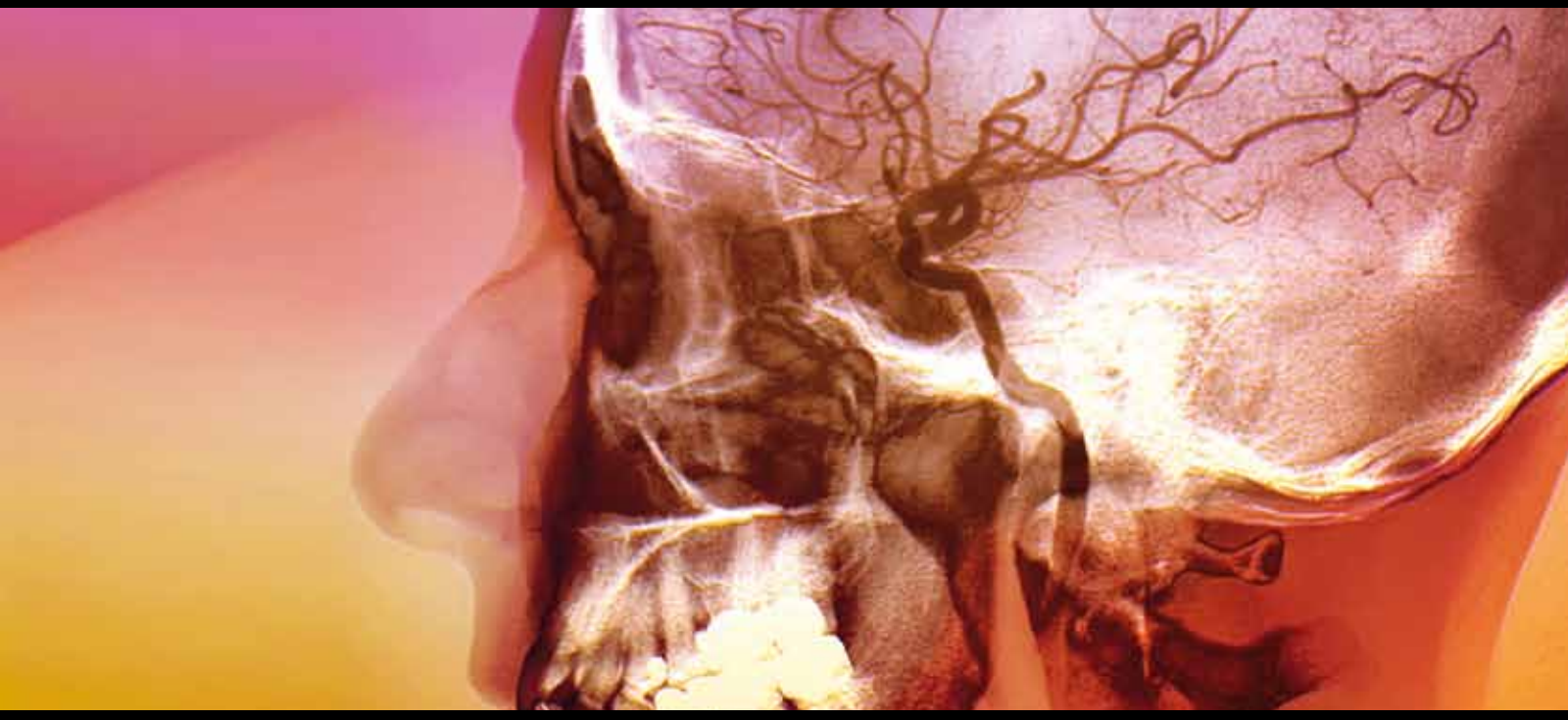
Stroke Research and Treatment

Advances and Potential New Treatments in Stroke Management

Guest Editors: Majaz Moonis, Padma Srivastava, Magdy Selim, and Marc Fisher



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Editorial Board

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Editorial

Advances and Potential New Treatments in Stroke Management

Majaz Moonis,[1] Padma Srivastava,[2] Magdy Selim,[3] and Marc Fisher[1]

[1] *UMass Memorial Medical Center, 55 Lake Avenue North, Worcester, MA 01655, USA*
[2] *All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India*
[3] *Beth Israel Deaconess Hospital, 330 Brookline Avenue, Boston, MA 02215, USA*

Correspondence should be addressed to Majaz Moonis; moonism@ummhc.org

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The last 3 decades have brought more advances in stroke management than any other era before. This special issue is an attempt to highlight some of these areas ranging from stroke prevention to stroke rehabilitation. The validation of tPA in improving outcome in 1995 is perhaps one of the most important milestones achieved in acute stroke management [1]. However, there is a small but significant risk of symptomatic hemorrhagic conversion with such treatment. Dr. D. J. Blacker and his group describe some novel strategies to reduce the risk of hemorrhagic transformation after thrombolysis with minocycline as well as other strategies.

Recurrent stroke prevention is highly linked to identification of the underlying mechanism[2]. This still remains a problem in 25–30% of incident cases. Drs. M. Khan and D. J. Miller review the existing literature and discuss the current approaches to improve detection of mechanisms underlying these cryptogenic stroke cases in "*Detection of paroxysmal atrial fibrillation in stroke/TIA patients*." Drs. V. Singh and N. J. Edwards, in their review article "*Advances in the critical care management of ischemic stroke*," discuss the advances in acute stroke management including advances in critical care and endovascular treatment. Drs. P. B. Gorelick and U. Farooq in their review article "*Advances in our understanding of "resistance" to antiplatelet agents for prevention of ischemic stroke*," provide an in-depth review of the current antiplatelet therapy and explore the concept of platelet resistance to antiplatelet agents, its place in clinical testing, and impact on outcomes.

Imaging techniques in acute stroke management continue to grow [2] and are addressed in context by Dr. P. Dubey and her colleagues in their review article "*Acute stroke imaging: recent updates*." This includes the controversy of CT versus MRI based imaging and the current controversies and consensus.

Stroke recovery besides the natural history is impacted by several additional factors including comorbid conditions, the hospital course, and subsequent rehabilitation. In this context, Dr. B. Husaini and his group investigated the impact of comorbid depression in a large Medicaid group from Tennessee. They explored this often ignored, poorly understood factor and demonstrated its impact on length of hospital stay and outcome broken down by race and gender in "*Depression increases stroke hospitalization cost: an analysis of 17,010 stroke patients in 2008 by race and gender.*" The subsequent two articles on stroke rehabilitation explore the concept of recovery and neural plasticity (Drs. N. Takeuchi and S.-I. Izumi) and the intriguing role of piano playing in improving fine motor control (Drs. M. Villeneuve and A. Lamontagne). Fine motor control in the upper extremities is often the last modality to recover and a cause of persistent disability for many stroke patients.

We hope that highlighting these ongoing multifaceted efforts in our endless pursuits to improve stroke care will provide new insights to trigger more active research and to bring about new treatment strategies for ischemic stroke.

Majaz Moonis
Padma Srivastava
Magdy Selim
Marc Fisher

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Review Article

Acute Stroke Imaging: Recent Updates

Prachi Dubey,[1,2] Sachin Pandey,[2] and Gul Moonis[2]

[1] *Department of Radiology, University of Massachusetts Medical School, Worcestor, MA 01655, USA*
[2] *Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA*

Correspondence should be addressed to Gul Moonis; gmoonis@bidmc.harvard.edu

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Acute ischemic stroke imaging is one of the leading causes of death and disability worldwide. Neuroimaging plays a crucial role in early diagnosis and yields essential information regarding tissue integrity, a factor that remains a key therapeutic determinant. Given the widespread public health implications of stroke and central role of neuroimaging in overall management, acute stroke imaging remains a heavily debated, extensively researched, and rapidly evolving subject. There has been recent debate in the scientific community due to divided opinions on the use of CT perfusion and access-related limitations of MRI. In this paper we review and summarize recent updates relevant to acute stroke imaging and propose an imaging paradigm based on the recently available evidence.

1. Introduction

Acute ischemic stroke is one of the leading causes of mortality and morbidity worldwide. Statistics from the American Heart Association estimate an average of 1 stroke every 40 seconds in the United States amounting to approximately 795,000 people experiencing new or recurrent strokes, per year [1]. In view of the widespread public health impact of stroke and its profound impact on patients, stroke research has remained in the forefront. A recent systematic review article reported no significant difference between reperfusion strategies based on the current literature, emphasizing need for future randomized clinical trials to determine the efficacy of alternative reperfusion strategies [2]. As noted by Gonzales R in a recent commentary, the failure to recognize relative efficacy of treatment strategies can be partially attributed to lack of appropriate patient selection due to ineffective, inconsistent, and contradictory neuroimaging approach. This was one of the potential causes that lead to the halting of the Interventional Management of Stroke III Trial [3].

There is a critical need for reproducible and sensitive imaging biomarkers that allow accurate assessment of efficacy of rapidly evolving thrombolytic treatments. This underscores the primary need for standardization of imaging techniques across institutions so data from multicenter trials can be collectively analyzed. The glaring lack such consensus amongst imaging techniques was highlighted in a recent systematic review which found wide variability in the employed thresholds for CT and MR perfusion imaging and significant inconsistency in definitions of tissue states; factors which add to the widespread variability in perfusion-based assessment [4].

Despite the inherent challenges and past failures, stroke imaging is rapidly evolving with enormous ongoing research and global public health impact. In this paper we sought to review recent cumulative evidence including evolving expert opinions and recommendation to assess the adequacy of current state of clinical practices in acute stroke imaging. Based on our assessment we propose an optimal imaging paradigm for patients presenting with suspected acute ischemic stroke.

2. Identification of Target Clinical Goals in the Acute Care Setting

The initial step in approaching the imaging paradigm is to summarize the targeted clinical goals for patients with suspected acute ischemic stroke in the acute care setting.

The fundamental objective of treatment is to enable rapid reperfusion for maximal tissue salvation. There is substantial evidence to suggest efficacy of intravenous thrombolytic therapy in the first 4.5 hours from onset of symptoms as well as increased risk of hemorrhagic complications and lower efficacy outside the therapeutic window. The European Cooperative Acute Stroke Study (ECASS) investigators demonstrated the efficacy of treatment instituted within the first 4.5 hours [5]. This was confirmed on a systematic review with pooled data from 11 randomized controlled trials evaluating intravenous thrombolysis (IVT) and 3 randomized controlled trials evaluating intra-arterial thrombolysis (IAT). This review concluded efficacy of IVT within 4.5 hours of onset of symptoms, beyond which the risk of treatment outweighed the benefit. The clinical utility of expanding the treatment window to 6 hours with IAT treatment is currently investigational [6].

Based on the above considerations the following goals must be achieved to allow early initiation of treatment. The choice of imaging approach and interpretation protocol should be designed with the intent of addressing the primary clinical goals such as to allow safe and prompt initiation of thrombolytic strategies.

2.1. Goal 1

Exclusion of Primary Intracranial Hemorrhage, Assessing for Alternate Etiologies for Symptoms and Treatment Contraindications. Once the patient presents to the ER with neurological symptoms possibly corresponding to a suspected acute stroke, the initial goal is a "rule out" approach. This is particularly critical in those patients with early presentation, as they are most likely to benefit from rapid institution of reperfusion therapy.

Initial evaluation focuses on exclusion of primary intracerebral hemorrhage (PICH), intracranial metastasis, tumor with herniation, or other alternate etiologies explaining the clinical picture.

2.2. Goal 2

Infarct Characterization: Identifying of Core, Quantification of Core Volume, Imaging of Penumbra and Pial Collateral Vessels. This has been thoroughly reviewed and concisely presented as the "core, clot, collateral" approach and is currently the mainstay of acute stroke neuroimaging [7].

2.3. Nonenhanced Head CT. Theoretically Goals 1 and 2 can be assessed on NECT/CTA combination, which is the most ideal single-step imaging solution. Guidelines published by American Heart Association and American Stroke Association Stroke Council in 2007 mandate universal and immediate availability of nonenhanced head CT (NECT) within 30 minutes of initial presentation to the ER [8].

There is no controversy regarding the utility of NECT with regards to accomplishing Goal 1. In particular it is widely accepted that NECT can reliably exclude intracranial hemorrhage, which is critical for therapeutic decision making.

In terms of infarct characterization to address Goal 2, NECT-based scoring system designed by the Alberta Stroke Program, commonly referred to as the ASPECTS scoring system, (Alberta Stroke Program Early CT Score) provides an effective tool for quantifying early ischemic changes in the MCA territory (Figure 1). This methodology has provided useful prognostic information with regards to response to reperfusion. Patients with high ASPECTS scores (8–10) corresponding to low infarct volume on initial imaging demonstrated the best clinical outcomes [9]. However, as noted by Demchuck et al. the greatest limitation of ASPECTS application is the inability to accurately visualize the early ischemic changes on NECT in the real world setting, [7]. This is more problematic in the setting of preexisting white matter changes. An interobserver reliability study demonstrated a 77% concordance for total ASPECTS score with lower agreement for scores based on a cut-off (>7 and ≤7) and also lower agreement for cortical and internal capsule regions [10]. Overall, there is substantial cumulative evidence indicating ASPECTS NECT scoring as a very objective, semiquantitative, prognostic tool and we recommend utilization of online resources to aid ASPECTS utilization in early acute stroke imaging; see http://www.aspectsinstroke.com/ [11].

2.4. MRI with Diffusion-Weighted Imaging. There is conclusive evidence regarding the sensitivity of MRI with diffusion-weighted sequences for the detection of infarct core including those cases in which the infarct core remains occult on standard T2-weighted imaging [12]. Evidence-based guidelines proposed by the Therapeutics and Technology Assessment subcommittee of the American Academy of Neurology, endorses the role of DWI in accurate diagnosis of acute ischemic stroke particularly in the first 12 hours as being superior to NECT and also suggest, that baseline DWI infarct volume has predictive ability towards final infarct volume and overall clinical outcomes [13].

Recent considerations for the same were reviewed by R. Gonzalez indicating a significant role of MRI with diffusion-weighted sequences in identifying infarct core and allowing assessment of core volume, which is a useful predictor of treatment efficacy [14]. In the past, pretreatment infarct core volume has been demonstrated to be a highly specific predictor for malignant middle cerebral artery infarction at a threshold core volume of greater than 82 mL. [15]. The MR Stroke study group investigators found a 5.8 fold increased risk of symptomatic intracerebral hemorrhage in patients with large-volume infarct cores (>100 mL) compared to small (<10 mL) and moderate (10–100 mL) ones [16]. A core volume threshold of approximately 70 mL has been suggested as having dichotomous prognostic implications with patients with higher core volumes having unfavorable outcomes regardless of treatment [17, 18].

