

厚生労働科学研究費補助金（医療機器開発推進研究事業）
分担研究報告書

低侵襲的低周波超音波脳血栓溶解法の臨床導入に向けて：
rt-PA静注療法の治療開始可能時間延長に伴う予測増加症例数に関する検討

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研究要旨

2012年8月にrt-PA静注療法の治療開始可能時間（TTW）が発症3時間以内から4.5時間以内へ延長された2011年1月から2012年8月に当センターに入院した急性期脳梗塞を対象に検討すると、このTTW延長によりrt-PA静注療法の対象症例数は約3割増加すると予測された。したがって、現在開発中の約500kHzを用いた貼付型ソフト超音波振動子による超音波脳血栓溶解法の対象患者も同程度の割合で増加するであろう。

A. 研究目的

2012年8月31日にrt-PA静注療法の治療開始可能時間（therapeutic time window：TTW）が発症後3時間以内から4.5時間以内へ延長されることが厚生労働省の薬事・食品衛生審議会で認められた。これに伴う、rt-PA静注療法対象の増加症例数を予測し、増加症例の臨床的特徴を明らかにすることを目的とした。

B. 研究方法

2011年1月から2012年8月31日までに国立循環器病研究センターに発症7日以内に入院した急性期脳梗塞患者を対象とした。発症3時間以内にrt-PA静注療法を受けた症例を3時間治療群、発症3.5時間以内に来院しrt-PA静注療法を受けていないもののうち適応外項目がなくNational Institutes of Health Stroke Scale（NIHSS）スコア>4の患者を4.5時間適応群、発症2-3.5時間で来院しrt-PA静注療法を受けていないもののうち適応外項目もしくはNIHSSスコア≤4を有する患者を4.5時間除外群とした。来院-治療開始時間は60分と仮定した。

予測される増加率は、（4.5時間適応群/3時間治療群）×100%から計算した。また、年間の予測増加数を計算した。3時間治療群と4.5時間適応群を比較し、

4.5時間適応群の特徴を調べた。さらに、4.5時間除外群では除外となった理由とその頻度を調べた。また、TTW延長後の2012年9月から12月までにrt-PA静注療法を受けた患者のうち実際にTTW延長によって増加した（来院-治療時間60分と仮定し発症2時間以降に来院し4.5時間以内に治療を受けた）患者の割合を調べた。

（倫理面への配慮）

本研究は患者の個人情報をも匿名化したデータベースを用いた後ろ向き研究である。患者から採取された試料を用いない研究であり、被験者からインフォームド・コンセントを受けることを必ずしも要しない。

C. 研究結果

対象期間20ヵ月に1002例（女性391例、73.5±12.6歳）の急性期脳梗塞が発症7日以内に当センターに入院した。そのうち、3時間群は101例（女性38例、74.2±12.2歳）、4.5時間適応群28例（女性13例、77.4±9.2歳）、4.5時間除外群44例（女性16例、75.6歳±10.3歳）であった。予測されるrt-PA静注療法の増加率は27.7%で、年間の予測増加数は16.8例となった。

4.5時間適応群と3時間治療群で、性別、年齢、脳卒中危険因子、虚血性心疾患や心不全の合併、来院時のNIHSSスコアに差はなかった。4.5時間適応群は、3時間治療群より脳卒中既往（39%対23%、 $p=0.079$ ）が多い傾向で、発症時に目撃者がいない割合（64%対35%、 $p=0.0048$ ）が高く、発症-来院時間（中央値175分対69分、 $p<0.0001$ ）が長く、心原性脳塞栓症の割合（46%対67%、 $p=0.0429$ ）が少なく、椎骨脳底動脈系の脳梗塞（36%対16%、 $p=0.0204$ ）が多かった。4.5時間除外群の除外理由は、NIHSSスコア ≤ 4 の軽症が31例（71%）、頭部画像所見上の広範早期虚血所見が8例（18%）、脳出血既往が5例（11%）、ワルファリン内服中のPT-INR >1.7 が3例（7%）、血糖異常が1例（2%）、大動脈解離が1例（2%）であった。TTW延長後の4ヶ月間に24例がrt-PA静注療法を受けた。TTW延長によって6例（33.3%）が増加した。

D. 考察

当センターの最近の脳梗塞入院患者を対象にTTWが延長した場合、これに伴うrt-PA静注療法対象は約1.3倍に増加すると予測された。「治療開始可能時間が1.5倍になるので対象患者も1.5倍になる」という訳ではなかった。このTTW延長で増加する症例は発症時に目撃者がいないことが多く、心原性脳塞栓症が少なく、椎骨脳底動脈系の脳梗塞が多いと予想された。増加の割合は、医療施設の特徴や周辺の医療環境、救急体制などが影響する可能性が高い。各医療施設の特徴を勘案して検討する必要があるだろう。現在開発中の約500kHzを用いた貼付型ソフト超音波振動子による超音波脳血栓溶解法の対象患者も同程度の割合で増加するであろう。

E. 結論

TTW延長によって約1.3倍の脳梗塞患者がrt-PA静注療法の対象となると予測され

た。現在開発中の約500kHzを用いた貼付型ソフト超音波振動子による超音波脳血栓溶解法の対象患者も同程度の割合で増加するであろう。

F. 研究発表

1. 論文発表

1. Sakamoto Y, Koga M, Toyoda K, Osaki M, Okata T, Nagatsuka K, Minematsu K. Low DWI-ASPECTS is associated with atrial fibrillation in acute stroke with the middle cerebral artery trunk occlusion. J Neurol Sci. 2012;323:99-103
2. 福田真弓, 古賀政利, 森真由美, 大崎正登, 長束一行, 峰松一夫, 豊田一則. rt-PA投与後の早期再発, 進行および症候性頭蓋内出血による早期神経症候増悪の検討. 脳卒中 2012;34: 47-50
3. 古賀政利. 脳を救え: 静注血栓溶解と超音波血栓溶解. 循環器内科 2012;72:275-281.
4. 古賀政利, 豊田一則. rt-PA静注療法における頭頸部血管の超音波検査. 第30回The Mt. Fuji Workshop on CVD Proceeding 2012;30:4-7.

2. 学会発表

1. 田中弘二, 古賀政利, 佐藤和明, 鈴木理恵子, 豊田一則, 峰松一夫. リアルタイム 3D 経食道心臓超音波検査を用いた急性期脳梗塞における心房細動と左心耳体積の検討 第31回日本脳神経超音波学会総会、大宮、2012, 6
2. 佐藤和明, 古賀政利, 植田初江, 田中弘二, 鈴木理恵子, 遠藤薫, 小林潤平, 住田善之, 豊田一則. 大動脈弓部動脈硬化性病変の病理と 3D エコー画像の比較. 第31回日本脳神経超音波学会総会、大宮、2012, 6
3. 坂本悠記, 佐藤和明, 古賀政利, 小林潤平, 住田善之, 豊田一則. 頸部内頸動脈狭窄症患者における連続波ドプラを用いた狭窄後推定血圧評価. 第31回日本脳神経超音波学会総会、大宮、2012, 6

4. 板垣成彦、古賀政利、齋藤こずえ、鈴木理恵子、大崎正登、飯原弘二、豊田一則. ソナゾイド[®]による造影超音波検査が有用であった内頸動脈高度狭窄の1例. 第15回日本栓子検出と治療学会、大阪、2012年10月
5. 大山賢、尾原知行、松島勇人、古賀政利、豊田一則. MES 所見が狭窄病変の消長や脳塞栓症再発と関連した症候性頭蓋内内頸動脈狭窄の1例. 第15回日本栓子検出と治療学会、大阪、2012年10月

G. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

厚生労働科学研究費補助金（医療機器開発推進研究事業）
分担研究報告書

TCCS/MRAによるrt-PA施行虚血性脳卒中の閉塞血管早期再開通率の検討

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研究要旨 経頭蓋カラードプラ（TCCS）は、非侵襲的検査であり、ベットのサイドで繰り返し行うことが可能であり、この方法を含む経頭蓋超音波検査は脳梗塞超急性期のアルテプラゼ（rt-PA）静注療法中に閉塞血管再開通現象をモニターできる唯一の方法である。慈恵会医大グループと共同で低侵襲的低周波超音波装置を用いた急性期血栓溶解療法の臨床試験を計画している。我々は現在計画中的である超音波血栓溶解療法の対照データ収集のため、急性期脳梗塞に対するrt-PA静注療法例で、TCCS、MRA、脳血管造影検査（DSA）による血管閉塞や再開通など頭蓋内血管の経時的観察を行い、TCCSの有用性や、超音波血栓溶解療法を併用しない場合のM1閉塞例における再開通時期や頻度を評価しておりデータを更新した。TCCS、MRA、DSAの再開通率データを合わせると、閉塞血管の再開通はrt-PA静注療法開始から1時間までが50%、2時間までが51%、24時間までが57%、14日までが74%であった。

A. 研究目的

我々は、慈恵会医大グループと共同で低侵襲的低周波超音波装置を用いた急性期血栓溶解療法の臨床試験を計画している。今回は、当該試験計画策定に必要な対照データ収集のため、急性期脳梗塞に対するrt-PA静注療法例において、TCCS、MRA、DSAによる血管閉塞や再開通など頭蓋内血管の経時的観察を行い、TCCSの有用性や、超音波照射を併用しない場合の閉塞血管再開通時期や頻度、臨床転帰のデータを更新する。

表1 本研究での検討項目

- ・患者背景（年齢、性別、基礎疾患など）
- ・診断名
- ・頭蓋内血管病変（頭部MRA、DSA、頸部血管エコー検査）
- ・TCCSの結果（経頭蓋カラードプラ検査の可否、閉塞血管の診断可否、再開通モニターの可否）
- ・症候性頭蓋内出血（発症36時間以内のNIHSS4点以上の増悪）
- ・3ヶ月後の日常生活自立度（mRS）

B. 研究方法

対象は平成17年10月から平成24年12月までの当院rt-PA静注療法施行の354例である。TCCS、MRA、DSAのいずれかを用いて閉塞血管部位、再開通を評価した。使用超音波装置は日立メディコ社製のPREIRUSとGE社製のLOGIQ E9とした。検討項目は表1に示すように、患者背景、診断名、責任血管（MRA、DSA、頸部エコー）、TCCSの結果（閉塞血管診断の可否、再開通モニターの可否など）、MRAやDSAでの再開通の結果とした。TCCSの再開通の評価にはCOGIFscoreを用い1grade以上の改善がみられる場合に再開通ありとした。MRAの再開通の評価にはModified Mori gradeを使用し、Grade2以上の場合に再開通ありとした。DSAの再開通の評価にはThrombolysis in Cerebral Infarction 分類を使用し、Grade2以上の場合に再開通ありとした。臨床転帰は、発症36時間以内のNIHSS4点以上の増悪を伴う症候性頭蓋内出血、3ヶ月後の日常生活自立度（mRS）を検討した。なお、rt-PA静注療法後に経皮経管的脳血栓回収用機器（Merciリトリーバ

一、PENUMBRAシステム)を使用した症例は再開通の解析から除外した。

(倫理面への配慮)

ヒストリカルデータの収集に関する研究は、国立循環器病研究センターの倫理委員会で承認を受けた。

C. 研究結果

患者背景を表2にまとめる。患者は354例、平均年齢は73±13歳であった。男性が64%、既往症は高血圧66%、糖尿病20%、脂質代謝異常33%、心房細動52%であった。臨床病型はラクナ梗塞1%、アテローム血栓性脳梗塞13%、心原性脳塞栓64%、その他の脳梗塞が22%であった。治療前の閉塞血管は内頸動脈(ICA)58例(16%)、前大脳動脈8例(2%)、中大脳動脈(MCA) M1 111例(31%)、M2 51例(14%)、後大脳動脈13例(4%)、椎骨脳底動脈11例(3%)、閉塞血管なし67例(19%)、評価不能27例(8%)、その他8例(2%)であった。

表2 患者背景

年齢	73±13歳
男性	64%
高血圧	66%
糖尿病	20%
脂質代謝異常	33%
心房細動	52%
臨床病型	
ラクナ	1%
アテローム血栓性	13%
心原性	64%
その他	22%
閉塞血管	
ICA	16%
ACA	2%
MCA	
M1	31%
M2	14%
PCA	4%
椎骨脳底動脈	3%
閉塞血管なし	19%
評価不能	8%
その他	2%

TCCSを施行した247例では、表3に示すように、側頭骨ウインドウ良好は102例(41%)、不良は145例(59%)であった。側頭骨ウインドウ不良には、女性(p<0.0001)、高齢(p=0.0016)が関係していた。

表3 TCCS施行247例：
側頭骨ウインドウ良否による比較

側頭骨ウインドウ	全体 n=247	良好 n=102 (41%)	不良 n=145 (59%)
男性(%)	64	84*	50
年齢(歳)	73±14	70±14**	75±14
高血圧(%)	66	57	72
糖尿病(%)	21	21	21
脂質異常症(%)	34	28	38
心房細動(%)	55	58	54
臨床病型			
ラクナ(%)	1	2	0
アテローム		11	7
13			
血栓性(%)			
心原性(%)		67	71
65			
その他(%)	21	21	22
閉塞血管			
ICA(%)	16	9	21
ACA(%)	2	0	3
MCA			
M1/M2(%)		36/16	35/16
37/16			
PCA(%)	3	4	2
椎骨脳底動脈(%)	2	0	3
閉塞血管なし(%)	15	22	11
評価不能	8	13	5
その他	2	2	3

*p<0.0001, **p=0.0016

MRA, DSAを用いた部分再開通あるいは完全再開通の検討では、次ページ表4に示すように、1時間後ICA 33% (再開通例数/検査例数:4/12)、M1 46% (16/35)、M2 67% (4/6)、2時間後 27% (4/15)、46% (16/35)、57% (4/7)、24時間後 48% (12/25)、56% (30/54)、80% (16/20)、14日目 54% (22/41)、72% (73/102)、75% (36/48) であった。

表4 MRA, DSAによる血管再開通評価
(全354例中ICA, M1, M2閉塞の221例)

責任血管	1時間	2時間	24時間	14日
ICA	33% (4/12)	27% (4/15)	48% (12/25)	54% (22/41)
M1	46% (16/35)	46% (16/35)	56% (30/54)	72% (73/102)
M2	67% (4/6)	57% (4/7)	80% (16/20)	75% (36/48)

TCCSを用いたM1閉塞の再開通率は、表5に示すように、1時間後57% (4/7), 2時間後56% (5/9), 24時間後75% (12/16), 14日後68% (15/22)であった。いずれかの検査を用いたM1閉塞の再開通率は、表6に示すように、各々50% (19/38), 51% (20/39), 57% (34/60), 74% (76/103)であった。症候性頭蓋内出血は図1に示すように、全354例中の8例 (2.3%) であった。3ヶ月後日常生活完全自立(mRS0-1)は図2に示すように、全体の37%で、ICA閉塞17%, M1閉塞26%, M2閉塞44%であった。

