．知的所有権に関すること
この調査の結果として特許権等が生じる可能性がありますが、その権利は国、研究機関及び研究遂行者などに属し、あなたには属しません。また、その特許権等に関して経済的利益が生じる可能性がありますが、あなたはこれらについても権利はありません。

9．費用負担に関すること
この調査に参加することで、新たな費用負担は生じません。

10．倫理的配慮
この研究は、国立循環器病研究センター倫理委員会などで研究計画書の内容及び実施の適否等について、科学的及び倫理的な側面から審議され承認されており、承認された研究計画書に従って行います。また、研究計画の変更、実施方法の変更が生じる場合には適宜審査を受け、安全性と人権に最大の配慮をいたします。

問い合わせ先：国立循環器病研究センター
吹田市藤白台5-7-1　TEL(06)6833-5012
脳神経内科部長　長束一行

11. 関連業績一覧

研究成果の刊行に関する一覧

長束　一行

〈雑誌〉

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Histologic characterization of mobile and nonmobile carotid plaques detected with ultrasound imaging

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Objectives: **Although mobile plaques in the carotid arteries detected by duplex ultrasound imaging are considered to cause unstable neurologic symptoms such as crescendo transient ischemic attack or progressive stroke, the histology of mobile plaques has not been sufficiently documented. This study examined the histopathologic features of mobile plaques of the carotid artery and compared the histopathology between mobile and nonmobile plaques.**

Methods: **Of 228 carotid plaques assessed by preoperative carotid ultrasound imaging, 21 (9.3%) were diagnosed as mobile symptomatic plaques. Of these, 18 were intact after excision by endarterectomy and enrolled for histologic examination. From the remaining 207 nonmobile plaque specimens, 17 nonmobile but symptomatic plaque specimens were extracted for histologic comparison. An investigator blinded to the ultrasound findings assessed both plaque specimens for fibrous cap thickness, fibrous cap rupture, fibrous cap area, necrotic core size, inflammatory cells, intraplaque hemorrhage, and mural thrombus. Clinical data, including progressive ischemic symptoms after admission, were also examined.**

Results: **Progressive ischemic symptoms were more frequently seen in patients with mobile plaques than in those with nonmobile plaques (33.3% vs 0%, $P = .02$). The ratio of the cross-sectional area of the necrotic core to that of the entire plaque was significantly larger for mobile plaques than for nonmobile plaques (mean, 0.660 vs 0.417, $P < .0001$). Mural thrombus was more prevalent among mobile plaques (89%) than among nonmobile plaques (59%), but the difference was not significant ($P = .06$). The median minimum thickness of the fibrous cap was extremely small in both groups (80 μm in mobile plaques and 100 μm in nonmobile plaques, $P = .33$).**

Conclusions: **The histologic characteristics of mobile carotid plaques are different from those of nonmobile symptomatic plaques, especially in the area of the necrotic core. This histologic difference may partly explain the unstable neurologic presentations of patients with mobile carotid plaques. (J Vasc Surg 2011;53:977-83.)**

Mobile components in symptomatic carotid plaques, as detected with a duplex ultrasound scan using the recently developed high-resolution real-time B-mode system, are assumed to cause unstable neurologic symptoms such as crescendo transient ischemic attack or progressive stroke. These types of plaque with mobility have been denoted variously in several case reports as "mobile plaques,"[1] "floating plaques,"[2-4] "mobile thrombi,"[5] or "floating thrombi."[6,7] Some authors have emphasized the high potential of the mobile plaque to cause recurrence of ischemic attacks within a short period.[5,8,9] They have also speculated that plaque disruption and mural thrombus resulted in mobile plaques.[5,6]

Previous reports have not, however, sufficiently documented the mechanism of that mobility or the histologic feature of such plaques. We hypothesized that certain histologic differences may exist between mobile and nonmobile symptomatic carotid plaques as long as clinical symptoms caused by mobile plaques are more unstable than those by nonmobile plaques. To confirm this hypothesis, we compared the prevalence of several histologic factors between mobile and nonmobile plaques in symptomatic patients, with the examination of clinical data including progressive ischemic symptoms after admission.