A recent study demonstrated that posttreatment final infarct volume (FIV) also has significant influence on clinical outcome in patients undergoing IAT [19]. This study showed high specificity for poor outcome with FIV of >90 cm^3. Therefore with regards to established management goals, MR with diffusion-weighted imaging provides the most accurate

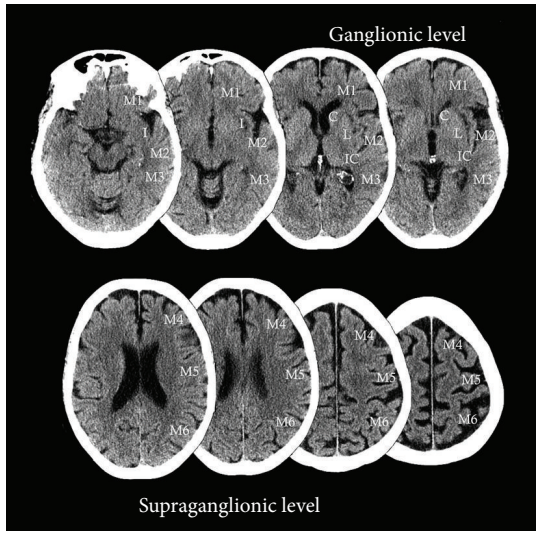

Figure 1: Obtained from http://www.aspectsinstroke.com/, demonstrating the ASPECTS scoring methodology, axial NCCT images showing the MCA territory regions as defined by ASPECTS. C, caudate, I, insularribbon, IC, internal Capsule, L, lentiform nucleus, M1, anterior MCAcortex, M2, MCA cortex lateral to the insular ribbon, M3, posteriorMCA cortex, M4, M5, M6 are the anterior, lateral, and posterior MCAterritories immediately superior to M1, M2, and M3, rostral to basal ganglia. Subcortical structures are allotted 3 points (C, L, and IC). MCA cortex is allotted 7 points (insular cortex, M1, M2, M3, M4, M5, and M6). (Reprint permission obtained from Dr. Mayank Goyal, professor of radiology and clinical neurosciences, Foothills Medical Centre, University of Calgary).

information related to Goal 2 principles of core identification and core volume quantification. However, diffusion-weighted imaging alone has limited utility for detection of penumbra for which MR perfusion estimates are more reliable and it provides little information about vascular substrates, including assessment of occluded vessel and degree of pial collateralization.

Additionally, there are accessibility issues due to individual contraindications to MR and limited availability of MRI leading to underutilization of MRI in emergent setting. A recent study evaluated the adherence to AAN guidelines of preferring MR over CT in the initial 12 hours of presentation and revealed that the target was met in less than 1/3 of patients in their study [20].

2.5. Mismatch Imaging: CT Perfusion and MR Perfusion. Perfusion imaging either CT or MR is most relevant in terms of ability to delineate the ischemic penumbra. The clinical utility of penumbra imaging has long remained an issue of debate. The hypothesis of penumbra identification is that identification of "at-risk" tissue may allow widening of the treatment window beyond 4.5 hours and allow detection of patients who will either benefit from treatment or those in whom treatment is not likely to cause improved outcome.

It is notable that the recent study by the MR Rescue investigators found no role of penumbra imaging in selecting patients likely to benefit from endovascular therapy within 8 hours from onset of symptoms. There was evidence of good functional outcome in patients with favorable penumbral pattern in the late time window regardless of recanalization. Interestingly, this study raises the possibility that patients who have a favorable penumbral pattern may be inherently more resilient to the effects of vascular occlusion and therefore harbor a favorable outcome regardless of treatment, thus explaining lack of differential effect of therapy when stratified on the basis of penumbral pattern [21].

Nevertheless there remains an interest in imaging penumbra due to its potential role as a prognostic biomarker. Previously, CT perfusion performed soon after the initial NECT has been supported as being a safe and efficacious strategy for imaging tissue at risk [22]. On the other hand a recent study demonstrated low sensitivity of MTT maps in predicting acute infarct detectable on DWI sequence. CBV also did not correlate with the DWI abnormalities. This study advocates against utilization of CTP in acute NVS [23].

Reliance on postprocessing, restricted brain coverage, and vendor related-differences in processing algorithm are primary limitations which have not yet been completely addressed and remain as mitigating factors in enabling wider utility of CTP. Additionally the inherent low contrast to noise ratio increases susceptibility to artifacts and lowers overall sensitivity. These considerations were reviewed by R. Gonzales and for the same reasons the clinical utility of CTP was felt to be doubtful in the current state of practice [3].

On a contrary note, a recent expert commentary by M. Lev acknowledges the aforementioned CTP limitations but continues to endorse this method due to its relative cost efficacy, rapid availability, and potential for quantitative assessment relative to MRI [24]. A recent study demonstrated that CTP-based penumbra volume was an independent predictor of clinical outcome in 90 days along with recanalization status. This study also demonstrated that the CT perfusion based penumbra volume could not be accurately assessed by clinical parameters, NECT or CTA [25]. CTP rCBF maps with appropriate threshold levels are felt to represent an accurate estimate of the infarct core [26, 27].

MR perfusion parameters are equally sensitive in depicting tissue at risk although expense, lack of universal applicability and access issues in the ER setting remain limiting factors. Recently the applicability of MR Perfusion was reviewed by M. Fisher, highlighting its utility in delineating tissue at risk of infarction and thus holding promise in expansion of the therapeutic window. A key aspect underscored in this review relates to the identification of "benign oligemia," which refers to hypo perfused tissue which will not proceed to infarction regardless of treatment. The MR perfusion parameter $T_{\max}$ with $T_{\max}$ delay of >5 to 6 seconds compared to normally perfused tissue was considered to be a useful indicator of impending infarction in the absence of reperfusion [28]. Using pooled data from the DEFUSE (diffusion and perfusion imaging evaluation for understanding stroke evolution) and EPITHET (echoplanar imaging thrombolytic evaluation trial) studies, Mlynash et al. found that based on $T_{\max}$ and diffusion-determined mismatch, patients with a mismatch who have large core volumes (size of DWI lesion) or large perfusion defect (large-volume, severe $T_{\max}$ delay) had unfavorable outcomes despite reperfusion. This study suggested a $T_{\max} > 8$ secs with a volume of approximately 100 mL as an adequate threshold for identification of patients with malignant profile of infarction who would be poor candidates for reperfusion therapy [29].

2.6. CT Angiography. CT angiography continues to be the superior method for characterization of vascular anatomy. Figure 2 in addition to allowing for assessment of the site of vascular occlusion, it also allows assessment of the presence of calcifications and atherosclerotic disease, which can influence recanalization techniques. It is also the most effective noninvasive means of assessment of leptomeningeal collaterals, which not only determines rate of core expansion but also influences possibility of hemorrhagic transformation [30]. A study by Bang et al. demonstrated higher risk of hemorrhagic transformation in patients with poor collateral status [31]. Another study demonstrated discriminatory ability of a poor collateral score in detecting a malignant profile (larger DWI lesion volume at baseline, higher median NIHSS and functional dependency at 3 months after stroke) [32].

A recent study showed that CTA evidence of occlusion of distal internal carotid, proximal middle cerebral, or basilar arteries as a predictor of poor outcome and added incremental predictive value to NIHSS. This suggests the utility of CTA in early phase treatment decision making [33].

A potential confounding factor is acquisition protocol-dependent overestimation of infarct core volume using CTA source images for detecting of early ischemic changes [34]. The source images acquired by slow CT acquisition demonstrated greater infarct volume correlation with MR diffusion core estimates compared to the multislice CT scanner. This overestimation has critical clinical implications given it may prevent institution of reperfusion treatments in patients who could have potentially benefited from reperfusion therapy [34].

Overall, CTA has a definite prognostic role in acute phase of stroke imaging. In particular, with relevance to our defined Goal 2, acute-phase CTA can enable assessment of site of occlusion, integrity of vessels in terms of atherosclerotic disease, and degree of collateral flow, all of which influence management decision making (Figure 2). It must, however, be kept in mind that CTA entails exposure to radiation and iodinated contrast, which are potential pitfalls of utilization.

2.7. Proposed Imaging Paradigm. Despite significant advances in our understanding of physiologic surrogates of imaging observations and the respective technical confounds, there are still considerable debate and lack of consensus particularly with relevance to penumbra imaging and role of perfusion imaging as it relates to core characterization and penumbra estimation.

If we take a minimalist approach, the expert opinion seems to converge most definitively on two standard queries prior to therapeutic decision making (1) is there primary intracranial hemorrhage? and (2) what is the volume of the infarct core? These two components combined with clinical neurological assessment seem to be most directly related to clinical outcome in postperfusion recovery phase and will help stratify patients appropriately for treatment decision-making.

The limitation of the minimalistic approach is that although it raises specificity, by helping us identify those that will have a favorable outcome after-reperfusion, it also at the same time lowers sensitivity, thereby potentially excluding patients who may have benefitted from more aggressive reperfusion therapy.

One of the ways to achieve efficient imaging selection for treatment triage is development of a unimodal imaging protocol. Simplistically stating, a one-stop, all-inclusive imaging protocol can accurately and reproducibly classify patients who will either (a) benefit from treatment or (b) have no impact or negative impact of treatment. NECT is the most obvious choice for Goal 1-related aspects of management. However, beyond that it would be ideal if the CT imaging and interpretation protocols can be optimized in such a way that Goal 2 can be consistently and reliably achieved in acute-phase urgent care setting on the same CT scanner without having to transfer the patient. We believe that in many cases this is feasible, particularly when the ASPECTS score is carefully interpreted, providing infarct core volume information. To assist in the latter, we encourage the use of online resource described by Modi et al. [11] (http://www.aspectsinstroke.com/) to optimize utilization of NECT. This can be followed by CTA/CTP to assess the remaining aspects of Goal 2 with relevance to site of occlusion, collateral flow assessment, and penumbra imaging, all of which have been established as either predictors of treatment efficacy or overall clinical prognosis in poststroke recovery phase. This approach minimizes scanner time and utilizes the most widely available technologies only. Based on the considerations presented in the Gonzalez and M. Lev commentaries, we agree that NECT with ASPECTS assessment along with CTA can provide sufficient information for adequate triage of patients who will benefit from treatment. The remainder of the imaging including penumbra imaging with CTP can be performed while the treatment implementation has begun minimizing the "door-to-needle" time [3, 24].

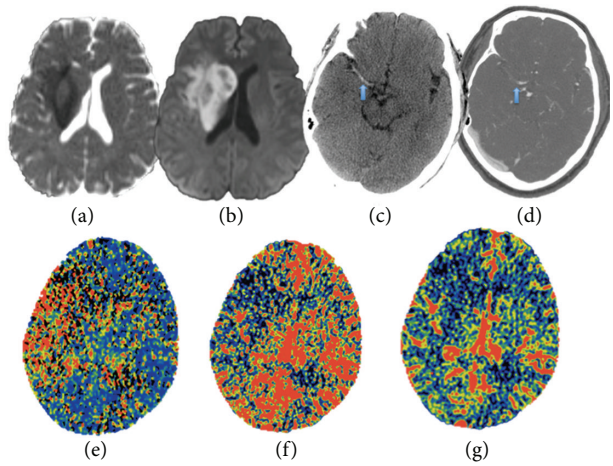

Figure 2: (a) and (b) ADC map and DWI map with restricted diffusion in the setting of cytotoxic edema from acute ischemic infarct in right MCA territory. (c) NECT showing hyperdense right MCA compatible with acute thrombosis. (d) CTA image with thrombosis in the corresponding segment of right MCA. (e), (f), and (g) CTP with elevated MTT, reduced cerebral blood flow, and blood volume in the right MCA territory.

However, we acknowledge coexistent evidence that indicates limitation of NECT in core characterization due to multitude of factors including inherently low sensitivity to early ischemic changes. It is agreed upon that core volume is a key determinant of treatment efficacy, for which MR with DWI is the imaging gold standard. In an ideal world with no cost, availability or individual applicability issues, an all inclusive MR protocol for acute stroke imaging would be more preferred from the viewpoint of obtaining accurate and consistent tissue specific information with minimum susceptibility to postprocessing variability.

As stated above we emphasize that if MRI is not available and decision for endovascular therapy has to been taken based on the initial NECT, then immediate CTA (to assess vessel occlusion and collateral status) and CTP (infarct core assessment on rCBF map) should be considered (Figure 2). This approach would require less than 10 minutes and can be performed while the intravenous thrombolytic agent is being initiated [3, 24].

The utility of mismatch imaging is undoubtedly promising; however, the recent body of evidence does not provide compelling arguments to necessitate a paradigm shift particularly in routine clinical settings outside of major academic institutions. This is especially true in light of the results from the recent penumbra-based trial of imaging selection by the MR Rescue investigators demonstrating no utility of penumbra imaging in detecting patients who would benefit from endovascular therapy of acute ischemic stroke [21].

At this time with proven efficacy of IVT within the first 4.5 hours, it is notable that the frequency of thrombolytic therapy in patients with acute ischemic stroke remains remarkably low. A large multicenter study found only 3% utilization of thrombolysis for all acute ischemic stroke patients and only 10% for those who presented within the first 3 hours [35]. This is largely related to complexity of imaging protocols and a general lack of consensus amongst the experts regarding imaging appropriateness leading to inability to select the appropriate patients who would benefit from treatment in a timely fashion. In light of these compelling statistics, we strongly encourage a minimalist imaging approach, which can be reliably and consistently reproduced regardless of variability in institutional capabilities. NECT with ASPECT emphasis with simultaneous CTA/CTP and prompt MR with diffusion remain the most rigorously optimized imaging tools.

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Review Article

Advances in Our Understanding of "Resistance" to Antiplatelet Agents for Prevention of Ischemic Stroke

Philip B. Gorelick[1,2] and Muhammad U. Farooq[1]

[1] *Hauenstein Neuroscience Center, 220 Cherry Street SE, Grand Rapids, MI 49503, USA*
[2] *Department of Translational Science and Molecular Medicine, Michigan State University College of Human Medicine, 333 Bostwick Avenue NE, Grand Rapids, MI 49503, USA*

Correspondence should be addressed to Philip B. Gorelick; pgorelic@trinity-health.org

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We review the role of aspirin and clopidogrel for prevention of ischemic stroke and explore the concept of antiplatelet therapy resistance both from a laboratory and clinical perspective and genetic polymorphisms that might influence platelet reactivity with clopidogrel administration. Debates have raged over the years about the application of platelet function tests in clinical practice. We conclude that platelet function testing is not indicated in routine clinical practice. This recommendation is supported by clinical guideline statements, a lack of a global platelet function measure, and limitations of current platelet function test methods as applied in practice. We discuss a recently hypothesized hierarchy of patient characteristics in relation to which patients are most likely to benefit from platelet function studies based on acuity (i.e., risk) of cardiovascular disease. A focus of antiplatelet therapy administration should include emphasis on compliance/adherence and in the example of aspirin, use of well-absorbed forms of aspirin and avoidance of drugs that may interact with aspirin to inhibit its mechanism of action (e.g., certain nonsteroidal anti-inflammatory drugs).

1. Introduction

In the 1700s, Edward Stone, a clergyman, pulverized the bark of the willow and created a tea that reduced fever [1]. Some 70 years later, salicin or salicylic acid, was identified as the active ingredient of the therapeutic brew. The active substance, however, was known to be bitter and irritating to the stomach. In the mid to late 1800s, a less toxic form of the agent was synthesized, and in 1898 Felix Hoffmann was credited for synthesizing acetylsalicylic acid, later named "aspirin" whereby the "a" denoted acetyl and "spirin," *Spiraea ulmaria*, the source of salicylic acid [1, 2]. In the era of modern cardiovascular prevention, Lawrence Craven reported that aspirin might prevent coronary artery thrombosis and ischemic stroke, but also might lead to hemorrhagic complications [3, 4]. Craven's insights were the forerunners to large scale, randomized controlled trials (RCTs) of aspirin in the prevention of cerebral ischemia and cardiovascular disease. It was not until the 1970s that John Vane elucidated the mechanism of aspirin—suppression of biosynthesis of prostaglandins [5]. Since that time we have witnessed a substantial growth of RCTs featuring aspirin and newer antiplatelet therapies for stroke and cardiovascular disease prevention.