表5 TCCSによる血流改善のタイミング
(TCCSを2回以上施行したM1閉塞22例)

検査時間	全検査患者数	再開通数	再開通頻度(%)
1時間	7	4	57
2時間	9	5	56
24時間	16	12	75
14日	22	15	68

表6 MRA/DSA/TCCSのいずれかの方法による血流改善のタイミング
(MRA/DSA/TCCS施行のM1閉塞94例)

検査時間	全検査患者数	再開通数	再開通頻度(%)
1時間	38	19	50
2時間	39	20	51
24時間	60	34	57
14日	103	76	74

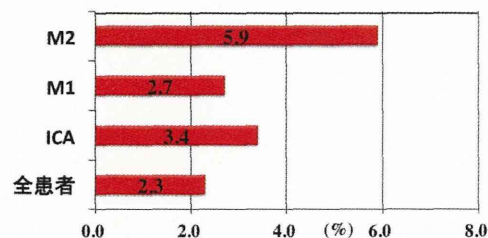


図1 症候性出血の割合 (発症36時間以内, NIHSS4点以上の増悪)

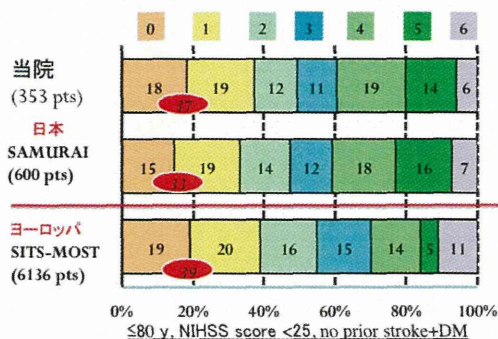


図2 予後の状態 (3ヶ月後のmRS)

D. 考察

現在計画中である超音波血栓溶解療法の対象データ収集を行った。発症24時間以内の再開通は57%であり、J-ACT2 (Mori E, et al. Stroke 2010) のM1閉塞の再開通69.0%よりやや低値であった。Eggersらが報告したrt-PA投与のみ群のTCCSによる中大脳動脈閉塞症例に対する再開通モニターのデータ (Eggers J, et al. Stroke 2008) と比べると、我々のTCCSによる1時間の再開通率は高値であったが (57%対22%)、24時間の再開通率はやや低値であった (75%対82%)。高齢、女性、日本人では、側頭骨ウィンドウが不良と報告されているが (Halse, et al. Stroke 1990, Itoh et al. Stroke 1993, Yagita et al. Ultrasound in medicine & biology 1996, Suzuki et al. Cerebrovasc Dis 2011), 今回の検討では59%でTCCSによる頭蓋内血管の評価が不可能であった。女性、高齢はTCCSの検査が困難関連しており既報告と矛盾しなかった。症候性出血は欧州の市販後調査であるSITS-MOSTの1.7% (Wahlgren, et al. Lancet 2007), 本邦の10施設の市販後調査であるSAMURAI rt-PA登録研究の1.3% (Toyoda, et al. Stroke 2009) と同様であった。3ヶ月後の日常生活完全自立も、SITS-MOSTの39%, SAMURAI rt-PA登録研究の33%と同様であった。

E. 結論

急性期脳梗塞に対するrt-PA静注療法時に、TCCS, MRA, DSAによる血管閉塞や再開通など頭蓋内血管の経時的観察を行い、超音波血栓溶解療法を併用しない場合の閉塞血管再開通頻度や時期を評価した。TCCS, MRA, DSAを用いたM1閉塞の再開通率は、1時間後50%, 2時間後51%, 24時間後57%, 14日後74%であった。これらのデータを基に、新規超音波血栓溶解装置の治験プロトコールの策定を始める。

F. 研究発表

1. 論文発表

なし

2. 学会発表

- 鈴木理恵子, 古賀政利, 田中弘二, 坂本悠記, 徳永敬介, 大山賢, 山本晴子, 豊田一則, 峰松一夫. MRA, 脳血管造影, 経頭蓋カラードプラによるrt-PA静注療法施行時の閉塞血管と再開通率の検討. 第32回日本脳神経超音波学会、徳島、2013年6月発表予定

G. 知的財産権の出願・登録状況 (予定を含む。)

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

厚生労働科学研究費補助金（医療機器開発推進研究事業）
分担研究報告書

経頭蓋カラードプラ法における探触子頭部固定具の改良

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研究要旨 経頭蓋カラードプラ法に用いる探触子頭部固定具はその固定の難しさから市販されていないため、有限会社アンリミット・ジャパンと共同で開発中である。過去に頭部固定型およびベッド固定型の双方より開発を行っていたが、ベッド固定型は機器が大型であり、また、血栓溶解療法を必要とする患者は急性期脳梗塞による意識障害に伴い長時間の安静が困難でありベッド固定型では、患者の動きに対応が難しいため頭部固定するヘルメット型を採用した。今までに作成した試作型1号と2号を改良した。主な改良点は①異なる様々な超音波装置の探触子サイズへ対応できるようにするため手締めねじによるクランプ方式での探触子固定へ変更、②額当てパッドの大型化により頭部装着感の改善、③アーム部可動ポイントの追加によるアーム可動範囲の拡大、④アームの反転方法の改善、⑤ヘルメットの安定性の改善であり、更に実用に値するものとなった。今後、臨床で評価していく方針である。

A. 研究目的

経頭蓋ドプラ法の探触子頭部固定具は市販されているが、経頭蓋カラードプラ法の探触子固定具は市販されていない。この探触子はより大型で重く固定が難しい。今回、有限会社アンリミット・ジャパンと共同開発中の経頭蓋カラードプラ法に用いる探触子を改良した。

B. 研究方法

頭部固定型の頭部固定具の試作機を我々の要望に沿ってアンリミット・ジャパン側が作成し、実際に試用しながら改善を試みた。

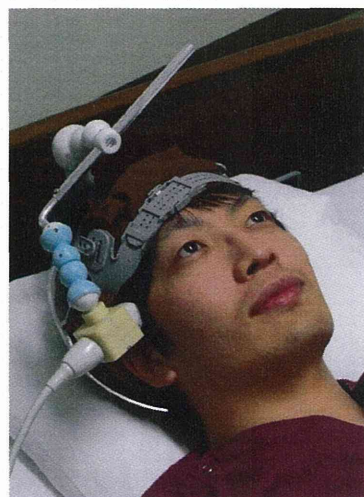
（倫理面への配慮）

患者への使用またはサンプル採取は一切行っておらず、必要ないと考えられた。

C・D. 研究結果および考察

過去に頭部固定型およびベッド固定型の双方より開発を行っていたが、ベッド固定型は固定具が大型で重く、また、血栓溶解療法を必要とする患者は急性期脳梗塞による意識障害に伴い従命困難、

長時間の安静が困難でありベッド固定型では患者の動きへの対応が難しいため頭部固定ヘルメット型を採用した。2010年4月に最初の試作型（ヘルメット試作型1号, 図1参照）を作成した。



- ・頭頂部より吊り下げ式を採用
- ・ボールジョイント3ヶ所で可動性を確保
- ・実験では固定性は良好

図1 試作型第1号

探触子は重いため頭頂部より吊り下げ式を採用し、ボールジョイント3か所にて可動性を確保した。本試作機では固定性は比較的良好であったが、画像の良好な描出のためには側頭部に探触子を押し付ける必要があり、仕様の調整が必要であった。また、アームが固く、スムーズに動かす使用が必要であった。2011年3月に試作2号型（ヘルメット試作型2号、図2参照）が完成した。改良点は①スプリングを用いた頭部密着機構、②ダイヤル式ヘッドバンドによるヘルメットの頭部固定、③3関節アームによるワイヤー式のロック機構、④スナップフィット型のホルダーによる探触子のアームへの固定であった。4つの改良点のうち代表的な改良点である、③については図3イラストにて図説する。