METHODS

This study was performed in accordance with the ethical guidelines of our institution and included patients' informed consent.

Plaque selection. Between April 2003 and March 2008, 228 carotid plaques were excised by carotid endarterectomy (CEA) at the National Cerebral and Cardiovascular Center, Osaka, Japan. All patients had been assessed with preoperative carotid ultrasound imaging, and 21 symptomatic patients (9.3%) had been diagnosed with mobile plaques. The study excluded 3 of 21 mobile plaque specimens after the histologic examination because they

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were damaged during plaque excision. From the remaining 207 nonmobile plaques, 20 symptomatic plaques were randomly extracted for histologic comparison. After the histologic examination, the study excluded 3 of the 20 nonmobile plaque specimens because they were too damaged. The remaining 35 plaque specimens, comprising 18 mobile plaques and 17 nonmobile plaques, were used in this study.

Clinical data. We reviewed clinical data of the 35 patients with excised plaques. Their symptoms at admission were classified into four categories: amaurosis fugax, transient ischemic attack (TIA), transient symptom associated with infarction (TSI), and stroke. Amaurosis fugax was defined as a transient ipsilateral blindness or visual field defect. TIA was defined as a transient neurologic symptom that lasts <24 hours without any evidence of brain infarction confirmed by diffusion-weighted images (DWI) in magnetic resonance imaging. TSI was defined as a transient neurologic symptom that lasts <24 hours with evidence of brain infarction, which is supposed to have higher in-hospital recurrent ischemic rate than TIA.[10] Stroke was confirmed by positive findings in the territory of the ipsilateral carotid artery on DWI. Progressive symptoms were also recorded when the patient experienced a recurrence and worsening of neurologic symptoms after admission, with an increase of ischemic lesions confirmed by DWI.

The degree of carotid stenosis was measured by digital subtraction angiography according to the method used in the North American Carotid Surgery Trial.[11] The other clinical data recorded were age, sex, treatment for hypertension, treatment for diabetes, treatment for hyperlipidemia, smoking within the preceding year, statin administration, and aspirin administration. Median intervals from the last ischemic event to CEA and then from the last ultrasound imaging to CEA were also examined.

Ultrasound imaging. All patients underwent preoperative carotid ultrasound scanning ≤1 month before CEAs using a commercially available, real-time 2-dimensional device equipped with a 7.5-MHz transducer. B-mode scans, B-mode scans with color Doppler imaging, and pulsed-Doppler scans were routinely performed. If a stroke physician suspected the presence of mobile plaques on duplex ultrasound imaging, the images would be recorded as video files. Two skilled stroke physicians, who had no previous knowledge of the patient's clinical information, including a coauthor (K.N.), reviewed video files and made a final diagnosis of mobile plaques. The findings of the mobile plaques were defined and classified as follows:

1. Mobile components that are localized at the surface of the plaque and that rise and fall in a manner inconsistent with or exceeding arterial pulsatile wall motion (jellyfish sign[12]),
2. Mobile components inside the plaque that change slowly and irregularly like viscous liquid (liquefaction sign),
3. Movements localized within an ulcer's inner surface (Fig 1; Video 1, online only), and