Aspirin has withstood the test of RCTs over time as a cost-effective approach to stroke and cardiovascular disease prevention [6]. The effectiveness of aspirin and other antiplatelet agents, however, has been subject to criticism related to possible "resistance" or biologic variability. In this discussion we provide a brief update of the latter topic in relation to aspirin and clopidogrel. We have chosen to review these two agents based on frequency of use in practice and availability of study data. Our review is not a formal meta- and systematic analysis but rather includes scientific data known to the authors in their personal study files.

2. Aspirin: Guidelines for Use in Stroke Prevention

We begin our discussion with a brief review of United States (US) guidelines to show the position of aspirin in stroke prevention. The American Heart Association (AHA) guidelines recommend an initial dose of aspirin 325 mg within 24 to 48 hours after ischemic stroke onset for treatment of most patients (Class I; Level of Evidence [LOE] A), and after 24 hours for those who have received intravenous fibrinolysis [7]. Similarly, the American College of Chest Physicians (ACCP) guidelines recommend early (48 hour) aspirin treatment at an initial dose of 160 to 325 mg (Grade 1A) for persons with ischemic stroke or TIA [8]. In addition, in both sets of guidelines aspirin mono-therapy at a dose of 75 to 100 mg/day (Grade 1A) [8] or 50 to 325 mg/day (Class I; LOE A) [9] is one of the recommended acceptable initial antiplatelet agents to reduce the risk of recurrent stroke and other cardiovascular events for patients with non-cardioembolic ischemic stroke.

The recommendation for primary prevention of cardiovascular disease slightly differs between US ACCP and AHA guidelines. Specifically, ACCP recommends low-dose aspirin, 75 to 100 mg/day for persons 50 years of age and older (Grade 2B) [8], whereas AHA guidelines recommend aspirin prophylaxis for persons at sufficiently high risk when the benefits outweigh the risks of treatment (e.g., 10-year risk of cardiovascular events of 6 to 10%; Class I; LOE A); aspirin in a dose of 81 mg/day or 100 mg every other day may be useful for first stroke prevention among women who have a sufficiently high enough benefit to risk equation (Class IIa; LOE B); and aspirin is not indicated for those at low risk (Class III; LOE A)and for preventing a first stroke in those with diabetes or diabetes plus asymptomatic peripheral artery disease when there is no established cardiovascular disease (Class III; LOE B) [10].

Furthermore, the Antithrombotic Trialists' (ATT) Collaboration assessed the benefits and risks of aspirin in primary prevention from 6 trials [11]. In one phase of the analysis they compared long-term aspirin versus control therapy in 6 primary prevention trials of 95,000 persons at low risk over 660,000 person-years that included 3554 vascular events. Overall, aspirin was associated with a 12% proportional reduction in serious vascular events ($P = 0.0001$) mainly due to a reduction by about 20% of non-fatal myocardial infarction though the net effect on stroke was not significant ($P = 0.4$) (hemorrhagic stroke 0.04% versus 0.03%, $P = 0.05$ and other stroke 0.16% versus 0.18%, $P = 0.08$) [11]. Major gastrointestinal and extracranial bleeds, however, were increased (0.10% versus 0.07%, $P < 0.0001$). In addition and overall, in the primary prevention trials, the proportional reduction in serious vascular events did not depend substantially on age, sex, smoking history, blood pressure, total cholesterol, body mass index, history of diabetes mellitus or risk of coronary heart disease.

In a more recent meta-analysis of 9 RCTs in the area of primary prevention that included 102,621 patients followed over 6 years, aspirin was estimated to significantly reduce non-fatal myocardial infarctions by about 20% and total cardiovascular events by 10% without a substantial reduction in death or cancer [12]. Furthermore, the risk of non-trivial bleeds was 31% higher among those who received aspirin therapy, and was believed to offset the benefits. The authors concluded that aspirin in primary prevention was not indicated based on a number-needed-to-harm of 73 for non-trivial bleeding events that dwarfed any benefits. Currently, there is interest in aspirin as a therapy to prevent deaths in cancer and distant metastases [13]. These observations are important ones, and genetic and molecular mechanisms of these possible effects are being elucidated. It has been hypothesized that aspirin administration for up to 5–10 years may be required before a beneficial effect on cancer risk reduction is observed [14].

3. Clopidogrel: Guidelines for Use in Stroke Prevention

In both the ACCP and AHA guidelines for recurrent stroke prevention, clopidogrel 75 mg/day is considered an acceptable initial option for non-cardioembolic recurrent ischemic stroke prevention (Grade 1A; Class I, LOE A, resp.) [8, 9]. Clopidogrel is not considered a first-line agent for first stroke prevention [10].

4. Metabolism, Resistance, and Laboratory Testing for Resistance to Aspirin and Clopidogrel

4.1. Metabolism of Aspirin. Aspirin (acetylsalicylic acid) is quickly absorbed from the stomach and upper small intestine by passive diffusion and reaches peak plasma levels in about 30–40 minutes after administration of the immediate-release oral formulation [15]. Enteric-coated preparations, however, may take up to 3-4 hours to achieve peak plasma levels. The oral bioavailability of aspirin is approximately 40 to 50% over a range of doses, whereas for enteric-coated and sustained-release preparations, it is substantially lower. The portal circulation is the first point of contact of aspirin with platelets, and the half-life of aspirin is 15 to 20 minutes [15]. Despite a short half-life, there is permanent inactivation of the platelet for its entire life. At the cellular level, aspirin inactivates the cyclooxygenase (COX) activity of prostaglandin H (PGH) synthase 1 (COX-1) and synthase 2 (COX-2). Thus, the conversion of arachidonic acid to PGH2 is affected and several downstream bioactive prostanoids such as thromboxane A2 (TXA2), a vasoconstrictor, inducer of vascular smooth muscle, a pro-atherogenic factor, and platelet aggregant, and prostacyclin (PGI2) which has essentially opposite effects to TXA2, are affected. Platelets produce TXA2 whereas the vascular endothelium produces PGI2. The balance between PGI2 and TXA2 is thought to be important. The molecular mechanism of inactivation of COX activity by aspirin is the blockade of a channel caused by acetylation of a serine residue, Ser529 on COX-1 and Ser516 on COX-2. Select details of platelet activation are listed in Table 1 [16].

Table 1: Select steps in platelet activation [16].

(1) Receptor complexes tether platelets to sites of vascular injury: glycoprotein Ib/V/IX and platelet surface collagen receptors glycoprotein VI and Ia
(2) Mediators of adhesion phase, and amplification and sustenance of platelet response: adenosine diphosphate (ADP), thrombin, epinephrine, and TXA2
(3) Final activation pathway by involvement of agonists: activation of platelet integrin glycoprotein IIb/IIIa receptor for adhesion and aggregation

TXA2: thromboxane A2.

4.2. Defining Resistance to Aspirin and Its Causes. Aspirin resistance may be classified as a laboratory or clinical phenomenon [17]. Laboratory resistance may be defined as a failure to inhibit platelet TXA2 production or tests of platelet function (e.g., platelet aggregation) dependent on platelet TXA2 production. Clinical resistance may be defined as failure of aspirin to prevent clinical atherothrombotic events which also may be referred to as aspirin treatment failure [17]. Traditionally in biologic systems, drug resistance is defined as being caused by microbes, viruses or cancer cells that change to reduce or eliminate a drug's effectiveness or genetic changes alter drug targets such as enzymes or transmembrane proteins that lead to reduced or no drug activity [18]. Thus, aspirin "resistance" differs from the traditional definition of resistance in that the change is not in the drug target per se as in the traditional use of the term. Furthermore, the effects may fluctuate and are at least partially reversible by changing the dose of aspirin [18].

Hankey and Eikelboom discuss possible causes for aspirin failure and include the following categories: (1) Reduced bioavailability (e.g., poor compliance or drug not prescribed, reduced absorption or metabolism); (2) Altered binding to COX-1 (e.g., ibuprofen administration); (3) Other sources of TXA2 production (sources from monocytes, macrophages and endothelial cells); (4) Alternative pathways of platelet activation (e.g., increased sensitivity of platelets to collagen and ADP); (5) Increased platelet turnover (increased platelet production by bone marrow in response to coronary artery bypass surgery); (6) Genetic polymorphisms (e.g., polymorphisms of COX-1, COX-2); (7) Loss of antiplatelet effect with long-term administration of aspirin (tachyphylaxis); and (8) Non-atherothrombotic causes of cardiovascular events not expected to respond to antiplatelet agents (e.g., vasculitis) [17].

4.3. Diagnosing Laboratory Resistance to Aspirin. The frequency of laboratory resistance to aspirin has been estimated to be up to 61% [17]. The estimates vary substantially based on disparate study populations, overall methods, and specific tests of platelet function. Importantly, as many as 40% of patients with cardiovascular disease may not be compliant with aspirin therapy.

Platelet function can be assessed by point-of-care and other laboratory tests. Most of the tests are *ex vivo* ones [18]. Table 2 provides a listing of the tests and a brief commentary about them. Thus far, point-of-care or other platelet function tests or genetic tests have not been mandated for use in practice according to guideline statements [18, 19]. Such testing has been employed in practice and research, but has not been considered a mandatory part of practice. In the case of clopidogrel, for example, one guidance statement concluded that genetic tests to detect poor metabolizers at moderate or high risk for poor outcomes may be considered [19]. As we will discuss below, these tests may have more value in certain clinical circumstances.

4.4. Metabolism of Clopidogrel. Clopidogrel is a prodrug that must be converted to its active form in the liver [20, 21]. Once ingested clopidogrel is absorbed in the intestine whereby absorption may be limited by P-glycoproteins encoded by the ABCB1 gene. Most of the drug (about 85%) is metabolized by esterases into an inactive form, whereas the remainder is converted from the prodrug to the active state at the cytochrome P450 (CYP) site by active isoforms. Whereas aspirin inhibits COX, clopidogrel irreversibly inhibits the adenosine diphosphate (ADP) receptor coded by the P2RY12 gene responsible for inactivating the fibrinogen receptor, glycoprotein IIb/IIIa, responsible for platelet aggregation. CYP-dependent oxidative steps are critical for the conversion of the prodrug to its active form, and carriage of certain CYP2C19 and CYP3A4 alleles, for example, may be associated with response to clopidogrel as oxidative-dependent metabolism of clopidogrel occurs. The CYP2C19 polymorphisms include a ^{*1} normal function isoform and ^{*2} and ^{*3} loss of function alleles. Poor metabolizers may be defined as those having two loss of function alleles and intermediate metabolizers as those with one loss of function allele. In addition, a gain-in-function allele, CYP2C19^{*17} exists and serves as a hyper- or ultra-rapid metabolic pathway for the conversion of clopidogrel to its active form. Certain drugs such as proton pump inhibitors (PPIs) may use the same pathway of liver metabolism as clopidogrel, and thus, may be associated with diminished clopidogrel response [21].

4.5. Diagnosing Laboratory Resistance to Clopidogrel. In the example of clopidogrel, possible laboratory resistance may be defined by platelet function tests or genetic tests. Table 2 lists and reviews platelet function tests that may be used to define clopidogrel resistance and the limitations of these tests [18, 21]. Such tests as VerifyNow, Thromboelastography, PFA-P2Y, and the degree of phosphorylation of VASP may be employed.

Loss of function alleles for the conversion of clopidogrel from the prodrug to its active form have been associated with diminished platelet inhibition and poorer outcomes in relation to occurrence of major events in persons with acute coronary syndromes or percutaneous coronary intervention [21–24]. The clinical circumstances are complex as multiple factors may be involved in the attribution of clopidogrel metabolism. For example, in high-risk coronary patients, loss-of-function alleles may occur in up to 20%, and it is estimated that at least one copy of the reduced function CYP2C19^{*2} allele occurs in 50% of Chinese, 34% of African Americans, 25% of Whites, and 19% of Mexican Americans

Table 2: Platelet function tests and commentary [18, 21].

(1) Thromboxane A2 synthesis	Measurement of metabolites such as serum thromboxane B2 or urinary 11-dehydro-thromboxane B2, direct metabolites of COX-1, a specific mechanistic target of aspirin may be made. These tests are limited by a nonlinear relationship between platelet COX-1 activity and thromboxane A2 activity, and extra-platelet sources of thromboxane A2 synthesis. Furthermore, urinary excretion of 11-dehydro-thromboxane B2 must be normalized according to urinary function (e.g., creatinine concentration).
(2) Aspirin response according to thromboxane dependent assays light transmittance aggregometry (LTA), impedance aggregometry (IA), platelet function analyser (PFA-100), and VerifyNow	LTA measures light transmission through a platelet suspension exposed to a platelet agonist such as ADP, but the agonists may activate pathways less dependent on COX-1. IA measures electrical impedance after exposure to whole blood suspension by a platelet agonist. There may be poor reproducibility, variation of response by age, race, sex, hematocrit, and concentration of the agonist. Like IA, LTA may be associated with poor reproducibility. PFA-100, an *in vitro* recorder, includes a membrane with an aperture coated with collagen plus an agonist (e.g., epinephrine, ADP). As platelets form aggregates, the aperture occludes, and flow factors may affect test results (e.g., nonsteroidal anti-inflammatory drugs, clopidogrel, GP IIb/IIIa expression on the platelet surface, von Willebrand factor, platelet count, hematocrit, and diurnal variation (lower closing times in the morning)). VerifyNow measures platelet function by light transmission through a suspension of lyophilized fibrinogen-coated beads and an agonist such as arachidonic acid. *Clopidogrel Response*. Platelet function measured by LTA using the agonist, ADP, before and after treatment, is the main standard test to assess clopidogrel. Point-of-care assays such as VerifyNow, Thromboelastography (discussed below), and PFA-P2Y may be employed. These tests all have limitations that are discussed elsewhere (see [21]).
(3) Thromboelastography	Measures the contribution of ADP-induced aggregation to tensile strength of platelet-fibrin clot and requires further validation studies as does the PFA P2Y test that measures clopidogrel response.
(4) Degree of phosphorylation of VASP	Clopidogrel irreversibly blocks the ADP receptor P2Y12 and activates a cAMP-dependent protein kinase a that inhibits VASP, vasodilator-stimulated phosphorylation. VASP is an inducer of platelet aggregation via GP IIb/IIIa. The degree of phosphorylation of VASP to an antiplatelet agent may be determined by flow cytometry, but there may be limited sensitivity.

[19, 21]. Furthermore, there may be polymorphisms of the P2Y12 receptor such that there is decreased affinity to clopidogrel, and drugs such as rifampin may lead to increased activation of the CYP3A4 site, and other drugs such as PPIs may compete with clopidogrel at the CYP metabolic activation site [21]. One specific PPI, omeprazole, has been cited by the US FDA in a "Black Box Warning" statement as a concern for administration with clopidogrel, though the topic remains controversial [25].

4.6. Summary Thoughts about Laboratory Resistance to Aspirin and Clopidogrel. Overall, and as summarized by a number of authors in relation to aspirin and other antiplatelet agent laboratory testing to detect resistance, there may be considerable differences between point-of-care and other platelet function test results. Therefore, these tests require additional prospective study in large trials and observational studies before they will be ready for routine use in clinical practice [18, 21, 26–28]. After reviewing the arguments for and against platelet function monitoring tests, we are most impressed by the lack of a suitable global platelet test measure and clinical supporting evidence that the results of such testing will clearly make a difference in stroke prevention management [29–34].