図2 試作型第2号

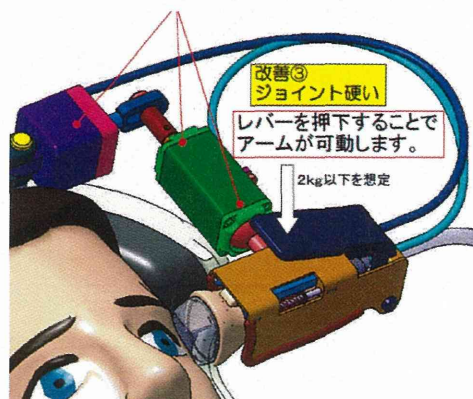


図3 試作型第2号の③の改良点

しかし、ヘルメットの安定性、頭部の装着感、アームの可動域や反転方法にさらなる改良が必要であり、2013年1月に試作3号型（ヘルメット試作型3号、図4参照）が完成した。改良点は①異なる様々な装置の探触子サイズへ対応できるようにするため手締めねじによるクランプ方式での探触子固定へ変更、②額当てパッドの大型化により頭部装着感の改善、③アーム部可動ポイントの追加によるアーム可動範囲の拡大、④アームの反転方法の改善、⑤ヘルメットの安定性の改善である。

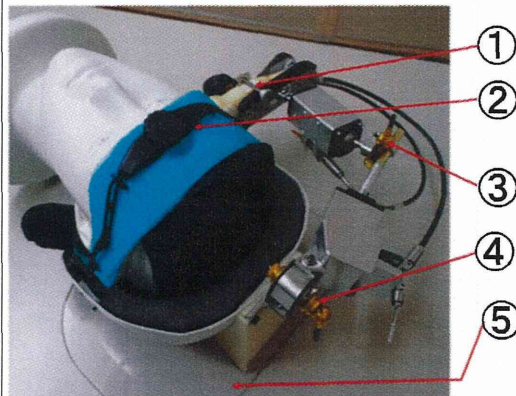


図4 試作型第3号とその改良点

F. 健康危険情報 なし

G. 研究発表

1. 論文発表

なし

2. 学会発表

1、大山 賢、古賀政利、遠藤 薫、鈴木理恵子、山本晴子、豊田一則、古幡 博、峰松一夫、経頭蓋カラードプラ法における探触子固定具の開発第2報～改良型の報告～. 第32回日本脳神経超音波学会総会、2013年6月13-15日、徳島、発表予定

H. 知的財産権の出願・登録状況

なし

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Naomi Miyamatsu, Kazumi Kimura, Tomonori Okamura, Yasuyuki Iguchi, Hirofumi Nakayama, Akihiro Toyota, Makoto Watanabe, Akiko Morimoto, Miho Morinaga, Takenori Yamaguchi.	Effects of Public Education by Television on Knowledge of Early Stroke Symptoms Among a Japanese Population Aged 40 to 74 Years : A Controlled Study	Stroke	43	545-549	2012
Kensaku Shibazaki, Kazumi Kimura, Shuichi Fujii, Kenichiro Sakai, and Yasuyuki Iguchi.	Brain Natriuretic Peptide Levels as a Predictor for New Atrial Fibrillation During Hospitalization in Patients With Acute Ischemic Stroke	The American Journal of Cardiology	109	1303-1307	2012
Takashi Shimoyama, Yasuyuki Iguchi, Kazumi Kimura, Hidetaka Mitsumura, Renpei Sengoku, Yu Kono, Masayo Morita and Soichiro Mochio	Stroke patients with cerebral microbleeds on MRI scans have arteriosclerosis as well as systemic atherosclerosis	Hypertension Research	35	975-979	2012
Kazumi Kimura, Juya Aoki, Yuki Sakamoto, Kazuto Kobayashi, Kenichi Sakai, Takeshi Inoue, Yasuyuki Iguchi, Kensaku Shibazaki	Administration of edaravone, a free radical scavenger, during t-PA infusion can enhance early recanalization in acute stroke patients — A preliminary study	Journal of the Neurological Sciences	313	132- 136	2012

T. Shimoyama, K. Shibazaki, K. Kimura, J. Uemura, T. Shiromoto, M. Watanabe, T. Inoue, Y. Iguchi and S. Mochio	Admission hyperglycemia causes infarct volume expansion in patients with ICA or MCA occlusion: association of collateral grade on conventional angiography	European Journal of Neurology	20	109-116	2013
Yasuyuki Iguchi, Kazumi Kimura, Keiichi Sone, Hiroshi Miura, Hiroshi Endo, Sen Yamagata, Hisashi Koide, Kenji Suzuki, Tomoichiro Kimura, Masaru Sakurai, Nobuya Mishima, Kenji Yoshii, Hiroyuki Fujisawa, and Sunao Ebisutani	Stroke Incidence and Usage Rate of Thrombolysis in A Japanese Urban City: The Kurashiki Stroke Registry	Journal of Stroke and Cerebrovascular Diseases	Vol. 22, No. 4 (May)	349-357	2013
Hiroshi Furuhata, Osamu Saito	Comparative study of standing wave reduction methods using random modulation for transcranial ultrasonication	Ultrasound Medicine and Biology	in press		2013
Sakamoto Y, Koga M, Toyoda K, Osaki M, Okata T, Nagatsuka K, Minematsu K	Low DWI-ASPECTS in associated with atrial fibrillation in acute stroke with the middle cerebral artery trunk occlusion.	J Neurol Sci	323	99-103	2012
Suzuki R, Koga M, Mori M, Endo K, Toyoda K, Minematsu K	Visibility of the lesser sphenoid wing is an important indicator for detecting the middle cerebral artery on transcranial color-coded sonography.	Cerebrovasc Dis	33	272-279	2012

Suzuki R, Koga M, Toyoda K, Uemura M, Nagasawa H, Yakushiji Y, Moriwaki H, Yamada N, Minematsu K	Identification of internal carotid artery dissection by transoral carotid ultrasonography.	Cerebrovasc Dis	33	369-377	2012
Suzuki R, Osaki M, Endo K, Amano T, Minematsu K, Toyoda K	Common carotid artery dissection caused by a frontal thrust in Ken do (Japanese swordsmanship).	Circulation	125	e617-e619	2012
福田真弓, 古賀政利, 森真由美, 大崎正登, 長束一行, 峰松一夫, 豊田一則	rt-PA投与後の早期再発、進行および症候性頭蓋内出血による早期神経症候増悪の検討.	脳卒中	34	47-50	2012
古賀政利	脳を救え：静注血栓溶解と超音波血栓溶解.	循環器内科	72	275-281,	2012
古賀政利, 上原敏志	欧米諸国での取り組み—rt-PA療法における看護師やコーディネーターの役割.	BRAIN	2	84-377	2012
古賀政利, 豊田一則	rt-PA静注療法における頭頸部血管の超音波検査.	The Mt. Fuji Workshop on CVD Proceeding	30	4-7	2012

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Effects of Public Education by Television on Knowledge of Early Stroke Symptoms Among a Japanese Population Aged 40 to 74 Years : A Controlled Study

Naomi Miyamatsu, Kazumi Kimura, Tomonori Okamura, Yasuyuki Iguchi, Hirofumi Nakayama, Akihiro Toyota, Makoto Watanabe, Akiko Morimoto, Miho Morinaga and Takenori Yamaguchi

Stroke. 2012;43:545-549; originally published online November 3, 2011;

doi: 10.1161/STROKEAHA.111.634196

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Effects of Public Education by Television on Knowledge of Early Stroke Symptoms Among a Japanese Population Aged 40 to 74 Years

A Controlled Study

Naomi Miyamatsu, RN, PhD; Kazumi Kimura, MD, PhD; Tomonori Okamura, MD, PhD; Yasuyuki Iguchi, MD, PhD; Hirofumi Nakayama, MD, PhD; Akihiro Toyota, MD, PhD; Makoto Watanabe, MD, PhD; Akiko Morimoto, RN, MSc; Miho Morinaga, RN, MSc; Takenori Yamaguchi, MD, PhD

Background and Purpose—An educational campaign by mass media has been associated with great increases in the knowledge about early symptoms of stroke. However, few studies were conducted with a controlled community intervention study.