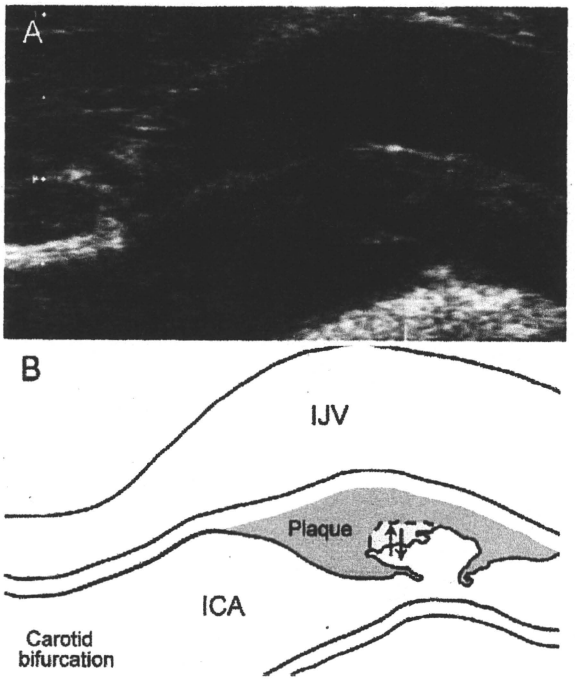

Fig 1. A, A longitudinal duplex ultrasound image of a mobile plaque demonstrates an ulcerated plaque in the extracranial internal carotid artery. **B,** A schema representing the mobile component in the plaque: an ulcer's inner surface rose and fell according to the pulsation, as indicated with *arrows,* which was defined as "movements localized within an ulcer's inner surface" (see also Video 1, online only). *ICA,* Internal carotid artery; *IJV,* internal jugular vein.

4. Movements of protuberances (Fig 2; Video 2, online only).

Plaque excision. General anesthesia was initiated, and CEA was performed using an operating microscope and somatosensory evoked potential monitoring to selectively place the shunt. For some cases with a mobile plaque, each surrounding artery (including the common, external, and internal carotid arteries) was clamped as soon as it was exposed to minimize the risk of distal embolism caused by the manipulation of the internal carotid artery. Upon cross-clamping, the common carotid artery was incised with scalpels to determine the dissection plane, usually made at the level of the internal elastic membrane, under the operating microscope. A microdissector was inserted meticulously, not to disturb the cleavage plane, until the distal end of the plaque and the patent lumen of the distal internal carotid artery were ascertained. The distal and proximal edges of the plaque were cut and finally pulled out from the orifice of the external carotid artery. In this way, most of the carotid plaque could be removed en bloc with minimum surgical trauma. If a cut penetrated the surface of the specimen to the lumen, it could be judged in the histologic examination that the cleavage resulted from surgical trauma, not plaque rupture.

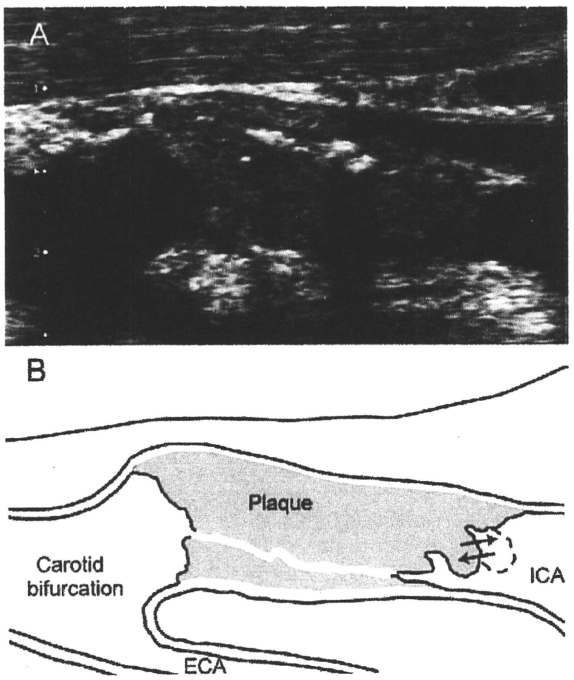

Fig 2. A, A longitudinal duplex ultrasound image demonstrates a massive mobile plaque almost occluding the internal carotid artery (*ICA*) and a protuberance from the distal end of the plaque. **B,** A schema representing the shaking movement of the protuberance (*arrows*): the original video also revealed a mobile component inside the plaque that changed slowly and irregularly like viscous liquid (liquefaction sign, see also Video 2, online only). *ECA,* External carotid artery.