4.7. New Clinical Information. Adjustment of aspirin dose to higher levels to provide more effective prevention of cerebrovascular disease has long been debated [35], however, over time most agree that lower doses of aspirin (e.g., 50–325 mg/day) provide similar point estimates of stroke or composite stroke, myocardial infarction or vascular death reduction as higher doses, but lower dose aspirin is safer [2]. Opportunity to get the most benefit out of aspirin and other antiplatelet agents may be as simple as encouraging compliance or adherence, and in the case of aspirin, avoiding use of certain concomitant drugs, when possible, such as ibuprofen which may competitively inhibit low-dose aspirin from leading to an irreversible inhibition of platelet function [36]. Or, by avoiding enteric-coated aspirin which may lead to delayed or reduced aspirin absorption [37].

Intensification of platelet inhibition and reduction of residual platelet activity in patients with acute coronary syndrome by treatment with clopidogrel or newer antiplatelet gents such as prasugrel or ticagrelor has been a recent focus of interest [38–40]. Interestingly, recent studies have shown no significant improvements in clinical outcomes with platelet function monitoring and treatment adjustment when there is coronary artery stenting [41]. Furthermore, among patients with acute coronary syndrome without ST-segment elevation in a platelet sub study, there was no significant association between platelet reactivity and major ischemic outcomes [42]. These studies cast further doubt on the clinical usefulness of platelet function monitoring in practice. Similar skepticism has been leveled against the CYP2C19 genotype and occurrence of cardiovascular events when clopidogrel is used [43, 44].

Currently, there is new evidence to suggest that the association between P2Y12-mediated platelet reactivity and clinical outcomes may depend on the clinical context within which platelet function is measured [45]. For example, there may be a hierarchy by disease acuity whereby platelet function becomes more meaningful. Specifically and in relation to coronary artery disease, patients with coronary syndromes requiring acute percutaneous coronary intervention (PCI) may be most affected by adverse outcomes (e.g., stent thrombosis) when there is on-treatment platelet reactivity, whereas the risk is less for those undergoing PCI for stable coronary disease, and is not strongly associated with outcomes in medically treated patients [42, 45]. Finally, the evidence base has expanded in relation to clopidogrel and cigarette smoking status to suggest a reduced or complete lack of clinical benefit in association with clopidogrel use in nonsmokers [46]. The explanation for this phenomenon is thought not to be an enhanced prothrombotic state in smokers but rather by an induction of activity of the CYP1A2 isoenzyme in smokers that leads to metabolic activation of clopidogrel. These two observations [45, 46] may help us to focus our study for meaningful clinical use of platelet function tests in stroke and cardiovascular disease practice.

5. Conclusion

"Resistance" to antiplatelet therapy has been defined as a laboratory or clinical phenomenon. Laboratory resistance may include failure to inhibit platelets based on platelet function tests or laboratory evidence of failure to inhibit the metabolic pathway that should be inhibited by a given drug. Clinical resistance may be defined as failure to prevent meaningful clinical atherothrombotic events which also may be referred to as treatment failure. Platelet function testing remains a clinical research tool. At this time, it is not recommended for routine clinical use as there is no global platelet function measure, and there are significant limitations of testing (see Table 2). As the science of platelet function testing advances, we are beginning to target groups of patients that might be more likely to benefit from such testing [45]. These patients preferentially may be those with acute cardiovascular disease, especially those undergoing acute revascularization interventions.

Conversion of c lopidogrel from its prodrug state to its active metabolite may be affected by a number of factors of which cigarette smoking may be one of them [46, 47]. Specifically, there has been a body of emerging evidence that shows a concordance between cigarette smoking, greater pharmacodynamic efficacy, and clinical response to clopidogrel therapy [47, 48]. Encouragement of cigarette smoking is not a public health option, however, newer more potent antiplatelet agents such as prasugrel and ticagrelor that are associated with better clinical outcomes than clopidogrel in high-risk coronary artery disease patients may be administered, if bleeding risk is permissive [48]. In relation to stroke, prasugrel and ticagrelor are not labeled for use by the US FDA and may be associated with brain bleeding risk. As for aspirin, adherence remains a challenge (47% or less in the US) and is an important point of informed discussion between the patient and healthcare provider about competing risks of bleeding and reduction of stroke and cardiovascular events [49]. Increasing the aspirin dose [50] or changing from one antiplatelet agent to another (e.g., aspirin to clopidogrel or clopidogrel to aspirin) has not been definitively shown to prevent subsequent recurrent stroke [9]. Therefore, in relation to aspirin, a focus on adherence and use of drugs that may alter aspirin absorption or effect makes sense in practice.

Disclosures

Dr. Gorelick serves on the Steering Committee for the Bayer sponsored ARRIVE clinical trial of aspirin for first stroke prevention and is a member of a speaker's bureau for Boehringer Ingelheim for stroke prevention in atrial fibrillation with dabigatran. Dr. Farooq has no disclosures.

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Review Article

Advances in the Critical Care Management of Ischemic Stroke

Vineeta Singh and Nancy J. Edwards

Department of Neurology, University of California-San Francisco, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110, USA

Correspondence should be addressed to Vineeta Singh; vineeta.singh@ucsfmedctr.org

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Given recent advances in diagnostic modalities and revascularization capabilities, clinicians are not only able to rapidly and accurately identify acute ischemic stroke, but may also be able to aggressively intervene to minimize the extent of infarction. In those cases where revascularization cannot occur and/or the extent of infarction is large, there are multiple strategies to prevent secondary decompensation as the stroke evolves, for instance, if malignant cerebral edema should develop. In this paper, we will review the indications for specialized ICU care for an ischemic stroke patient, the treatment principles, and strategies employed by neurointensivists to minimize secondary neuronal injury, the literature in support of such strategies (and the questions to be addressed by future studies), all with the ultimate goal of increasing the likelihood of favorable neurologic outcomes in our ischemic stroke population.

1. Introduction

There has been considerable evolution in the treatment of acute ischemic stroke in recent years,including progressive improvements in our ability to revascularize patients and in aggressive therapies to decrease secondary brain injury (such as early decompressive hemicraniectomy for large hemispheric strokes). As such, the role of the neurointensivist in the care of ischemic stroke patients has evolved as well. Approximately 15 to 20% of ischemic stroke patients will require care in an intensive care unit (ICU) [1]—this includes patients at considerable risk of hemorrhagic transformation or the development of malignant cerebral edema, patients who require intubation due to brainstem stroke or a decline in the level of alertness, and patients exhibiting hemodynamic instability ranging from atrial fibrillation with rapid ventricular rate to symptomatic hypotension with extension of infarction. And, as studies of other groups of critically ill neurologic patients have suggested [2], the care of unstable ischemic stroke patients in a neurosciences ICU staffed by trained neurointensivists results not only in greater efficiency of care, but also in improved patient outcomes. In one retrospective study by Bershad et al., critically ill ischemic stroke patients treated by a dedicated neurointensivist team not only had shorter stays in the ICU and in the hospital in general, but also a greater likelihood of being discharged to home [3]. As a result, the Joint Commission's 2011 proposed requirements for comprehensive stroke center certification included the recommendation for "an intensive care unit for complex stroke patients that includes staff and licensed independent practitioners with the expertise and experience to provide neurocritical care." In this paper, we will discuss the indications for admission of an ischemic stroke patient to a neurosciences ICU; we will also examine the treatment principles and strategies employed by neurointensivists in an effort to increase the proportion of patients with favorable neurologic outcomes.

2. Postthrombolysis and/or Intra-Arterial Revascularization

Within the past decade or so, advances in acute revascularization have truly transformed the care of patients presenting with ischemic stroke. Intravenous tissue-type plasminogen activator (tPA) is of proven and substantial benefit for selecting patients with acute cerebral ischemia. Patients with occlusions of large intracranial arteries may also undergo intervention with intra-arterially deployed devices (such

as the recently developed stent retrievers) in an effort to achieve rapid and effective vessel recanalization, although the role of these devices is uncertain at present given recently published trials suggesting that the functional outcomes are not improved with further intra-arterial therapy compared to intravenous tPA alone [4, 5].

Nevertheless, these aggressive revascularization strategies are not without risk—specifically, the risk of life-threatening intracranial hemorrhage. Thrombolysis with intravenous tPA is associated with symptomatic intracranial hemorrhage (sICH) in approximately 3 to 6% of patients [6–8]. For this reason, patients who have received intravenous tPA, intra-arterial tPA, or intra-arterial embolectomy require intensive neurologic monitoring in an ICU or a dedicated stroke sciences unit for at least 24 hours. To minimize the risk of hemorrhagic transformation in this particularly vulnerable population, blood pressure should be frequently monitored, and elevated pressures must be treated accordingly. Specifically, systolic pressures should be less than 180 mm Hg and diastolic pressures less than 105 mm Hg for the first 24 hours after thrombolysis [9]. As stroke patients are often hypertensive (even those without a history of hypertension may be hypertensive in the acute stroke period), intravenous agents may be required—Labetalol (10 mg IV every 10–15 minutes) or even a Nicardipine infusion (2.5–5 mg/hr; titrated to a maximum of 15 mg/hr) is frequently used for strict blood pressure control.

If a patient neurologically deteriorates during or shortly after the infusion of intravenous (or intra-arterial) tPA, emergent neuroimaging should be obtained to determine if hemorrhagic transformation has occurred. In the case of sICH, a type and cross, prothrombin time/partial thromboplastin time, platelet count, and fibrinogen level should be drawn. Reversal agents should be considered; though protocols vary, fresh frozen plasma (two units every 6 hours for 24 hours), cryoprecipitate (10–20 units), and platelets (4–8 units) are often transfused [10]. If these agents fail, the antifibrinolytic aminocaproic acid (Amicar) may be considered (5 grams in 250 mL NS). And, as with spontaneous intracranial hemorrhage, therapies to reduce intracranial pressure (mannitol or hypertonic saline) or even neurosurgical decompression (posterior fossa hemorrhage, lobar/superficial hemorrhage refractory to medical therapy) may be required.

Serious systemic hemorrhages after revascularization are rare, although if undetected, may also be life-threatening. Interventional procedures begin with the cannulation of the femoral artery. Occasionally, hemorrhage from the cannulation site, including severe retroperitoneal hemorrhage, may occur. Such bleeding may be intensified if intravenous tPA was administered as a bridge to intra-arterial therapies. In these cases, manual compression of the groin site in addition to volume replacement with red cells, platelets, and fresh frozen plasma may be required. Finally, the administration of tPA can result in one other serious complication—the development of orolingual angioedema. Orolingual angioedema reportedly occurs in 1 to 5% of patients; the angioedema is typically mild, transient, and contralateral to the ischemic hemisphere [11]. If severe enough, the angioedema may result in partial airway obstruction. Intravenous antihistamines, corticosteroids, and histamine type 2 receptor antagonists are often given; patients who develop frank stridor should be intubated.

3. Large Hemispheric Stroke and Malignant Cerebral Edema

Patients with large hemispheric stroke often deteriorate neurologically and are therefore frequently managed in the intensive care unit. Symptomatic hemorrhagic transformation and the evolution of cerebral edema are the primary causes of deterioration. Classically, cerebral edema peaks 2 to 5 days after the onset of infarction [12]. A subset of patients with large hemispheric stroke, primarily those with complete middle cerebral artery (MCA) territory infarction, will dramatically deteriorate within the first 24 to 48 hours, with evidence of massive edema, severe midline shift, and compression of the basal cisterns on neuroimaging. These "malignant" MCA infarctions constitute 1 to 10% of all supratentorial ischemic strokes, and, historically, mortality is considerably high, ranging from 50 to 80% [13, 14]. Early identification of patients likely to develop malignant cerebral edema is essential as certain therapies (such as decompressive hemicraniectomy) are particularly helpful if performed early, prior to complete neurologic deterioration and herniation. The NIH Stroke Scale (NIHSS) score often surpasses 16–20 if the dominant hemisphere is involved, 15–18 in malignant infarctions of the nondominant hemisphere. Radiologic predictors of malignant cerebral edema include (1) early hypodensity greater than 50% of the MCA territory on CT or diffusion lesion volume greater than 82 mL within 6 hours of stroke onset, and (2) involvement of adjacent vascular territories such as the anterior cerebral artery (ACA) or posterior cerebral artery territories [15].

There has been considerable interest within the past decade in surgical decompression for those patients with large hemispheric stroke and malignant cerebral edema. The primary goal of decompression (hemicraniectomy and duraplasty) is to give edematous tissue space to expand outside the cranial vault, reducing tissue shifts and pressure within the intracranial compartment, thereby restoring cerebral perfusion and minimizing derangements in oxygenation of noninfarcted tissue. In 2007, a pooled analysis of three European randomized controlled trials (DECIMAL, HAMLET, and DESTINY) compared decompressive hemicraniectomy with best medical management in patients from 18 to 60 years old with an NIHSS score greater than 15, decreased level of consciousness without bilaterally fixed/dilated pupils, with a hypodensity involving at least 50% of the MCA territory on CT [16]. For this pooled analysis, a maximum time window of 48 hours from stroke onset to surgical decompression was adopted. The case fatality rate was substantially lower in the surgical decompression group (28% versus 78% in the conservative arm), with an absolute risk reduction of 50%. With regards to functional outcome, decompression improved the odds of a favorable one, defined in the analysis as a modified Rankin Scale (mRS) score of 1 to 4 (75% versus 24%). However, whether to interpret a mRS score of 4 (moderately severe disability, unable to walk, or attend to

one's own bodily needs without assistance) as favorable is a question best answered in conjunction with those closest to the individual patient. There is also considerable debate regarding surgical decompression in patients older than 60, although this represents approximately 40 to 50% of the patients with malignant MCA infarction [17]. DESTINY II is a large randomized controlled trial of patients 61 and older to specifically address whether these patients may benefit from surgical decompression, particularly in terms of functional outcome.

The other approach to cerebral edema and elevated intracranial pressure involves the use of hyperosmolar agents such as mannitol and hypertonic saline. Essentially, both mannitol and hypertonic saline work by the formation of a relatively hypertonic intravascular space; this promotes the osmotic flow of water outward from the brain parenchyma. Mannitol is often administered as a bolus in doses of 0.25 to 1.0 g/kg every 4 to 6 hours, whereas hypertonic saline may be administered as a bolus (23.4%) in roughly equiosmolar doses to mannitol or as a continuous infusion (3%). One small prospective trial by Schwarz et al. investigated the use of mannitol versus hypertonic saline (7.5% hypertonic saline hydroxyethyl starch) specifically in ischemic stroke patients. 16 of 16 "episodes," defined as an ICP greater than 25 mm Hg or the development of pupillary abnormalities, responded to hypertonic, saline whereas 10 of 14 episodes responded to mannitol. The mean ICP reduction was 11 mm Hg with hypertonic saline, 5 mm Hg with mannitol [18]. Kamel et al. conducted a meta-analysis in 2011 of the five prospective trials comparing hypertonic saline with mannitol; 3 of these trials included stroke patients. ICP was successfully reduced 78% of the time with mannitol, 93% of the time with hypertonic saline [19]. A large scale, prospective, blinded study using equiosmolar doses and assessing functional outcomes is essential to determine if a true comparative benefit exists with either of these agents. In addition, no studies have addressed the prophylactic use of mannitol or hypertonic saline to reduce edema and tissue shifts prior to the onset of intracranial hypertension.