Methods—To clarify the effects of a 1-year television campaign for the whole population on improvement of knowledge about stroke symptoms in 2 cities, a campaign area and a control area in Japan were selected. Before and after the campaign, 1960 randomly selected residents aged 40 to 74 years answered a telephone survey regarding knowledge of early stroke symptoms. We calculated the percentage and 95% CIs of participants who correctly chose all 5 early symptoms of stroke in each area and in each year.

Results—Before the campaign, 53% of participants (95% CI, 50%–55%) in the campaign area and 46% (95% CI, 44%–49%) in the control area correctly chose 5 early symptoms. After the 1-year television campaign, knowledge was significantly improved only in the campaign area (campaign area, 63%; 95% CI, 60%–66%; control area, 51%; 95% CI, 48%–54%). After sex stratification, only women showed improved knowledge of early symptoms. The audience rate for the campaign television programs was found to be higher in women than in men.

Conclusions—A 1-year stroke educational television campaign effectively improved knowledge about early stroke symptoms among Japanese women aged 40 to 74 years. No impact was found among men in this age group. Future studies should examine the impact of this approach on stroke knowledge among younger individuals and whether there are any behavioral changes that contribute to earlier presentation for treatment. (*Stroke*. 2012;43:545-549.)

Key Words: acute stroke ■ educational campaigns ■ knowledge ■ prevention ■ symptoms ■ warning signs

Delayed access to medical care in patients with stroke is associated with poor outcome. Knowledge of the early symptoms of stroke and the need to call an ambulance should therefore be widespread. The importance of ensuring timely treatment has grown dramatically since the introduction of thrombolytic treatment with tissue-type plasminogen activator¹⁻³ for cerebral infarction.

Various strategies for community education have been examined in previous studies.⁴⁻⁸ Some reports have noted that television campaigns show greater efficacy for public education than other media.^{4,6} However, few controlled studies have evaluated the effects of community education by television on knowledge about the early symptoms of stroke.⁷

Furthermore, to our knowledge, there is no community education by television for stroke in Asian countries, where mortality due to stroke is high.⁹

The purpose of this study was to verify that television campaign could improve knowledge about early symptoms of stroke.

Methods

Study Setting

A community intervention providing information on early symptoms of stroke was conducted by television. The preintervention survey was performed in April 2009 and the postintervention survey was performed in April 2010. Because mortality of stroke varies between

Received August 8, 2011; final revision received August 26, 2011; accepted August 30, 2011.

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Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.111.634196

Table 1. Exposure to Intervention During the Campaign Period Among Participants in the Campaign Area: Postintervention Telephone Survey 2010

Educational Intervention by Television	Exposure to Intervention, No. (%)			
	Overall (n = 968)	Sex Differential		P*
		Men (n = 484)	Women (n = 484)	
1-min spots†	381 (39.8)	161 (33.3)	220 (45.5)	<0.001
Highlight programs‡	274 (28.3)	108 (22.3)	166 (34.3)	<0.001
Both of 1-min spots† and highlight programs‡	207 (21.4)	74 (15.3)	133 (27.5)	<0.001
At least 1 of 1-min spots† and highlight programs‡	447 (46.2)	195 (40.3)	252 (52.2)	<0.001

*P value for χ^2 test.

†One-min spots: approximately 900 times of TV spots about stroke, each airtime was 60 s.

‡Highlight programs: a total of 60 times of documentaries and reports about stroke, each airtime was 5–15 min.

western and eastern Japan, 2 cities were selected from adjoining prefectures located in western Japan: Okayama city in Okayama prefecture for the campaign area and Kure city in Hiroshima prefecture for the control area.

A local branch of Japan Broadcasting Corporation (NHK, the largest noncommercial broadcasting in Japan) produced a series of television programs for the present study and broadcast them throughout the 1-year campaign period from April 2009. Okayama city was located in the broadcasting area of this local branch (Okayama broadcasting station of NHK). Residents living in the control area had few chances to watch these educational contents, because contents of broadcasting of a local branch of NHK vary by prefectures, and 2 cities do not have a common border and are located far from each other (approximately 150 km).

Participants

Sample size was calculated based on our previous surveys without television programs.¹⁰ The number of participants required was estimated to be 780 people for each area ($\alpha=0.05$, $\beta=0.8$). We decided to recruit approximately 1000 people from both areas for each of pre- and postintervention surveys.

Potential participants were randomly selected from the telephone directory in each area in each survey. A telephone survey was then continued until 140 complete interviews had been obtained for both men and women in their 40s, 50s, and 60s; and 70 complete interviews had been obtained for both men and women at 70 to 74 years old. A total of 3920 citizens were surveyed to find 980 in the campaign area and 980 in the control area for each pre- and postintervention survey. Approximately two thirds of available contacts were nonrelevant contacts, representing contacts with individuals <40 years old or ≥ 75 years old. Because the population was aged 40 to 74 was 300 389 in the campaign area and 114 670 in the control area in 2009, the sampling rate was approximately 0.33% and 0.85%, respectively.

Community Education

Because television programs produced by NHK are systematically distributed, similar television programs are broadcast by all local branches of NHK. However, sometimes slots are at the discretion of the local branch, such as 1-minute spots before serial dramas or 15-minute slots for local news before national news programs. The television campaign in the present study was thus mainly performed using these time slots.

The major points of the campaign by television programs were as follows. The first point was to make broadcasting content based on accurate scientific evidence. The second point was to provide repeated audiovisual information, that is, 1-minute spots were broadcast at least twice almost everyday, whereas highlight programs were broadcast at least once a week. Both types of programs were continued throughout the study period from April 2009 to March 2010.

The Okayama broadcasting station for NHK, Kawasaki Medical School, and the Japan Stroke Association supervised the campaign programs. The 1-minute spots comprised a total of 10 versions covering stroke, both of early symptoms and risk factors, prevention, up-to-date medical treatments, and rehabilitation. Highlight programs featuring 33 topics were broadcast during the campaign period.

Main Outcome Measures

Participants were asked to choose which of 10 listed symptoms fit as early symptoms of stroke. The 10 symptoms listed consisted of 5 early symptoms of stroke¹¹ and 5 incorrect or atypical symptoms (“sudden nasal bleeding,” “sudden hot flush,” “sudden pain in the left shoulder,” “numbness or palsy of both hands and/or fingers,” and “sudden difficulty breathing”).

At the postintervention survey in the campaign area, participants were also asked whether they had seen any of the television spots and special programs.

Statistical Analysis

We estimated 95% CIs of population proportions for those who correctly chose all 4 early symptoms of stroke in surveys according to F-distribution. Sex-specific analysis was also performed. Participants who chose all 10 symptoms (n=45) were excluded from these analyses.