Histopathology. The excised plaques were immediately fixed in Histochoice fixative (Amresco, Cleveland, Ohio) for 48 hours and decalcified by ethylenediaminetetraacetic acid (EDTA). To preserve the immunoreactivity, we used Histochoice for fixation and EDTA for decalcification of specimens before embedding in paraffin blocks.[13] Each plaque was sectioned transversely at the carotid bifurcation, and further sections were taken at 5-mm intervals along the length of internal carotid arteries for embedding in paraffin.[14] Adjacent 5-μm transverse sections were stained with hematoxylin and eosin, elastin van Gieson, Masson trichrome, and von Kossa. When a certain section seemed near the plaque rupture site, additional subserial slices were performed to avoid skipping focal instability. For immunohistochemistry analyses, we performed immunostaining for T cell (CD3, DAKO, Glostrup, Denmark), macrophages (CD68, DAKO). Immunostaining with glycophorin A (CD235a, DAKO) was also performed to detect intraplaque hemorrhage.[15] An experienced cardiovascular pathologist (H.I.) histologically examined all sections without any knowledge of clinical details and findings of carotid ultrasound imaging.

The histologic features of plaques assessed in this study were minimum cap thickness, prevalence of the rupture of fibrous cap and ulceration, necrotic core size, quantity of inflammatory cells (including macrophages and lymphocytes), degree of intraplaque hemorrhage, and prevalence of mural thrombus. Minimum cap thickness was defined as the thinnest part of the fibrous cap in total cross-sections of each plaque measured by a manometer attached to the microscope.[16] Plaque rupture, a break in the fibrous cap, was recorded when there was clear interaction between the lipid core and the lumen, usually at a point of thinning and inflammation and when the break in the cap did not seem to have been created during surgery (Fig 3, *A*). A necrotic core was defined as an amorphous material containing cholesterol crystals (Fig 3, *B*).[17]

To measure the area of necrotic core, we sampled three cross-sections: on the carotid bifurcation, 5 mm distal to the bifurcation, and 10 mm distal to the bifurcation. On each cross-section, the necrotic core and the entire plaque area were measured by WinROOF 5.0 morphometry software (Mitani Co, Kanazawa, Japan), and the ratio of the mean cross-sectional area of the necrotic core to that of the entire plaque area was calculated. We also measured the actual area of the fibrous cap for mobile and nonmobile plaques on the three cross-sections, and the median value of the fibrous cap area in each plaque was calculated.

A "recent" intraplaque hemorrhage was recorded when an area of erythrocytes within the plaque caused disruption of plaque architecture, whereas an "old" intraplaque hemorrhage was recorded when evidence showed organized hemorrhage with the accumulation of hemosiderin-laden macrophages or iron deposits on plaque connective tissue.[18] Old intraplaque hemorrhage was also recorded when the ratio of the glycophorin A-positive area to the whole plaque area was >40%. Plaque inflammation with macrophage and lymphocyte infiltration was recorded according to the number of CD68-negative or CD3-positive cells: infiltration of >20 inflammatory cells in the fibrous cap was defined as positive inflammation to the fibrous cap. Mural thrombus was defined as a fibrin organization of the endothelium or the fibrous cap of plaques (Fig 3, *C*).

Statistical analysis. Patients with mobile plaques and those with nonmobile plaques were compared for baseline characteristics, the prevalence of progressive symptoms, and plaque histologic features using a *t* test, the Wilcoxon rank sum test, or the Fisher exact test, as appropriate. Two-sided values of $P < .05$ were considered significant. Statistical analysis was performed with JMP 7.12 software (SAS Institute, Cary, NC).

RESULTS

Patients displaying mobile plaques and nonmobile plaques exhibited no significant difference in age, sex, diabetes mellitus, hyperlipidemia, smoking, coronary artery disease, administration of statins, administration of aspirin, or degree of stenosis (Table I). All statins were administrated with the usual doses (atorvastatin ≤20 mg, pravastatin ≤20 mg, or pitavastatin ≤2 mg), and no patients received high-dose statin therapy. Hypertension was observed more frequently in patients with nonmobile plaques.