In the future, we may be able to prevent the development of malignant cerebral edema entirely. Within the past decade, experimental models of ischemic stroke have been used to identify the cellular mediators responsible for cytotoxic edema formation. One such mediator is a nonselective cation channel regulated by sulfonylurea receptor 1 (SUR1). Blockade of SUR1 by glibenclamide (glyburide) has been demonstrated to reduce the formation of cytotoxic edema, infarct volume, and mortality by approximately 50% in a mouse model of MCA occlusion [20]. In fact, in one study of severe MCA ischemia/reperfusion in rats, glibenclamide administered during the first 6 hours after ischemia was as effective as the use of early decompressive craniectomy in preventing death from malignant cerebral edema [21]. Recently, a prospective, open label Phase IIa trial of RP 1127—an intravenous formulation of glyburide—was completed in 10 patients with severe anterior circulation ischemic strokes (mean infarct volume 82 mL; mean NIHSS score 19). Malignant cerebral edema requiring the use of hyperosmolar agents or decompressive craniectomy occurred in only 2 of the 10 patients; 9 of the 10 patients had a 30-day mRS score of greater than or equal to 4 [22]. A larger, multicenter, randomized controlled trial comparing RP 1127 to placebo in patients with severe anterior circulation ischemic stroke, the GAMES trial, has recently begun.

4. Blood Pressure—General Parameters, Augmentation via Vasopressors

Hypertension in the acute stroke period is frequent. Elevated blood pressures are documented in approximately 80% of patients, including those without a history of hypertension. Severe arterial hypertension may aggravate cerebral edema and contribute to hemorrhagic transformation of infarcted tissue. Conversely, severe arterial hypotension is also detrimental, as rapid reductions in mean arterial and cerebral perfusion pressures (CPPs) may extend areas of ischemia. Studies suggest that even relative hypotension may be an independent predictor of poor outcomes in ischemic stroke patients [23]. In the SCAST trial, 2029 acute stroke patients with a mean blood pressure of 171/90 mm Hg were randomized to candesartan versus placebo during the first 7 days after stroke [24]. During this period, blood pressures were significantly lower in the candesartan group (mean blood pressure 147/82 mm Hg versus 152/84 mm Hg in the placebo group). Interestingly, analysis of 6 months functional outcomes suggested a higher risk of poor outcomes in the candesartan-treated group (adjusted odds ratio 1.17). As such, blood pressures are generally permissive in the first several days after stroke, with a systolic pressure threshold of 220 mm Hg and a diastolic pressure threshold of 120 mm Hg during the first 24 hours as per AHA/ASA guidelines [9]. Pressures may require earlier reduction, though, if patients develop angina/myocardial infarction, significant pulmonary edema, or renal dysfunction.

On the other hand, there are certain stroke patients who may benefit from augmentation of blood pressure via the administration of isotonic fluids or even vasopressors. For instance, patients with severe stenosis of the carotid or basilar artery may develop fluctuating symptoms if relatively hypotensive (Figure 1). In 2001, Rordorf et al. published the results of one prospective trial investigating the induction of hypertension in a series of acute stroke patients. Neosynephrine was administered to augment systolic pressures to 160 or by at least 20%; responders were those patients demonstrating neurologic improvement (NIHSS score increase of at least 2 points) with higher pressures. 7 of 13 patients were considered responders—86% of these responders had evidence of very severe carotid stenosis or occlusion of the MCA stem on cerebrovascular imaging [25]. No adverse events were documented throughout the period of induced hypertension. Larger trials are required to delineate whether induced hypertension significantly improves functional outcomes and to confirm the safety of pressor administration in stroke patients—particularly those after thrombolysis or those with suboptimal endovascular recanalization.

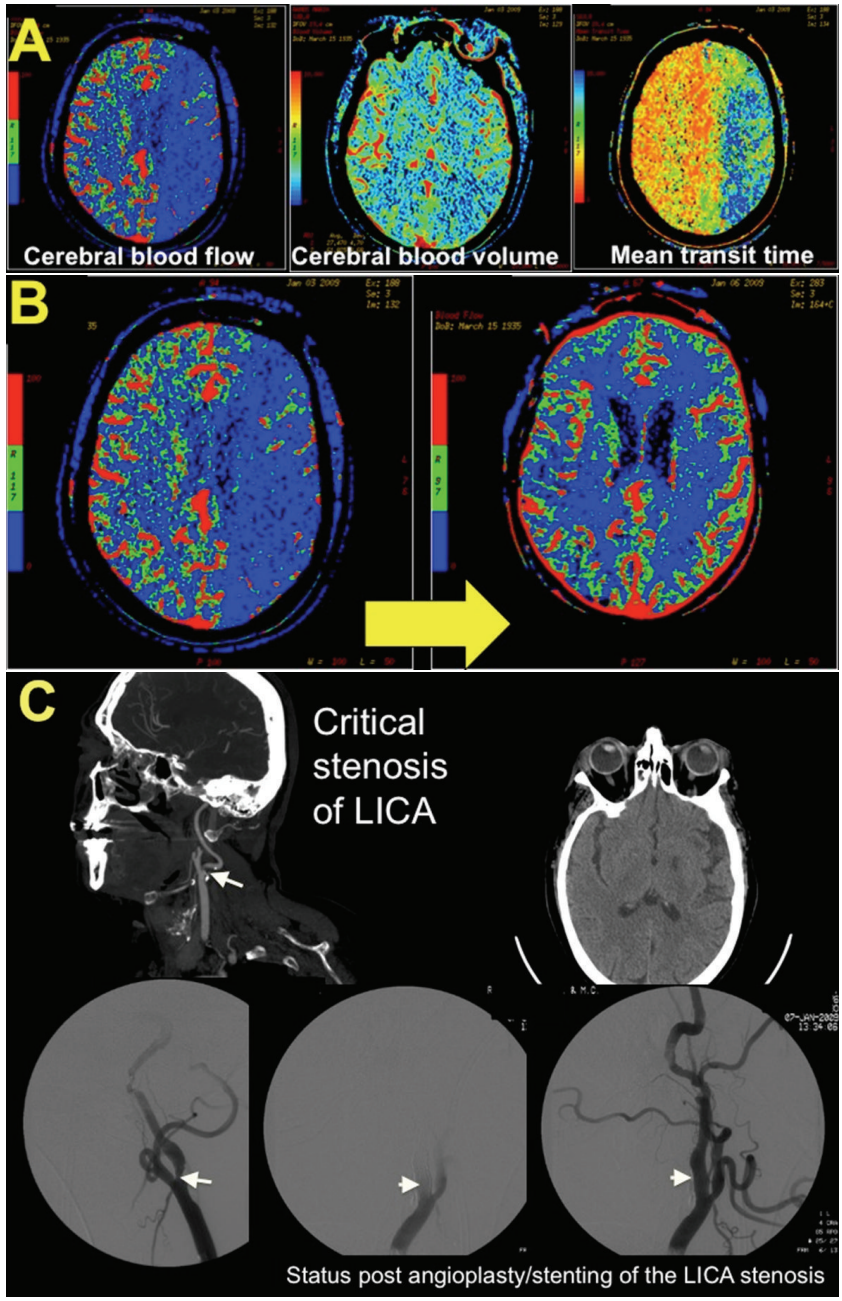

Figure 1: A 73 year-old woman underwent intramedullary fixation of a fractured right femur. She received 2 doses of Hydralazine for elevated BPs the evening after surgery, resulting in a decline in her SBP from 190 mm Hg to 110 mm Hg. The following morning, she was noted to be confused, nonverbal, and paretic in her right arm. An inpatient stroke code was called, and a CT/CTA/CTP was obtained. The perfusion imaging revealed a prolonged MTT, decreased CBF, and relatively preserved CBV within the left hemisphere suggestive of ischemia within this territory (A). She was transferred to the ICU for further management. (B) diagrams the resolution of these perfusion deficits with a marked improvement in CBF following aggressive intravenous fluid resuscitation, blood transfusion for anemia, and BP augmentation with pressors. This was accompanied by a significant clinical improvement as well. Her CTA neck revealed the etiology of her stroke to be a critical stenosis of her left internal carotid artery (C); she underwent angioplasty and stent placement and ultimately had minimal residual symptoms in the form of naming and paraphasic errors. There was no hemorrhagic transformation post-induced hypertension or postprocedurally.

5. Advanced Neuromonitoring?

Advanced neuromonitors—those devices able to quantitatively and continuously measure intracranial pressure, brain temperature, brain tissue oxygenation, oxygen saturation of the jugular vein, and even the biochemical milieu of the cerebral interstitium—are increasingly being used for patients with severe central nervous system injury such as traumatic

brain injury and subarachnoid hemorrhage. Theoretically, these monitors signal the presence of derangements capable of causing secondary neuronal injury (and poorer functional outcomes) if left unchecked. The question begs could these monitors be helpful in patients likely to deteriorate from ischemic stroke? In the ischemic stroke population, it is presently unclear whether these monitors add helpful information above and beyond that provided by a relatively crude yet entirely noninvasive monitor—the neurological examination. For instance, in one recently published randomized controlled trial of intracranial pressure monitoring (ICP) in patients with traumatic brain injury, functional outcomes were not superior in those cared for with an ICP monitor (the target being an ICP of less than 20 mm Hg) compared to those whose treatment was guided by the neurological examination and neuroimaging without any advanced monitors [26]. In regards to ICP monitoring in patients with large hemispheric stroke, patients often deteriorate clinically without evidence of global ICP elevation or CPP reduction [27]. Schwab et al. reported intracranial hypertension (defined as an ICP greater than 15 mm Hg) in only 26% of their patients with large hemispheric stroke; CPP was reduced (less than 55) in only 11% [28]. Indeed, those patients who clinically herniate often do so without an elevation in measured ICP. And, for those patients with malignant infarction who undergo decompressive hemicraniectomy, absolute ICP measurements are likely less reliable (although the general trend of ICP measurements may be valid).

There is even less data on the subject of continuous jugular venous oximetry in ischemic stroke patients. Theoretically, measurement of venous oxygen saturation in the jugular bulb ($SjvO_2$) provides information regarding global cerebral oxygen metabolism. In one study of $SjvO_2$ monitors in 10 patients with large hemispheric stroke, of the 101 measurements obtained, only 2 were less than 50%, the threshold suggestive of secondary ischemia (at least in traumatic brain injury patients). These patients also had cerebral blood flow (CBF) probes inserted for frequent CBF measurements; CBF was substantially decreased without concurrent reductions in $SjvO_2$ on 19 occasions [29]. This study emphasizes cautious interpretation of global oxygen monitors in patients with large, focal, fixed lesions such as hemispheric infarction. Oxygen extraction is likely minimal in infarcted tissues and may result in falsely reassuring jugular saturations unless the remainder of the parenchyma is dramatically ischemic.

6. Prevention of Secondary Neuronal Injury—Glucose and Temperature Control

Hyperglycemia is quite frequent in patients presenting with acute ischemic stroke, even in nondiabetics. Large infarcts and those involving the insular cortex in particular predispose to hyperglycemia. In experimental models, hyperglycemia provokes metabolic demand in the ischemic penumbra; lactic acid and various free radicals are liberated, resulting in neuronal cell lysis and/or degradation of the blood-brain barrier [30]. Numerous studies have reported several negative outcomes in hyperglycemic stroke patients, including higher rates of hemorrhagic transformation, larger volumes of cerebral edema, and greater odds of disability and death [31]. It is therefore reasonable to try and reduce significantly elevated serum glucose levels, although there is considerable controversy in how to do so. In 2009, the results of the NICE-SUGAR study were published; this large, international, randomized controlled trial compared intensive glucose control (target glucose 81–108) with conventional glucose control (180 or less) in medical and surgical ICU patients. Surprisingly, intensive glucose control increased the absolute risk of death at 90 days by 2.6 percentage points, representative of a number needed to harm of 38 [32]. In addition, severe hypoglycemia (less than 40) was recorded in 6.8% of intensive glucose control patients versus 0.5% of conventional control patients. To further investigate optimal glucose control in acute ischemic stroke patients specifically, the NINDS is currently sponsoring the SHINE trial—a multicenter, randomized trial evaluating whether glucose control with intravenous insulin (target glucose 80–130) will result in improved functional outcomes in acute ischemic stroke patients. At present, the AHA/ASA and European Stroke Initiative guidelines recommend a target glucose of less than 140–180 mg/dL.

Temperature regulation in the neurosciences ICU is becoming essential, particularly as the goal may extend beyond fever control to hypothermia. Fever, akin to hyperglycemia, causes secondary neuronal injury; as such, the target temperature for patients with acute central nervous system injury of any etiology should be normothermia (36 to 37 degrees Celsius), at the very least. Hypothermia for neuroprotection in patients with global cerebral hypoxia/ischemia secondary to cardiac arrest is fairly routine; in the future, hypothermia as a neuroprotectant may be extended to acute ischemic stroke patients. Hypothermia is also considered in those with medically refractory elevations in ICP. Whether the goal is normothermia or hypothermia, temperature control can be challenging, particularly in stroke patients who are awake. Antipyretics such as Tylenol are often ineffective, and surface cooling (even endovascular cooling) can be quite uncomfortable and often prompts shivering. Several institutions have generated "antishivering protocols"—buspirone, meperidine, and cutaneous counterwarming are often firstline measures; opiates and dexmedetomidine may be useful if these fail [33]. If shivering continues, sedation with high-dose propofol or even neuromuscular blockade may be required.

In conclusion, the outcomes of devastating neurological emergencies such as acute ischemic stroke may be measurably improved by treatment in a dedicated neurosciences intensive care unit utilizing the principles and strategies outlined in this paper. Multiple trials currently underway will hopefully further define care of the ischemic stroke patient and result in superior functional neurologic outcomes.

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Review Article

Rehabilitation with Poststroke Motor Recovery: A Review with a Focus on Neural Plasticity

Naoyuki Takeuchi and Shin-Ichi Izumi

Department of Physical Medicine and Rehabilitation, Tohoku University Graduate School of Medicine, 2-1 Seiryo-cho, Aoba-ku, Sendai 980-8575, Japan

Correspondence should be addressed to Naoyuki Takeuchi; naoyuki@med.hokudai.ac.jp

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Motor recovery after stroke is related to neural plasticity, which involves developing new neuronal interconnections, acquiring new functions, and compensating for impairment. However, neural plasticity is impaired in the stroke-affected hemisphere. Therefore, it is important that motor recovery therapies facilitate neural plasticity to compensate for functional loss. Stroke rehabilitation programs should include meaningful, repetitive, intensive, and task-specific movement training in an enriched environment to promote neural plasticity and motor recovery. Various novel stroke rehabilitation techniques for motor recovery have been developed based on basic science and clinical studies of neural plasticity. However, the effectiveness of rehabilitative interventions among patients with stroke varies widely because the mechanisms underlying motor recovery are heterogeneous. Neurophysiological and neuroimaging studies have been developed to evaluate the heterogeneity of mechanisms underlying motor recovery for effective rehabilitation interventions after stroke. Here, we review novel stroke rehabilitation techniques associated with neural plasticity and discuss individualized strategies to identify appropriate therapeutic goals, prevent maladaptive plasticity, and maximize functional gain in patients with stroke.