Results

Response rates of telephone surveys were 31.6% and 34.7% for pre- and postintervention surveys in the campaign area and 30.3% and 35.5% in the control area, respectively. In the postintervention survey in the campaign area, approximately 40% of participants reported “I saw some of the 1-minute spots about stroke on NHK between April 2009 and March 2010,” whereas 30% reported seeing the highlight programs (Table 1). These audience rates for both types of programs were significantly higher for women than for men.

Proportions of participants who correctly chose 5 early symptoms are shown in Table 2. In all groups, regardless of area or sex, we observed tendencies toward improvement in knowledge about early symptoms of stroke; however, 95% CIs of those proportions demonstrated that only the campaign area showed a significant improvement in stroke knowledge (Figure). After sex stratification, only women in the campaign area showed a significant improvement (Figure).

In addition, the participants who watched either program had better knowledge about early symptoms of stroke (age- and sex-adjusted ORs and 95% CIs, 1.41 and 1.07–1.86).

Table 2. Proportion of Participants Who Correctly Chose 5 Early Symptoms of Stroke

	Campaign Area		Control Area	
	Preintervention 2009	Postintervention 2010	Preintervention 2009	Postintervention 2010
Overall				
No. of participants	965	968	971	971
Correct answer about stroke symptoms (%)				
Sudden numbness or weakness of the face, arm, or leg	868 (89.9)	869 (89.9)	805 (82.9)	812 (83.6)
Sudden confusion or trouble speaking or understanding others	907 (94.0)	901 (93.1)	895 (92.9)	879 (90.5)
Sudden trouble seeing with 1 or both eyes	674 (69.8)	764 (78.9)	651 (67.0)	642 (66.1)
Sudden dizziness, walking difficulties, or loss of balance or coordination	806 (83.5)	815 (84.2)	756 (77.9)	787 (81.1)
Sudden severe headache with no known cause	810 (83.9)	821 (84.8)	773 (79.6)	812 (83.6)
No. of selected correct answer about stroke symptoms (%)				
None	24 (2.5)	41 (4.2)	34 (3.5)	47 (4.8)
1	13 (1.3)	14 (1.4)	33 (3.4)	33 (3.4)
2	43 (4.5)	23 (2.4)	44 (4.5)	35 (3.6)
3	83 (8.6)	59 (6.1)	129 (13.3)	89 (9.2)
4	293 (30.4)	222 (22.9)	283 (29.1)	273 (28.1)
5*	509 (52.7)	609 (62.9)	448 (46.1)	494 (50.9)
Men				
No. of participants	478	484	484	486
Correct answer about stroke symptoms (%)				
Sudden numbness or weakness of the face, arm, or leg	422 (88.3)	421 (87.0)	389 (80.4)	388 (79.8)
Sudden confusion or trouble speaking or understanding others	444 (92.9)	437 (90.3)	437 (90.3)	429 (88.3)
Sudden trouble seeing with 1 or both eyes	342 (71.5)	365 (75.4)	328 (67.8)	325 (66.9)
Sudden dizziness, walking difficulties, or loss of balance or coordination	386 (80.8)	386 (79.8)	350 (72.3)	373 (76.7)
Sudden severe headache with no known cause	399 (83.5)	400 (82.6)	364 (75.2)	399 (82.1)
No. of selected correct answer about stroke symptoms (%)				
None	14 (2.9)	28 (5.8)	23 (4.8)	28 (5.8)
1	7 (1.5)	12 (2.5)	25 (5.2)	19 (3.9)
2	23 (4.8)	14 (2.9)	23 (4.8)	24 (4.9)
3	50 (10.5)	30 (6.2)	65 (13.4)	47 (9.7)
4	130 (27.2)	121 (25.0)	138 (28.5)	134 (27.6)
5*	254 (53.1)	279 (57.6)	210 (43.4)	234 (48.1)
Women				
No. of participants	487	484	487	485
Correct answer about stroke symptoms (%)				
Sudden numbness or weakness of the face, arm, or leg	446 (91.6)	448 (92.6)	416 (85.4)	424 (87.4)
Sudden confusion or trouble speaking or understanding others	463 (95.1)	464 (95.9)	458 (94.0)	450 (92.8)
Sudden trouble seeing with 1 or both eyes	332 (68.2)	399 (82.4)	323 (66.3)	317 (65.4)
Sudden dizziness, walking difficulties, or loss of balance or coordination	420 (86.2)	429 (88.6)	406 (83.4)	414 (85.4)
Sudden severe headache with no known cause	411 (84.4)	421 (87.0)	409 (84.0)	413 (85.2)
No. of selected correct answer about stroke symptoms (%)				
None	10 (2.1)	13 (2.7)	11 (2.3)	19 (3.9)
1	6 (1.2)	2 (0.4)	8 (1.6)	14 (2.9)
2	20 (4.1)	9 (1.9)	21 (4.3)	11 (2.3)
3	33 (6.8)	29 (6.0)	64 (13.1)	42 (8.7)
4	163 (33.5)	101 (20.9)	145 (29.8)	139 (28.7)
5*	255 (52.4)	330 (68.2)	238 (48.9)	260 (53.6)

*This proportion was defined as "participants who have knowledge about early symptoms of stroke" in the present study.

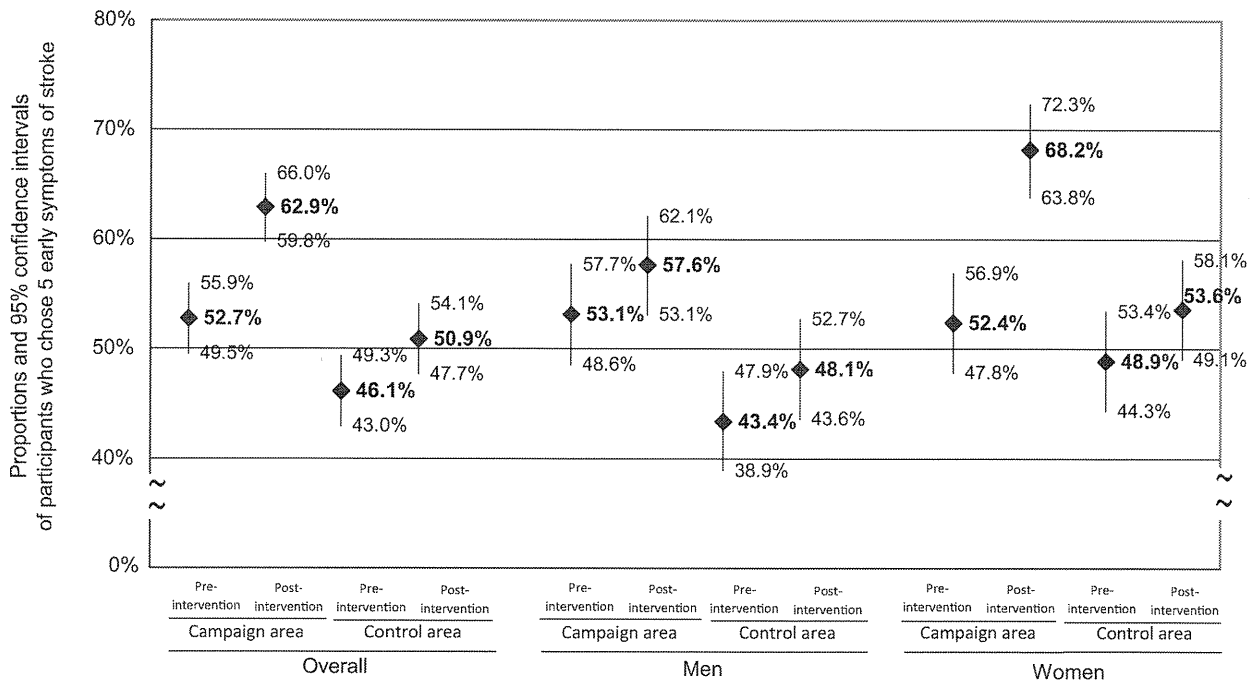


Figure. Overall and sex-stratified proportions and 95% confidence intervals (CIs) for participants who correctly chose 5 early symptoms of stroke before and after community education. Lozenge points indicate proportions of participants who correctly chose 5 early symptoms of stroke. Flickers indicate 95% CIs.