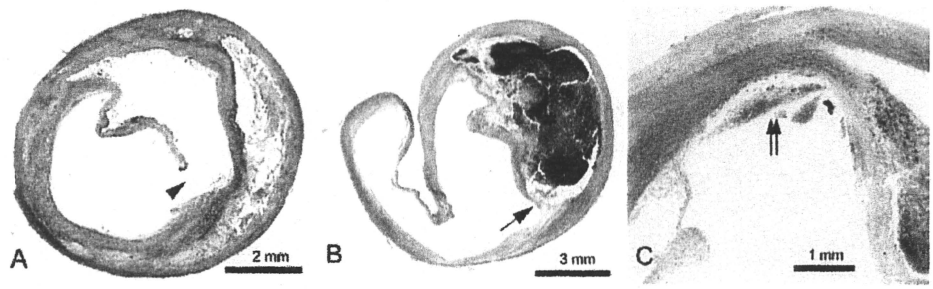

Fig 3. An example of histologic features of a mobile plaque (the same plaque as shown in Fig 1). **A**, A photomicrograph of the carotid bifurcation (Masson's trichrome staining, original magnification ×1) demonstrates complete disruption of the fibrous cap (*arrowhead*). **B**, Another cross-section (Masson's trichrome staining, original magnification ×1) demonstrates a large necrotic core with a fresh intraplaque hemorrhage (*asterisk*), which was covered with thin fibrous cap (*arrow*). **C**, A photomicrograph (Masson's trichrome staining, original magnification ×2) shows intramural fibrin deposit, indicating mural thrombus (*double arrow*).

Table I. Clinical characteristics at the time of carotid endarterectomy of study patients

Characteristics	*Mobile plaques (n = 18)*	*Nonmobile plaques (n = 17)*	P
Age, mean (SD), year	70.8 (11.5)	66.2 (8.7)	.19
Female, No. (%)	3 (16.7)	1 (5.9)	.60
Stenosis, mean (SD), %	73.2 (24.4)	76.5 (15.2)	.63
Risk factors, No. (%)			
Hypertension	11 (61.1)	17 (100)	.01
Diabetes mellitus	4 (22.2)	7 (41.2)	.29
Hyperlipidemia	11 (61.1)	12 (70.6)	.72
Smoking	9 (50.0)	13 (76.5)	.16
Medications, No. (%)			
Statin	7 (38.9)	7 (41.2)	1.00
Aspirin	10 (55.6)	13 (76.5)	.29
Interval to CEA, median (IQR) days			
From last ischemic event	12.5 (7.5-26.75)	33 (13.5-70.5)	.01
From last ultrasound study	3 (1-8.25)	9 (3.5-21.5)	.03
MRI-DWI positive, No. (%)	14 (77.8)	14 (82.4)	1.00

DWI, Diffusion-weighted image; *IQR*, interquartile range; *MRI*, magnetic resonance imaging; *SD*, standard deviation.

The median interval from the last ischemic event to CEA was 12.5 days (maximum, 41 days) in patients with mobile plaques, and the interval between the onset of symptoms and CEA, as well as that between ultrasound imaging and CEA, was significantly longer in patients with nonmobile plaques. No patients in this study had atrial fibrillation or other embolic sources. The incidence of the acute cerebral infarction detected with preoperative DWI did not show significant difference between mobile and nonmobile plaques (77.8% vs 82.4%, $P > .99$).

Clinical symptoms. The first ischemic symptoms among the 18 patients with mobile plaques were cerebral infarct in 11 patients, TSI in 5, TIA in 1, and amaurosis fugax without positive DWI finding in 1. Symptoms among 17 patients with nonmobile plaques included cerebral infarct in 6, TSI in 6, TIA in 3, and amaurosis fugax without positive DWI finding in 2. Progressive symptoms after admission were observed in six patients (33.3%) with mobile plaques, whereas no progression was seen in the patients with nonmobile plaques ($P = .02$).

Histologic features. All histologic features in mobile plaques and nonmobile plaques are summarized in Table II. The ratio of the mean cross-sectional area of the necrotic core to that of the entire plaque area was significantly larger in mobile plaques than in nonmobile plaques (mean, 0.660 vs 0.417, $P < .0001$).