1. Introduction

Despite advances in acute management, stroke remains a major cause of disability worldwide [1–6]. A number of neurological functions are impaired by stroke, the most common of which is motor disability contralateral to the stroke lesion side [7]. Therefore, many rehabilitation techniques based on motor learning paradigms have been developed to facilitate the recovery of impaired movement in patients with stroke [3, 8–11].

Neural plasticity can change central nervous system structure and/or function [12–15]. Recently, advances in technologies enabling noninvasive exploration of the human brain have increased our understanding of neural plasticity and its relationship to stroke recovery [9, 12, 16, 17]. Various novel stroke rehabilitative methods for motor recovery have been developed based on basic science and clinical studies characterizing brain remodeling due to neural plasticity [9, 11, 18]. The effectiveness of these approaches has been verified by systematic reviews and meta-analysis studies [8, 19–22]. However, responses to rehabilitative interventions show large inter-individual variation because the mechanisms underlying motor recovery are heterogeneous across patients [3, 8, 11, 23]. Furthermore, these mechanisms involve complex processes including restitution, substitution, and compensation that rely on a combination of spontaneous and learning-dependent processes [3, 24]. Therefore, elucidating the mechanisms underlying motor recovery can help to identify the most appropriate type, duration, and goals of individual rehabilitation strategies after stroke [11]. Neurophysiological and neuroimaging approaches have recently been developed to evaluate the heterogeneity of motor recovery mechanisms to better understand and predict the effectiveness of different rehabilitation interventions after stroke [12, 16, 25, 26].

In this review, we first discuss the principles of stroke rehabilitation in task-specific training and enriched environments. Then, we focus on novel strategies in stroke

rehabilitation that are supported by evidence of associated neural plasticity. These approaches include constraint-induced movement therapy (CIMT), body weight-supported treadmill training (BWSTT), robotic training, transcutaneous neuromuscular electrical stimulation, noninvasive brain stimulation (NIBS), action observation, virtual reality (VR) training, and brain-computer interface (BCI). Finally, we discuss individualized strategies to inform the identification of therapeutic goals, to prevent maladaptive plasticity, and to maximize functional gain in patients with stroke.

2. Principles of Stroke Rehabilitation

Most protocols for stroke rehabilitation are based on motor learning, which induce dendrite sprouting, new synapse formation, alterations in existing synapses, and neurochemical production [10, 27]. These changes are thought to provide a mechanistic substrate to facilitate motor recovery after stroke [10, 27]. Motor learning is known to be greater if the practice method is meaningful, repetitive, and intensive [10, 17]. Further, it is recommended that stroke rehabilitation is applied in stroke care units where multidisciplinary teams can support active patient participation [9]. In this section, we review task-specific training and enriched environment therapeutic approaches that facilitate neural plasticity.

2.1. Task-Specific Training. Motor training after stroke should be targeted to goals that are relevant to the functional needs of the patient [10, 11]. Therefore, focusing on task-specific training to facilitate activities of daily living or other relevant motor tasks is a well-accepted principle of stroke rehabilitation [3]. This approach has been described by a variety of terms, including repetitive task practice, repetitive functional task practice, and task-oriented therapy [10, 28, 29]. Thus, task-specific training emphasizes the repetitive practice of skilled motor performance to improve individual functional abilities [10, 30]. Task-specific training can effectively recover a wide array of motor behaviors involving the upper limbs, lower limbs, sit-to-stand movements, and gait after stroke [29, 31–33]. Furthermore, repetitive task-specific training has been found to achieve better functional gains compared to nonrepetitive training [34, 35].

Increasing evidence suggests the involvement of neural plasticity in task-specific training [36, 37]. A meta-analysis of neurophysiological and neuroimaging studies has reported that neural changes in the sensorimotor cortex of the affected hemisphere accompany the gains in functional paretic upper extremity movements achieved with task-specific training [37]. Compared to traditional stroke rehabilitation approaches such as simple motor exercises, task-specific training induces long-lasting motor learning and associated cortical reorganization [30, 37]. Thus, there is strong evidence demonstrating that task-specific training can assist with functional motor recovery, which is driven by adaptive neural plasticity [8, 24, 30, 37, 38].

2.2. Enriched Environment. In addition to task specificity, the therapeutic environment plays an important role in stroke rehabilitation [39]. Environments that provide greater opportunity for physical activity and motivation are referred to as enriched environments [39]. Animal studies involving rat models of stroke have demonstrated that enriched environments facilitate motor recovery and neural plasticity because they present greater opportunities for physical activity, play, and social interactions compared to standard laboratory cages [39–41].

Clinically, stroke unit (SU) care administered by a well-coordinated multidisciplinary team can provide an enriched environment for patients with stroke [42]. SU care provides an organized package of care through a cyclical process involving the necessary elements of assessment, goal setting, intervention, and reassessment [3, 11]. Moreover, SU care provides individuals with a clear understanding of what is expected of them during task-specific training, resulting in neural plasticity that improves their performance [43]. Patient involvement in patient-centered interdisciplinary goal setting has been shown to encourage their motivation and engagement in therapy, resulting in better rehabilitation outcomes of impaired movement in patients with stroke [3]. Several studies have demonstrated that SU care had the greatest positive impact on disability levels after stroke [42, 44]. Moreover, the reported benefits of SU care extend to patients of all ages and to patients with varying stroke severity [44]. Thus, stroke rehabilitation programs should include meaningful, repetitive, intensive, and task-specific movement training in an enriched environment in order to promote neural plasticity and motor and functional recovery [10, 17].

3. Novel Strategies Based on Motor Training

During the last several decades, many studies have reported the use of novel motor learning-based stroke rehabilitation strategies [3, 8–11]. In this section focused on neural plasticity, we discuss several representative neurorehabilitation methods, including CIMT, BWSTT, and robot training.

3.1. CIMT. Patients with stroke often use the nonparetic limb instead of the paretic limb to perform daily activities. Dominant use of the nonparetic limb induces the phenomenon of learned nonuse in the paretic limb, which limits the capacity for subsequent gains in motor function [38, 45]. CIMT is a therapeutic strategy that was developed to overcome learned nonuse of the paretic limb. It forces paretic arm use by requiring a patient to perform functionally oriented activities while the nonparetic arm is physically restrained with a sling or glove. Mechanistically, the repetitive training of the paretic arm and constraint of the nonparetic upper arm used in CIMT might both be important for promoting neural plasticity. Skill acquisition with the nonparetic limb has been reported to negatively impact the use-dependent plasticity of the affected hemisphere in animal models of stroke [46]. The reasons underlying this constraint remain unclear, but this phenomenon may reflect use-dependent alterations in interhemispheric connectivity [47, 48]. Therefore, constraint of the nonparetic limb itself might ameliorate the impairment of use-dependent plasticity of the paretic limb after stroke

[15, 45]. Several studies reported neural plasticity after CIMT as evidenced by neuroimaging and neurophysiological techniques [49–51]. Previous studies using transcranial magnetic stimulation (TMS) found that the cortical representation size of the paretic hand was increased after therapy [49, 50]. Neuroimaging studies also demonstrated altered neural network activity after CIMT [49, 51]. Moreover, a structural magnetic resonance imaging (MRI) study reported that CIMT increased gray matter in the bilateral sensorimotor cortices compared with control therapy [52]. Thus, there is evidence that CIMT induces both structural brain and physiological changes in patients with stroke [10].

Wolf et al. conducted a multicenter single-blind randomized controlled trial known as the Extremity Constraint-Induced Therapy Evaluation Trial to compare the effects of 2-week CIMT with customary care in 222 individuals within 3–9 months of a first stroke [53]. At 1 year, the CIMT group performed better on functional tasks using the paretic upper limb. Moreover, the 2-year follow-up documented no decline from the 1-year assessment, and there were trends toward continued improvement of strength during the second year [54]. Most reviews of CIMT also report trends towards positive results of motor recovery in patients with chronic stroke [8–10]. However, previous studies had reported no significant differences in motor recovery between CIMT and an equal dose of traditional therapy for patients with acute stroke [55, 56]. This could be due to minimal or no learned nonuse during the acute phase [10]. Moreover, in the acute stage of stroke, high-intensity CIMT results in less improvement than low-intensity CIMT [56]. Therefore, additional studies are needed to explore optimal CIMT timing and intensity for motor recovery after stroke [11].

3.2. BWSTT. BWSTT is a rehabilitation method in which patients with stroke walk on a treadmill with their body weight partially supported. BWSTT augments the ability to walk by enabling repetitive practice of complex gait cycles [57, 58]. In patients who have experienced a stroke, hemiparesis can cause abnormal control of the paretic lower limb, resulting in an asymmetrical gait pattern [59, 60]. Partial unloading of the lower extremities by the body weight support system results in straighter trunk and knee alignment during the loading phase of walking [61, 62]. BWSTT also improves swing time asymmetry, stride length, and walking speed [60, 62, 63]. Therefore, BWSTT allows the patient to practice nearly normal gait patterns and avoid developing compensatory walking habits, such as hip hiking and circumduction [58, 64].

There is evidence of gait improvement after BWSTT, including use of robotic device systems, compared to conventional therapy in patients with acute stroke and those with chronic stroke [60, 65, 66]. However, a recent study reported that the benefits of BWSTT were not superior to that achieved with home-based physical therapy that emphasized strength and balance, regardless of whether BWSTT was started 2 or 6 months after the stroke [67]. Moreover, among patients with severe walking impairments, multiple falls were more common in the group that received early BWSTT compared to the group that received late BWSTT and physical therapy [67]. Therefore, BWSTT programs should include balance training that helps prevent falls in patients, especially those with acute stroke and severe impairment.

Mechanistically, BWSTT is believed to increase brain activity in the bilateral primary sensorimotor cortices, cingulate motor areas, caudate nuclei, and thalamus of the affected hemisphere [68]. Moreover, BWSTT has been found to alter central pattern generator activation in animal studies [69, 70]. In patients who have experienced a stroke, cerebral cortex function is impaired while that of the spinal cord is preserved. However, spinal cord changes may also be important for gait recovery after stroke due to changes in signals received following cerebral reorganization [71]. Thus, BWSTT can be used in patients with stroke to induce reorganization at the spinal and supraspinal levels, reduce gait parameter asymmetries, and increase walking speed. However, evidence of neural plasticity involved in this process is restricted to animal studies [71].

3.3. Robot Training. Robotic training offers several potential advantages in stroke rehabilitation, including good repeatability, precisely controllable assistance or resistance during movements, and objective and quantifiable measures of subject performance [72]. Moreover, robot training can provide the intensive and task-oriented type of training that has proven effective for promoting motor learning [8, 72]. These characteristics of robot training are thought to be useful for motor recovery after stroke.

During the last decades, mechanically assisted robot training therapies have been developed for stroke rehabilitation to improve arm function [21, 73–75]. However, a multicenter, randomized controlled trial of patients with chronic stroke who had moderate-to-severe upper-limb impairment reported no difference in motor recovery between intensive physiotherapy and robot-assisted rehabilitative therapy [76]. Moreover, systematic reviews and meta-analyses have found no significant changes in activities of daily living ability after robotic training [77, 78]. Automated electromechanical gait machines have also been developed to facilitate lower limb rehabilitation. These machines consist of either a robot-driven exoskeleton orthosis or 2 electromechanical footplates that simulate gait phases [79–81]. Such machines are useful because they do not require therapists to set the paretic limbs and control weight shift, as is required for treadmill training [79, 80]. The use of electromechanical-assisted gait-training devices in combination with physiotherapy increases the chance of regaining independent walking ability after stroke but does not produce improvements in walking speed [82]. Therefore, in addition to automatic repetitive motor training, it is important for augmentation of robot training that robotic assistance is carried out in a minimum difference of input-output timing using electromyography (EMG) and/or position feedback [75, 83, 84]. Reducing these lag times is important because synchronization between sensory and motor information facilitates neural plasticity [85, 86]. Future studies are needed to determine the most appropriate

characteristics of subjects and whether robot training has advantages over conventional therapy [75].

4. Augmentation of Use-Dependent Plasticity

Although the use-dependent plasticity induced by motor training is important for motor recovery after stroke, it has been reported that use-dependent plasticity is impaired in the affected hemisphere [87, 88]. Therefore, it is important to augment neural plasticity after stroke to facilitate motor recovery. In this section, we discuss the following possible methods of augmenting use-dependent plasticity in patients with stroke: transcutaneous neuromuscular electrical stimulation and NIBS.

4.1. Transcutaneous Neuromuscular Electrical Stimulation. Transcutaneous neuromuscular electrical stimulation can improve neuromuscular function in patients with stroke by strengthening muscles, increasing motor control, reducing spasticity, decreasing pain, and increasing range of motion [89]. Methods of transcutaneous neuromuscular electrical stimulation are generally categorized as either therapeutic electrical stimulation or functional electrical stimulation (FES). The defining feature of FES is that it provokes muscle contraction and produces a functionally useful movement during stimulation [89]. Several upper extremity FES devices are available, and the use of these devices seems to have a positive effect on upper-limb motor function in both acute and chronic stages of stroke [90–92]. FES has also been combined with different walking training strategies and has been shown to result in improvements in hemiplegic gait in both acute and chronic stages of stroke [93–95].

In addition to functional effects, FES is thought to have therapeutic effects, which are postulated to arise through the facilitation of neural plasticity by increasing the strength of afferent inputs [89]. In particular, FES supported by an EMG- or position-triggered system could induce appropriate proprioceptive feedback and promote motor learning [89, 96]. Patients can actively participate in intensive and repetitive task-specific training when they are responsible for initiating practice. Moreover, the synchronization of afferent feedback with voluntary movement by a biological signal-triggered system is useful for motor recovery because synchronization between the sensory and motor information facilitates neural plasticity [85, 86]. In fact, better performance is observed if paretic muscles are stimulated by voluntary muscular activity compared with nonsynchronized passive stimulation [97]. However, future research is needed to determine the most effective type and dose of electrical stimulation [98].

4.2. NIBS. Repetitive TMS (rTMS) and transcranial direct current stimulation (tDCS) are NIBS techniques that can alter human cortex excitability [99]. NIBS therapy for motor recovery following stroke aims to augment neural plasticity and improve motor function based on the interhemispheric competition model, which proposes that motor deficits in patients with stroke are due to reduced output from the affected hemisphere and excessive interhemispheric inhibition from the unaffected hemisphere to the affected hemisphere [18, 100, 101]. Therefore, NIBS achieves improvement in motor deficits by either increasing the excitability of the affected hemisphere or decreasing the excitability of the unaffected hemisphere [18, 102, 103]. Inhibitory NIBS increases excitability in the ipsilesional motor cortex by reducing excessive interhemispheric inhibition from the contralesional motor cortex [101, 104, 105]. Excitatory NIBS over the affected hemisphere directly increases the excitability of the ipsilesional motor cortex [105–108]. Motor cortex excitability enhancement appears to be required for motor learning [109, 110]. In fact, pairing of rehabilitative training with NIBS results in more enduring performance improvements and functional plasticity in the affected hemisphere compared with motor training or stimulation alone in patients with chronic stroke [101–104, 111]. Furthermore, cumulative NIBS has been shown to be important for continuous motor improvement in patients with stroke [112, 113]. This result indicates that neural plasticity is consolidated by cumulative NIBS intervention. Therefore, NIBS induces a more suitable environment for neural plasticity by artificially modulating the ipsilesional motor cortex, thus counteracting use-dependent plasticity impairment by facilitating plasticity in the affected hemisphere [18].