Discussion

This study is the first study of community education of stroke early symptoms in an Asian country. One advantage of the present study was the evaluation of the efficacy of television programs in the controlled trial with all participants randomly selected from the populations of the 2 areas. Another advantage was the use of a 1-year campaign, in which medically accurate contents were made by the collaboration of not only researchers and medical professionals, but also many staff from the largest noncommercial broadcasting corporation in Japan, that is, with mass media communication experts. As a result, this collaboration might have made the television programs more attractive for the audience, and many subjects reported that they had seen the 1-minute spots and the highlight programs during the campaign. In addition, our programs were repeated many times, which should have increased the likelihood of people seeing them, remembering them, and also remembering how to act if someone experiences early symptoms of stroke.

In previous studies that focused on public education about knowledge of stroke symptoms, the effectiveness of campaigns was assessed according to the ability to name ≥ 2 early symptoms of stroke without being shown multiple-choice items.^{6,12} However, patients with stroke are unable to choose their own symptom at the time of onset, so people should be aware of all the typical early symptoms of stroke. Accordingly, the present study assessed improvements in knowledge about early symptoms of stroke based on the proportion of respondents who correctly chose all 5 early symptoms from a list of 10 symptoms.

We did not find significant improvements in knowledge about early symptoms of stroke among men. The improve-

ment only in women may be explained by the greater exposure to television programs associated with the campaign, as suggested by the higher audience rates in women than in men. Furthermore, in previous studies of Western populations, knowledge about early symptoms of stroke was found to be better in women than in men during periods both with and without educational campaign.^{12,13} Our results demonstrated not only similar sex differences to these previous studies, but also sex differences in the effects of the television campaign in a controlled trial. These results raise the possibility that men may have less general interest about health information compared with women. Therefore, it may be important to provide men various occasions to watch educational programs; for example, to increase a total number of on-air times, especially around programs that men are likely to watch such as sports, news, and action movies.

There are several limitations in the present study. First, we only evaluated the improvement in knowledge about early symptoms of stroke by broadcasting campaign; therefore, further study is necessary to assess its effectiveness in actual behaviors of patients with stroke; for example, the number of patients with stroke calling an ambulance, time from symptom onset to hospital presentation, how soon bystanders called the emergency center after having noticed early symptoms, and numbers of patients able to undergo therapy with tissue-type plasminogen activator should be evaluated. A previous cross-sectional study indicated that the knowledge about stroke symptoms was not associated with the intent to call 911 for stroke.¹⁴ A gap may exist between the improvements in knowledge and actual changes in patient behavior. A second limitation is the lack of information about the costs involved in the campaign. The television programs were

made by NHK Okayama as its own project. Researchers thus did not need to worry about the costs of content production and broadcasting. Third, this study did not include individuals <40 years, who may be a person identifying a stroke onset of his or her family members and accessing the emergency medical services system. In addition, it is also important to distribute information about stroke to children and adolescent by television programs they are watching. They would probably advise their parents even if parents are not too interested about health information. This should be assessed in future studies.

Acknowledgments

We thank Mr Ken Goto and Ms Sakiko Yamada from NHK (Nippon Hōsō Kyōkai; Japan Broadcasting Corporation) for their excellent program production. Approval for this study was obtained from the institutional review board at Shiga University of Medical Science (No. 20-124, 2008).

Sources of Funding

This study was supported by grants from the Ministry of Health, Labor and Welfare (H19-Shinkin-Ippan-002) in association with the project prepared by the Japan Stroke Association and NHK Japan Broadcasting Corporation).

Disclosures

None.

References

1. The National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
2. Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). *Stroke*. 2006;37:1810–1815.
3. Kimura K, Iguchi Y, Shibazaki K, Aoki J, Watanabe M, Matsumoto N, et al. Early stroke treatment with IV tPA associated with early recanalization. *J Neurol Sci*. 2010;295:53–57.
4. de Walle HE, van der Pal KM, de Jong-van den Berg LT, Jeeninga W, Schouten JS, de Rover CM, et al. Effect of mass media campaign to reduce socioeconomic differences in women's awareness and behaviour concerning use of folic acid: cross sectional study. *BMJ*. 1999;319:291–292.
5. Luepker RV, Raczynski JM, Osganian S, Goldberg RJ, Finnegan JR Jr, Hedges JR, et al. Effect of a community intervention on patient delay and emergency medical service use in acute coronary heart disease: the Rapid Early Action for Coronary Treatment (REACT) Trial. *JAMA*. 2000;284:60–67.
6. Silver FL, Rubini F, Black D, Hodgson CS. Advertising strategies to increase public knowledge of the warning signs of stroke. *Stroke*. 2003;34:1965–1968.
7. Fogle CC, Oser CS, McNamara MJ, Helgeson SD, Gohdes D, Harwell TS. Impact of media on community awareness of stroke warning signs: a comparison study. *J Stroke Cerebrovasc Dis*. 2010;19:370–375.
8. Fortmann SP, Varady AN. Effects of a community-wide health education program on cardiovascular disease morbidity and mortality: the Stanford Five-City Project. *Am J Epidemiol*. 2000;152:316–323.
9. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, et al. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation*. 2008;118:2702–2709.
10. Okamura T, Miyamatsu N, Nakayama H, Higashiyama A, Morinaga M. Effects of public education about stroke. In: *Report of Health and Labor Science Research Grants (H19-Shinkin-Ippan-002)*. Kawasaki Medical School; 2009:133–154.
11. American Stroke Association. Warning Signs. Available at: www.strokeassociation.org/STROKEORG/WarningSigns/WarningSigns_UCM_308528_SubHomePage.jsp. Accessed November 2010.
12. Hodgson C, Lindsay P, Rubini F. Can mass media influence emergency department visits for stroke? *Stroke*. 2007;38:2115–2122.
13. Marx JJ, Klawitter B, Faldum A, Eicke BM, Haertle B, Dieterich M, et al. Gender-specific differences in stroke knowledge, stroke risk perception and the effects of an educational multimedia campaign. *J Neurol*. 2010;257:367–374.
14. Fussman C, Rafferty AP, Lyon-Callo S, Morgenstern LB, Reeves MJ. Lack of association between stroke symptom knowledge and intent to call 911: a population-based survey. *Stroke*. 2010;41:1501–1507.