Plaque ruptures were seen in 83% of mobile plaques. The median minimum cap thickness was 80 μm, which is smaller than that considered to be the critical value of minimum cap thickness for cap rupture.[16] There were no significant differences in the prevalence of cap rupture (83% vs 82%) or median minimum cap thickness (80 vs 100 μm) between mobile plaques and nonmobile plaques. The median area of the fibrous cap was, however, significantly smaller in the mobile plaques than in nonmobile plaques (9200 vs 15,900 μm^2; $P = .02$).

Although mural thrombus was more prevalent in mobile plaques (89%) than in nonmobile plaques (59%), the difference was not significant ($P = .060$). There was also no significant difference between mobile and nonmobile

Table II. Histologic features of mobile and nonmobile plaques

Feature	*Mobile plaques (n = 18)*	*Nonmobile plaques (n = 17)*	P
Fibrous cap			
Plaque rupture, No. (%)	15 (83)	14 (82)	>.99
Minimum cap thickness, median (IQR) μm	80 (60-162.5)	100 (60-250)	.33
Fibrous cap area, median (IQR) μm^2	9200 (6300-13,100)	15,900 (9000-21,800)	.02
Mural thrombus, No. (%)	16 (89)	9 (59)	.06
Ratio of necrotic core area, mean (SD)	0.660 (0.098)	0.417 (0.176)	<.0001
Inflammation of fibrous cap, No. (%)			
Macrophages	17 (94)	16 (94)	1.00
Lymphocytes	12 (67)	12 (71)	1.00
Intraplaque hemorrhage, No. (%)			
Fresh	11 (61)	9 (53)	.74
Previous	11 (61)	10 (59)	1.00

IQR, Interquartile range; *SD*, standard deviation.

plaques in the prevalence of cap inflammation or intraplaque hemorrhage.

DISCUSSION

One of our results showed that progressive symptoms occurred more frequently in patients with mobile plaques than those with nonmobile plaques. This result is in line with unstable neurologic presentations depicted in previous case reports of symptomatic mobile plaques.[5,8] A recent study also concluded that the jellyfish sign, which is an ultrasonographic appearance of mobile plaques, was an important predictive factor for repeated ischemic stroke.[12] These findings, along with our results, promoted us to confirm the hypothesis that some histologic differences may exist between mobile and nonmobile plaques, even if both are symptomatic plaques.

There are several reports about mobile plaques in large arteries, including the carotid artery,[2-8,19,20] and some reports have described the histology of mobile plaques. Nakajima et al[5] reported the pathologic findings of a mobile plaque in the brachiocephalic artery that caused fatal recurrent strokes and pointed out that plaque disruption was a cause of the mobility. Arning et al[6] also found a mural thrombus in the histology of a mobile carotid plaque. Our results are compatible with previous pathologic reports about mobile plaques. However, the features of plaque rupture and mural thrombus may not be sufficient to describe the specific histopathology of a mobile plaque, because according to our result, the prevalence of plaque disruption or mural thrombus of mobile plaques is not significantly higher than that of nonmobile plaques. The findings of the present study suggest that the existence of a large, soft, lipid-rich necrotic core is also important for the mechanism of plaque mobility.

This speculation conforms with the results on intravascular ultrasound elastography, a recently developed technique to assess the elasticity of plaque tissue using intravascular ultrasound imaging by measuring the "strain" or small movement of plaque tissue under an applied force.[21,22] The authors of those studies demonstrated that the strain could distinguish lipid-rich components from hard and fibrous components. Mobile structures on carotid plaques may be caused not only by the mural thrombus formed by a fibrous cap rupture but also by a large, lipid-rich necrotic core exposed into the blood lumen.