The effectiveness of NIBS is not limited to the chronic stage; it has been reported that both inhibitory and excitatory NIBS facilitate motor recovery in patients with stroke at the acute stage [108, 114–116]. However, another study reported that inhibitory and excitatory NIBS does not facilitate motor recovery in patients in acute stages of stroke [117, 118]. These discrepant findings underscore the importance of identifying the more effective type of NIBS, as well as optimal timing after stroke. A recent meta-analysis study of rTMS on upper-limb motor function in patients with stroke reported that inhibitory rTMS over the unaffected hemisphere might be more beneficial than excitatory rTMS over the affected hemisphere [22]. Although additional research has begun to evaluate the effectiveness of different NIBS stimulation protocols for motor recovery after stroke, further well-designed studies in larger populations are required to determine whether NIBS in the acute stroke stage can improve motor function and to identify the most effective NIBS protocols, including tDCS for stroke treatment [18].

5. Integration between Motor Learning and Multisensory Feedback

Multisensory feedback plays an important role in motor learning by reestablishing the sensorimotor loop that is disrupted by stroke [9]. Several multisensory feedback approaches have been reported for motor recovery in patients with stroke, including action observation and VR training [19, 119]. Recently developed BCI technology might also facilitate motor recovery by using robot devices and/or electrical stimulation [120].

5.1. Action Observation. There is increasing experimental evidence that some motor neural structures are recruited not only when actions are actually executed but also when the actions of another person are simply observed [121]. The neurophysiological basis for this recruitment is associated with mirror neurons, which have been identified in nonhuman primates [122, 123]. Human studies have also described a "mirror neuron system" involved in action understanding, imitation, motor learning, and modulating training effects [124–127]. According to the mirror neuron paradigm, action observation appears to activate the motor system similar to execution by generating an internal representation of action that can be targeted for motor learning [128–130]. A previous study in healthy subjects reported that observing another person learn a novel task improves subsequent performance of the same task [126]. Moreover, data from a recent virtual lesion study using TMS further supports the hypothesis that action observation coupled with physical practice may enhance use-dependent plasticity through the mirror neuron system in healthy controls [131].

Several clinical studies have reported that a combination of action observation therapy and physiotherapy improve upper-limb motor function in patients with chronic stroke [132, 133]. A recent multi-center randomized control trial demonstrated that action observation with physiotherapy has a positive effect on motor recovery in the acute stage of stroke [134]. Another study that employed functional MRI (fMRI) found that action observation facilitated motor recovery after stroke by reactivating the neural circuit containing the action observation/action execution matching system, which includes the bilateral ventral premotor cortex, supplementary motor area, and the contralateral supramarginal gyrus [132]. Therefore, increased activation of these areas suggests that the mirror neuron system (or its human homolog) may play an important role in motor learning and recovery related to action observation in patients with stroke [132, 134]. Moreover, action observation is safe and can be repetitively conducted without dependency on residual motor function. Despite the increasing evidence that action observation may become a useful strategy in stroke rehabilitation, future research is required to determine optimal practice intensity and duration before its translation into standard clinical practice [119].

5.2. VR. VR is a computer-based technology that engages users in multisensory simulated environments, including real-time feedback (e.g., visual, auditory, and tactile feedback), allowing users to experience simulated real-world objects and events [135]. VR applications range from nonimmersive to fully immersive depending on the degree to which the user is isolated from the real surroundings when interacting with the virtual environment [136]. Immersive VR systems use large-screen projections, head-mounted displays, cave systems, or videocapture systems to immerse the user in a virtual environment [136]. In contrast, nonimmersive VR systems simply use a computer screen to simulate an experience with or without interface devices, such as a computer mouse, joystick, or force sensation [136]. VR exercise applications can easily provide patients with stroke with repetitive, intensive, and task-specific training and can apply relevant concepts for driving neural plasticity that produce motor function improvements after stroke [8, 136, 137]. Several studies have shown that the use of immersive VR results in practice-dependent enhancement of the affected arm by facilitating cortical reorganization [138, 139]. Moreover, a recent study has shown that video game applications that are classified as nonimmersive VR systems can be combined with conventional rehabilitation for upper arm improvement after stroke [140]. Video game systems have already been developed for home use, making this technology less costly and more accessible to clinicians and individuals [137]. Moreover, VR-based game systems can easily adjust task difficulty according to user capability [141, 142]. This encourages the user to train at optimal-level errors, inducing appropriate motivation and arousal, which are important for learning [143]. Therefore, VR-based game systems might be able to facilitate motor learning due to increased motivation of patients with stroke. However, the use of VR is not yet commonplace in clinical rehabilitation settings; only a few studies have been conducted, and the sample sizes were too small to draw firm conclusions [19].

5.3. BCI. BCI systems record, decode, and translate measurable neurophysiological signals into effector actions or behaviors without the use of peripheral physiological activities [144]. Several methods are available for detecting and measuring brain signals, including electroencephalography, electrocorticography, intracortical recordings, magnetoencephalography, fMRI, and functional near-infrared spectroscopy [144, 145]. One of the most popular neurophysiological phenomena assessed in BCI research is the modulation of sensorimotor rhythms through motor imagery [120, 144, 145]. The output of the BCI provides multisensory feedback to users, and this allows them to modulate their brain activity accordingly [144]. The feedback consists of sensory stimuli, such as visual, auditory, or tactile stimuli, and kinesthesia by robotic devices or FES [120, 145]. Therefore, BCI devices can couple intention with action and enable patients with stroke to achieve intended motor action [120, 144]. Considering that BCI technology is based on feedback and exploits learning mechanisms, BCI technology could be used to design and develop specific neurorehabilitation therapies for patients with stroke [120]. In fact, a recent study that combined motor training and motor imagery-based BCI reported a positive trend of upper-limb movement control in patients with stroke [146, 147]. BCI systems also might be useful for patients with severe stroke because they provide an alternative way of executing motor outputs through robotic devices [120, 144, 145]. Moreover, invasive BCI systems that utilize an intracortical recording technique have been developed in animal studies; these systems can detect signals, including synaptic and neuronal activities, and might facilitate neural plasticity due to accurate matching between motor intention and sensory feedback [145, 148–150]. However, the number of studies evaluating stroke recovery after BCI training is still limited. Future studies must evaluate the effect of BCI use

on motor recovery after stroke and the role of BCI in neural plasticity [120].

6. Potential Individualized Rehabilitation Strategies for Appropriate Reorganization

An accurate prognosis of motor recovery after stroke can help to select individual rehabilitation strategies that promote appropriate reorganization [11]. It also is important for rehabilitation strategies to prevent maladaptive plasticity, which weakens motor function and limits motor recovery [15]. In this section, we discuss several potential individualized rehabilitation strategies to inform therapeutic goal setting, prevent maladaptive plasticity, and maximize functional gains in patients with stroke.

6.1. Imaging and Neurophysiological Findings Predict Motor Recovery. The simplest indicator of prognosis for patients with stroke is the degree of motor impairment. Many studies have suggested that motor outcomes are positively correlated with initial motor impairment after stroke [151–153]. However, the patterns of motor recovery are largely heterogeneous among patients with stroke; accurate prediction based on current motor impairment status alone can be difficult [11, 25]. Therefore, it has been suggested that motor recovery after stroke may be predicted more accurately using neurophysiological and neuroimaging findings [16, 25, 154]. Neurophysiological studies using TMS have revealed that ipsilesional corticospinal motor projection function is a good predictor of motor outcome after stroke [16, 25]. Neuroimaging studies using diffusion tensor imaging also have revealed that impairment of the ipsilesional corticospinal motor projections could predict motor recovery after stroke [25, 154]. Moreover, evaluation of the ipsilesional corticospinal tract function might facilitate the selection of rehabilitation strategies based on the prediction of potential functional gain, which is an individual's capacity for further functional improvement during the chronic stage of stroke recovery [25]. A recent study reported that the extent of injury to motor projections from supplementary and premotor areas of the affected hemisphere is also useful for predicting potential functional gains of paretic upper limbs from robot therapy in subjects with chronic stroke [26]. These results suggest that measures of motor tract function could be useful in estimating potential motor recovery of patients with stroke entering experimental neurorehabilitation trials and for patient selection in clinical trials [26]. Conversely, other studies have reported that the degree of ipsilesional corticospinal tract damage is not strongly associated with walking function [63, 155]. Moreover, the extent of lesion overlap with the corticospinal motor projections is only weakly correlated with therapy-related gains of gait function [63]. These findings support the importance of subcortical control, including the spinal cord, for lower-limb movements such as walking [156, 157]. Moreover, there is some evidence that ipsilateral motor projections are important in the recovery of walking function [158]. Therefore, the ipsilesional corticospinal motor projections appear to be less important in the control of walking than in the control of upper-limb dexterity after stroke [63].

In addition to motor tract function, identifying individual pattern of cortical activation may predict the effect of rehabilitation technique for patients with motor stroke. An fMRI study reported that lower baseline activity of the ipsilesional motor cortex during paretic hand movement was associated with greater functional gains after 6 weeks of rehabilitation therapy in chronic patients [159]. This result indicates that low baseline cortical activity might represent underuse of surviving cortical resources and possible responsiveness to rehabilitation therapy [159, 160]. Therefore, the motor projections may set a limit on the extent of recovery, but other parameters (e.g., preserved cortical activity) might be important when considering whether a patient has the capacity or potential to improve [160]. However, predicting functional gains by using individual cortical activity patterns may be more difficult than that by utilizing motor tract function. For example, a previous study reported that ipsilesional motor cortex excitability in good responders with chronic subcortical stroke for excitatory rTMS over the affected hemisphere is strongly activated, but not weakly, when moving the paretic hand before rTMS [161]. Moreover, functional gain has no direct correlation with ipsilesional motor cortex activity in the acute stage of stroke, but a pattern of cortical activation including the postcentral gyrus and cingulate cortex correlates with subsequent motor recovery [162]. Furthermore, in patients with stroke and severe initial hemiparesis, subsequent motor recovery was not predicted by task-related fMRI activation [163]. Thus, the effective neural activation pattern for neurorehabilitation might be different depending on time since stroke, lesion site, impairment of motor function, and/or rehabilitation technique due to the heterogeneous mechanisms underlying motor recovery and neurorehabilitation techniques.

Genetic factors of neural plasticity-related components should also be considered to affect the capacity of an individual patient's brain to recover motor function [164, 165]. Moreover, genetic variation might be able to explain some of the variability encountered in motor rehabilitation efficacy [23, 165, 166]. It has been reported that various genetic factors influence neural plasticity in animals and humans (for review see [165]). However, there is no evidence regarding individualized rehabilitation strategies using genetic information.

6.2. Preventing Maladaptive Plasticity. Although some neural plasticity undoubtedly contributes to motor recovery after stroke, it remains unclear whether all forms of neural plasticity contribute to genuine motor recovery [12, 14, 167]. Maladaptive plasticity that weakens motor function and limits recovery has recently been reported after stroke [15, 46, 48, 100, 168]. Therefore, it is important for individual stroke rehabilitation strategies to prevent maladaptive plasticity.

Several studies have suggested that neural plasticity associated with compensatory movement might contribute to maladaptive plasticity after stroke [15, 38]. To perform daily tasks, patients with stroke often develop a compensatory hyperreliance on the nonparetic side, proximal paretic side,

or trunk movement [169–172]. However, this strong and efficient motor compensation may prevent the affected side from generating normal motor patterns for daily activities [38, 169]. In particular, dominant use of the nonparetic limb induces learned nonuse of the paretic limb and limits its functional improvement [38, 45]. The facilitation of neural plasticity underlying compensatory learning with the nonparetic limb after stroke also exacerbates use-dependent plasticity impairment of the affected hemisphere via abnormal interhemispheric inhibition [47, 48]. CIMT that combines a rehabilitative training regime for the paretic limb with constraint of the nonparetic limb can overcome learned nonuse of the paretic limb and has been shown to improve motor function in patients with stroke [45, 53, 173]. Therefore, clinicians should consider CIMT for patients having stroke who fit its criteria to facilitate appropriate reorganization and prevent maladaptive plasticity. However, patients with stroke and severe motor function impairments are not suitable candidates for CIMT therapy. Studies of animal stroke models suggest that compensatory use of the nonparetic limb while the paretic limb is being used does not necessarily result in learned nonuse [46]. Therefore, patients with stroke and poor motor function who engage in compensatory use of the nonparetic limb in daily activities may benefit from bilateral movement training to prevent learned nonuse of the paretic side [15, 25].

Increased activity of the paretic proximal arm due to compensatory movement may contribute to the abnormal interjoint movement in the proximal limb that is, often observed after a stroke [172]. Therefore, the selected rehabilitation program may have to avoid intense training of the paretic proximal side. To our knowledge, no rehabilitation program currently addresses this problem, and compensatory movement of the paretic proximal muscle is useful for reaching in some patients with stroke and poor motor function [38, 174]. Thus, at least in cases where patients with stroke have good motor function, a rehabilitation program that avoids compensatory use of the paretic proximal side may be helpful.

7. Conclusion

Most stroke rehabilitation protocols are based on motor learning to induce neural plasticity, which refers to the ability of the brain to develop new neuronal interconnections, acquire new functions, and compensate for impairment. These changes are greater if the practice method is meaningful, repetitive, and intensive. It is recommended that rehabilitation take place in stroke care units that can provide an organized package of care through a cyclical process involving assessment, goal setting, intervention, and reassessment. Systematic reviews and meta-analyses have verified the effects of developed techniques in stroke rehabilitation. CIMT that combines a rehabilitative training regime for the paretic limb with constraint of the nonparetic limb can overcome learned nonuse of the paretic limb and has been shown to improve motor function in patients with stroke. BWSTT may induce reorganization at the spinal and supraspinal levels by providing normal gait programs, reducing asymmetries of gait parameters, and increasing walking speed. Robotic training can provide repetitive motor training and reduce the therapists' physical load. Transcutaneous neuromuscular electrical stimulation and NIBS can improve motor recovery by ameliorating use-dependent plasticity impairment after stroke. Moreover, novel stroke rehabilitation strategies such as action observation, VR, and BCI have been developed based on multisensory feedback, which plays an important role in learning to control human brain signals and in reestablishing the sensorimotor loop disrupted by stroke.

Current clinical practice for stroke rehabilitation is based on accumulating evidence from neural plasticity studies. However, responses to rehabilitative interventions show large interindividual variation due to the heterogeneity of mechanisms underlying motor recovery. Therefore, an accurate prediction of motor recovery can help to determine the type, duration, and goals for individual stroke rehabilitation strategies. An assessment of corticospinal integrity using neurophysiological and imaging techniques might be useful for predicting motor recovery and setting individualized rehabilitation goals. However, numerous other factors influence behavioral responses to therapy, including injury to other brain structures, psychosocial factors, and age. Moreover, it is important for appropriate reorganization after stroke to prevent maladaptive plasticity, which weakens motor function and limits motor recovery.

Early stroke rehabilitation is critical for enhancing motor recovery, but the optimal time window for specific neurorehabilitation has yet to be elucidated. The intensity and duration of the rehabilitation strategy are also important factors that influence effectiveness. Although the evidence base for stroke rehabilitation continues to grow, future studies must be conducted to ascertain the optimal time, intensity, and duration for specific rehabilitation techniques and to facilitate the translation of basic scientific evidence into routine clinical application.