Brain Natriuretic Peptide Levels as a Predictor for New Atrial Fibrillation During Hospitalization in Patients With Acute Ischemic Stroke

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The aim of this study was to investigate the relation between brain natriuretic peptide (BNP) levels and the detection rate of new documented atrial fibrillation (AF) after ischemic stroke. Consecutive patients with ischemic stroke prospectively enrolled within 24 hours of onset. Patients with AF on admission electrocardiography or with histories of AF were excluded. The plasma BNP level was measured on admission, and the factors associated with new documented AF were investigated by multivariate logistic regression analysis. Furthermore, the detection rates of AF according to BNP level were evaluated. A total of 584 patients were enrolled. AF was detected in 40 patients (new AF group; 6.8%). The median BNP level of the new AF group was significantly higher than for the non-AF group (186.6 pg/ml [interquartile range 68.7 to 386.3] vs 35.2 pg/ml [interquartile range 15.9 to 80.1], $p < 0.0001$). The cut-off level, sensitivity, and specificity of BNP levels to distinguish the new AF group from the non-AF group were 65.0 pg/ml, 80%, and 70%, respectively. Multivariate logistic regression analysis demonstrated that National Institutes of Health Stroke Scale score >7 (odds ratio 3.4, 95% confidence interval 1.685 to 7.006, $p = 0.0007$) and a plasma BNP level >65.0 pg/ml (odds ratio 6.8, 95% confidence interval 2.975 to 15.359, $p < 0.0001$) were independently associated with new AF. The detection rates of AF according to BNP level were as follows: 2% of patients with <50 pg/ml, 4% of those with 50 to <100 pg/ml, 12% of those with 100 to <200 pg/ml, 26% of those with 200 to <400 pg/ml, and 38% of those with ≥ 400 pg/ml. In conclusion, BNP levels can predict new AF in patients with acute ischemic stroke. Elevated BNP levels result in an increase in the frequency of detection of new AF. © 2012 Elsevier Inc. All rights reserved. (Am J Cardiol 2012;109:1303–1307)

Brain natriuretic peptide (BNP) is a 32-amino acid polypeptide containing a 17-amino acid ring structure that was isolated from porcine brain in 1988 and is a diuretic factor with vasodilator activity.¹ BNP is primarily released from ventricular myocardium and has been shown to be useful in the assessment of patients with cardiac dysfunction.² In addition, plasma BNP levels have also been shown to be elevated in patients with acute ischemic stroke,^{3–13} in particular those with atrial fibrillation (AF).^{5–13} Recently, several studies determined a BNP level threshold as a predictor of delayed AF after ischemic stroke or transient ischemic attack,^{7,11} but the sample sizes of these studies were small. No previous study has examined the association between the detection rate of new AF and BNP level. In the present study, we investigated the relation between elevated BNP levels and the detection rate of new AF during hospitalization in patients with acute ischemic stroke.

Methods

From March 2006 to August 2010, we prospectively enrolled consecutive patients with acute ischemic stroke within 24 hours of onset. Patients with AF on admission 12-lead electrocardiography (ECG) or with histories of AF were excluded. Patients with dialysis-dependent chronic renal failure were also excluded from the present study, because plasma BNP levels are increased in these patients.¹⁴ The plasma BNP level was measured on admission. This study complied with the Declaration of Helsinki with regard to investigations in humans, and the study protocol was approved by the ethics committee of Kawasaki Medical School Hospital.

Diagnosis of acute ischemic stroke was made by stroke neurologists and confirmed by computed tomography or magnetic resonance imaging. The following factors were assessed: age, gender, previous ischemic stroke, previous coronary artery disease, previous heart failure, vascular risk factors, treatment before ischemic stroke, stroke subtype, National Institutes of Health Stroke Scale (NIHSS) score¹⁵ on admission, and blood testing (serum creatinine and plasma BNP).

To identify the mechanism of cerebral infarction, we performed duplex carotid ultrasonography, ECG, transthoracic echocardiography, transcranial Doppler, magnetic res-

Department of Stroke Medicine, Kawasaki Medical School, Kurashiki, Japan. Manuscript received September 30, 2011; revised manuscript received and accepted December 19, 2011.

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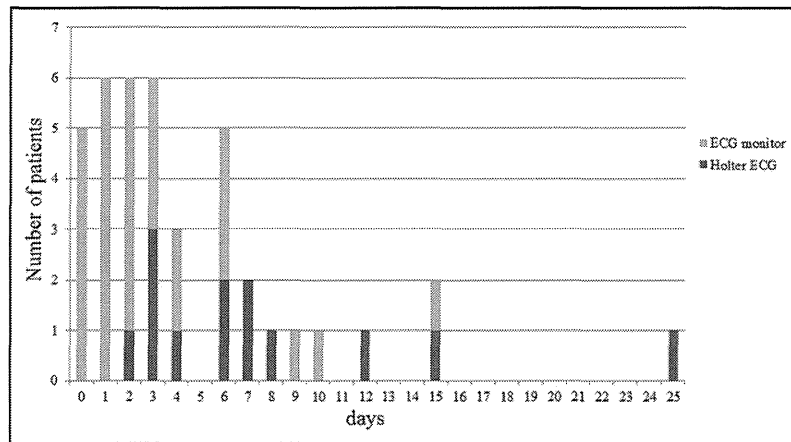


Figure 1. Interval to detection of AF and method of identifying AF.

Table 1
Clinical, radiographic, and laboratory variables

Variable	Non-AF Group (n = 544)	New AF Group (n = 40)	p Value
Age (years)	72 (62–80)	78 (71–84)	0.0007
Women	189 (35%)	20 (50%)	0.0520
Previous ischemic stroke	107 (20%)	10 (25%)	0.4162
Previous coronary artery disease	53 (10%)	4 (10%)	0.9578
Previous heart failure	1 (0.2%)	1 (2.5%)	0.1324
Hypertension	361 (66%)	24 (60%)	0.4127
Diabetes mellitus	139 (26%)	11 (28%)	0.7854
Hyperlipidemia	155 (28%)	8 (20%)	0.2478
Smoker	283 (52%)	15 (38%)	0.0762
Preadmission medications			
Warfarin	17 (3%)	1 (3%)	1.0000
Antiplatelet agents	114 (21%)	7 (18%)	0.6065
β blockers	23 (4%)	2 (5%)	0.6861
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	93 (17%)	9 (23%)	0.3849
Calcium channel blockers	106 (19%)	9 (23%)	0.6435
Digitalis	7 (1%)	0 (0%)	1.0000
Diuretics	26 (5%)	0 (0%)	0.2456
Stroke subtype			<0.0001
Large artery atherosclerosis	125 (23%)	0 (0%)	
Small vessel occlusion	69 (13%)	0 (0%)	
Cardioembolism	38 (7%)	37 (93%)	
Others/undetermined	312 (57%)	3 (7%)	
NIHSS score on admission	4 (2–9)	14 (5–20)	<0.0001
Creatinine (mg/dl)	0.72 (0.57–0.90)	0.77 (0.59–0.91)	0.4296
BNP (pg/ml)	35.2 (15.9–80.1)	186.6 (68.7–386.3)	<0.0001

Data are expressed as median (IQR) or as number (percentage).

onance angiography, and/or computed tomographic angiography. Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment.¹⁶

We also evaluated the following vascular risk factors: hypertension (defined as the use of antihypertensive agents, systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg before stroke onset or 2 weeks after stroke onset), diabetes mellitus (defined as the use of oral hypoglycemic agents or insulin, fasting blood glucose level ≥ 126 mg/dl, or glycosylated hemoglobin level $\geq 6.4\%$), hyperlipidemia (defined as the use of antihyperlipidemic agents or serum total cholesterol level ≥ 220 mg/dl), current

smoking habit (defined as a history of smoking during the preceding 3 months), and AF (diagnosed by 12-lead ECG, continuous electrocardiographic monitoring, or 24-hour Holter ECG).

Baseline blood samples of all patients were taken on admission. We prospectively measured plasma BNP for all patients on admission. Samples were collected from a peripheral vein into tubes containing aprotinin and ethylenediamine tetraacetic acid, and the plasma was isolated and then stored at -80°C until analysis. The plasma BNP concentration was measured using a chemiluminescence enzyme immunoassay for human BNP (Shionogi & Company,