Several pathologic reviews have reinforced the evidence that a large necrotic core is one of the important features of so-called vulnerable plaque.[23-27] Studies on aortic plaques,[28,29] an in vivo study on magnetic resonance imaging,[30] and histologic studies of carotid plaque[16,31] have also shown that a large necrotic core was strongly associated with thrombosis, fibrous cap rupture, fibrous cap thinning, or neurologic symptoms. Moreover, when the large lipid-rich necrotic core is exposed to blood lumen by plaque rupture, the mural thrombus or debris from the lipid core may become a persistent source of embolism, which may result in an unstable ischemic stroke. On the other hand, Redgrave et al[16] showed that thinning of the fibrous cap covering the necrotic core is another important factor for plaque vulnerability. These authors advocated critical cap thickness (minimum cap thickness <200 μm and a representative cap thickness <500 μm) as a marker for ruptured plaque.

Using these criteria, the fibrous cap of both groups in our study is extremely thin. One possible reason that we did not find a significant difference in minimum fibrous cap thickness in the two plaques is that mobile and nonmobile plaques had an almost equally high prevalence of cap rupture. Given that the actual fibrous cap area was smaller in mobile plaques than in nonmobile plaques (Table II), it is possible that the overall thickness of fibrous caps in mobile plaques is smaller than that in nonmobile plaques.

To our knowledge, only one recent study demonstrated the histologic features of mobile carotid plaques, although it did not include a controlled group in histologic assessment. Kume et al[12] examined histologic features of 15 plaques with ultrasonographic jellyfish sign, and the results showed that the proportional area of the fibrous cap correlated negatively with jellyfish-positive plaque surface movement rate. Our results regarding the fibrous cap area

coincides with their results. They could not, however, document significant correlation between atheromatous lesion area and the plaque motion rate, which is inconsistent with our results. This may be attributed to the differences in a patient population, in definitions of ultrasonographic and histopathologic findings, and in research designs between the two studies. The large necrotic core can still be one of the representative features of mobile plaques because the present results were conducted in a controlled study.

Our study has some limitations. First, the number of the cases we studied was small, and not all of the nonmobile plaques were examined. Larger studies are necessary to confirm higher prevalence of mural thrombus and thinner fibrous cap in mobile plaques.

Second, because nonmobile plaques had a longer duration until CEA, stabilization of the plaque, which can occur within approximately 90 days after the presenting neurologic symptom,[31,32] could have led us to underestimate some of the histologic factors of nonmobile plaques. However, one study showed that the prevalence of a large lipid core and mural thrombus was not influenced by the span of time since the last ischemic events.[31] Spagnoli et al[33] also revealed that a fresh thrombus can present several months after the first cerebrovascular event.

Third, we only studied symptomatic plaques and did not include asymptomatic plaques. Our study, therefore, did not answer the question of whether mobile plaques are more "vulnerable" than nonmobile plaques as long as the word "vulnerable" means the tendency for fibrous cap rupture and the potential of subsequent embolic stroke. That was not, however, the purpose of this study. Further studies including both symptomatic and asymptomatic patients might be essential to determining whether mobile plaques are more "vulnerable" than nonmobile plaques.

A higher prevalence of mobile plaques is shown in this report (9.3% of excised plaque) than in previous study.[1] The most recent study demonstrated an even higher prevalence (19%) of mobile plaques.[12] This high prevalence of mobile plaques may be explained by the evolution of the duplex ultrasound imaging system and sheds light on the clinical importance of mobile plaques.

CONCLUSIONS

In this study, we have clarified the histologic difference between mobile and nonmobile symptomatic carotid plaques. This result may partly explain unstable neurologic presentations of patients with mobile carotid plaques and may add information to the debate regarding the management of mobile plaques. Further studies on the histopathology and natural history of the mobile carotid plaque are needed to establish the most effective acute management for symptomatic mobile plaques.

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AUTHOR CONTRIBUTIONS

Conception and design: TF, KI
Analysis and interpretation: TF, KN, HI
Data collection: TF, KN, TH
Writing the article: TF
Critical revision of the article: KI, SM
Final approval of the article: KI, HI
Statistical analysis: TF
Obtained funding: Not applicable
Overall responsibility: TF

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