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Research Article

Reducing Haemorrhagic Transformation after Thrombolysis for Stroke: A Strategy Utilising Minocycline

David J. Blacker,[1] David Prentice,[2] Anthony Alvaro,[3] Timothy R. Bates,[4] Michael Bynevelt,[5] Andrew Kelly,[3] Lay Kun Kho,[6] Edith Kohler,[2] Graeme J. Hankey,[7] Andrew Thompson,[5] and Taryn Major[8]

[1] *Department of Neurology and Clinical Neurophysiology, Sir Charles Gairdner Hospital, Nedlands, Western Australia and School of Medicine and Pharmacology, University of Western Australia, Nedlands, WA 6009, Australia*
[2] *Department of General Medicine, Royal Perth Hospital, Perth, WA 6000, Australia*
[3] *Department of Neurology, Fremantle Hospital, Fremantle, WA 6160, Australia*
[4] *Stroke Unit, Swan District Hospital, Middle Swan WA 6056, School of Medicine and Pharmacology, University of Western Australia, Nedlands, WA 6009, Australia*
[5] *Department of Neurological Intervention and Imaging Service of Western Australia, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia*
[6] *Stroke Unit, Swan District Hospital, Middle Swan, WA 6056, Australia*
[7] *Department of Neurology, Royal Perth Hospital, Perth WA 6000, School of Medicine and Pharmacology, The University of Western Australia, Nedlands, WA 6009, Australia*
[8] *Data Analysis Australia, Nedlands, WA 6009, Australia*

Correspondence should be addressed to David J. Blacker; david.blacker@health.wa.gov.au

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Haemorrhagic transformation (HT) of recently ischaemic brain is a feared complication of thrombolytic therapy that may be caused or compounded by ischaemia-induced activation of matrix metalloproteinases (MMPs). The tetracycline antibiotic minocycline inhibits matrix MMPs and reduces macroscopic HT in rodents with stroke treated with tissue plasminogen activator (tPA). The West Australian Intravenous Minocycline and TPA Stroke Study (WAIMATSS) aims to determine the safety and efficacy of adding minocycline to tPA in acute ischaemic stroke. The WAIMATSS is a multicentre, prospective, and randomised pilot study of intravenous minocycline, 200 mg 12 hourly for 5 doses, compared with standard care, in patients with ischaemic stroke treated with intravenous tPA. The primary endpoint is HT diagnosed by brain CT and MRI. Secondary endpoints include clinical outcome measures. Some illustrative cases from the early recruitment phase of this study will be presented, and future perspectives will be discussed.

1. Introduction

Haememorrhagic transformation (HT) of recently infarcted brain causing intracerebral haemorrhage (ICH) is a feared complication of ischaemic stroke that is clearly increased with thrombolytic and anticoagulant medications [1]. It should be noted that ICH can occur spontaneously, typically at the core of an ischaemic infarction, likely related to breakdown of the blood brain barrier (BBB). Activation of proteins such as the metalloproteinases (MMPs) by the ischaemic cascade is likely one of the elements in BBB leakage [1], resulting in haemorrhagic transformation and increased oedema. Various studies of thrombolysis have demonstrated increased rates of ICH compared with placebo, ranging from 1.7% [2] to 8.8% [3], with some of the differences accounted by different definitions of ICH. In the pivotal NINDS study [4], ICH occurred in 6.4% of tPA treated patients (compared with 0.6% in the placebo group), and mortality was 47%. There appears to be different "forms" of ICH following thrombolysis, ranging from symptomatic parenchymal haematoma with a very high

mortality through to asymptomatic minor haemorrhagic transformation which is considered an epiphenomena of reperfusion and has been seen in up to 39.5% of patients in one series [5]. Although it has been suggested [5] that minor haemorrhagic transformation may not have any impact on clinical outcome, some recent observational data [6] suggests that even asymptomatic HT is linked to poor outcome in ischaemic stroke patients.

Any treatment that could reduce the risk of tPA related ICH could substantially reduce mortality, given the high case fatality rate of symptomatic haematoma. Such a treatment would thereby improve the risk/benefit ratio for thrombolytic therapy. One potential candidate medication is minocycline, particularly because of its ability to inhibit the expression of matrix metalloproteinases (MMPs). The MMPs are a group of proteins involved in the physiological breakdown of extracellular matrix. Animal models of cerebral ischaemia have found elevated levels of the MMPs [7, 8]. TPA may increase the risk of HT by amplifying MMP levels in the setting of ischaemia [9, 10], thereby reducing potential benefits of recanalization.

Two animal studies [11, 12] combining minocycline with tPA in rodent models of ischaemic stroke have demonstrated significant reductions in MMP-9 levels and shown as much as a twofold reduction in ICH compared with placebo. Human stroke studies have shown safety and tolerability of orally [13] and intravenously (IV) [14] administered minocycline preparations. There is also safety and pharmacokinetic data on the combination of minocycline and tPA in animal [12] and human studies [14]. There have been three randomised trials of minocycline in human stroke. An open label study [13] of oral minocycline administered a mean of 12.4 hours after stroke onset showed promising results with improvement in NIHSS being seen as early as one week. A further similar study was also positive [15]. The two studies did not include patients treated with tPA. Our group has recently completed a pilot study [16], The Perth Intravenous Minocycline Stroke Study (PIMSS), of IV minocycline in ischaemic and haemorrhagic stroke, up to 24 hours after symptom onset, with a mean time to treatment of 10.6 hours. This study was neutral but provided further safety data and included a small number of patients concurrently treated with tPA. We are presently conducting a meta-analysis of these three small and somewhat heterogeneous studies. PIMSS [16] included 14 subjects treated with tPA, 8 of whom received minocycline and 6 standard care; there was one subject with haemorrhagic transformation in each group. The Minocycline to Improve Neurological Outcome in Stroke (MINOS) trial [14] was a dose-finding study of 60 subjects with ischaemic stroke assigned to receive 3, 4.5, 6, or 10 mg/kg of intravenous minocycline daily for 72 hours, commencing within 6 hours of stroke onset. Thirty-six subjects were also treated with tPA, and there were no cases of severe HT reported. These limited data therefore provide some information regarding the combination of IV minocycline and tPA in human subjects with acute ischaemic stroke.

The West Australian Intravenous Minocycline and TPA Stroke Study (WAIMATSS) [17] is a multicentre, prospective, and randomised pilot study of intravenous minocycline, 200 mg 12 hourly for 5 doses, compared with standard care, in patients with ischaemic stroke treated with intravenous tissue plasminogen activator (tPA). The first dose will be administered within 6 hours of stroke onset. The objectives of WAIMATSS are the following.

(1) To test the hypothesis that subjects with acute stroke treated with IV minocycline and tPA have fewer intracranial haemorrhages (ICH) compared with those treated with IV tPA and standard care, seen on routine followup CT scans, 24 ± 8 hours posttreatment.

(2) As a substudy, to test the hypothesis that subjects with acute stroke treated with IV minocycline and tPA have fewer intracranial haemorrhages (ICH) compared with those treated with IV tPA and standard care, seen on MRI scans performed on day 5–7 posttreatment.

(3) To determine the magnitude of this effect, with a view to estimating the sample size required for a phase III study.

(4) To determine the feasibility of a phase III study, based on this pilot study design and preliminary data.

(5) To test the hypothesis that subjects treated with both IV minocycline and IV tissue plasminogen activator (tPA) have improved clinical outcomes compared with those treated with IV tPA and standard care.

2. Materials and Methods

2.1. Setting. Emergency departments of the four metropolitan teaching hospitals with stroke units in Perth, Western Australia.

2.2. Design. A prospective randomised open label blinded endpoint evaluation (PROBE) pilot trial.

2.3. Study Population

Inclusion Criteria. Subjects must meet the standard inclusion criteria for use of intravenous tPA, be at least 18 years of age, and provide informed consent.

IV tPA to be administered within 4.5 hours of stroke onset.

Trial intervention can be administered within 6 hours of stroke onset.

Exclusion Criteria. Standard exclusion criteria are routine use of tPA, as per local and national guidelines, and patients treated with both tPA and thrombectomy or another endovascular technique.

Specific Exclusion Criteria for the Trial.

(1) Evidence of other significant CNS diseases that interfere with assessment (e.g., tumor, multiple sclerosis).

(2) Known allergy to tetracyclines/intolerance of minocycline.

(3) Known systemic lupus erythematosus.

(4) Idiopathic intracranial hypertension.

(5) Concurrent treatment with vitamin A or retinoids.

(6) Participation in another clinical drug trial.

(7) Known significant renal failure, CLcr <30 mL/min by the Cockcroft-Gault equation.

(8) Known significantly abnormal liver function tests (ALT > ×3 ULN).

(9) Known thrombocytopaenia $<100 \times 10^9$/L.

(10) Concurrent infection requiring antibiotic treatment.

(11) Pregnancy.

(12) Severe stroke or other comorbidities likely to result in the patient dying within a week.

2.4. Baseline Measures. The baseline clinical assessment is part of routine stroke unit care and comprises a complete medical history, physical examination including vital signs, and NIHSS.

2.5. Randomisation. Once consent is obtained, a sealed envelope containing treatment allocation to either IV minocycline or standard care (i.e., no minocycline) will be opened. These sealed envelopes will be kept with the "Stroke kit" that is used at each of the teaching hospitals and used by clinicians from the stroke units. Batches of envelopes with equal numbers of randomly assigned treatment allocation will be provided to each study site. This procedure may be upgraded to a web-based randomisation system in the near future.

2.6. Intervention. Following randomisation patients will be treated with either intravenous minocycline 200 mg then 12 hourly for a total of 5 doses, that is, for 48 hours, or no minocycline. All participants will receive routine stroke unit care. The minocycline is to be commenced as soon as possible, ideally whilst the tPA infusion is still running but no later than 6 hours after stroke onset. The dose has been selected to approximate the "mid-range" of a recent dose-finding study [14] of IV minocycline in human acute stroke patients.

2.7. Primary Outcome. The primary outcome measure is the presence of any ICH on the routine followup CT brain scan, performed 24 ± 8 hours posttreatment with tPA. This has been selected as an intentionally broad endpoint, to maximise the detection of events. Standard baseline CT brain will be performed as per usual practice in the assessment of acute stroke patients. As per usual practice, a followup noncontrast CT is performed on the second day; for the purpose of the study, the timing of this scan will be standardised to occur 24 hours ± 8 hours after the onset of the tPA infusion. Two neuroradiologists blinded to treatment allocation will independently review all pairs of CT scans and classify the presence of any ICH and ICH according to the European Cooperative Acute Stroke Study (ECASS) [3] criteria.

The ECASS Classification is as follows.

Haemorrhagic infarction type 1 (HI-1): small petechiae along the margins of the infarct.

Haemorrhagic infarction type 2 (HI-2): confluent petechiae within the infarcted area but without space occupying effect.

Parenchymal haematoma type 1 (PI-1): a haematoma in <30% of the infarcted area with some slight space occupying effect.

Parenchymal haematoma type 2 (PI-2): a dense haematoma >30% of the infarcted area with substantial space occupying effect.

Additionally, note will be made of any other ICH, defined as any area of increased attenuation consistent with blood, and seen within the intracranial compartment, that was not present on the pretreatment CT. This will account for the rare circumstance where HT is noted outside the infarct area.

2.8. Secondary Outcome

(1) Symptomatic ICH: any ICH temporally related to deterioration in the patient's condition during the hospital admission.

(2) Symptomatic ICH with worsening by 4 or more points on the NIHSS score, during the hospital admission.

(3) NIHSS on days one and seven.

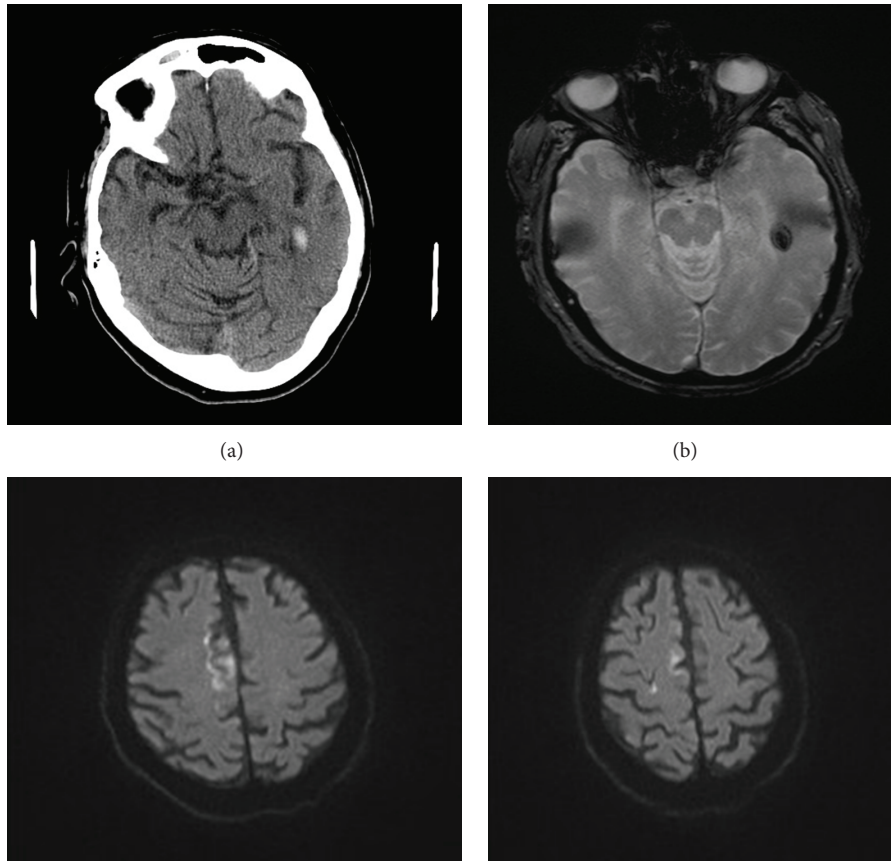
(4) The modified Rankin score and Barthel index by "blinded" telephone interview at days 30 and 90.

2.9. MRI substudy. Subjects will be invited to participate in an MRI substudy in which an MRI with the examination being performed between days 5 and 7 after stroke. The images will be examined by two neuroradiologists blinded to treatment allocation, for signs of ICH. The 1.5T MRI will be used at each hospital site, and a standard stroke protocol will be utilised, also including gradient echo and susceptibility weighted (SWI) sequences, which are more sensitive for the detection of blood products than conventional MRI sequences.

The most sensitive definition of ICH will be any area of focal markedly reduced signal within the infarcted tissue seen on the gradient echo or SWI sequences. This will be used to enable the greatest sensitivity and hence detection of ICH. ICH outside the area of infarct will also be counted.

The ICH will be quantified and recorded in terms of absolute volume (the greatest orthogonal three-dimensional diameter) and relative volume compared with the volume of infarction. In the final report on the study, the plan is to present a montage of all CTs and MRIs with ICH in each group.

2.10. Statistical Analysis and Sample Size Calculations. The study has been designed as a pilot study, with a view to estimating the strength of a possible treatment effect. One animal model [12] demonstrating a twofold reduction in macroscopic haemorrhagic transformation was based on 35 rats treated with tPA and 31 with combined tPA and minocycline. It is estimated that the number of patients



(a) (b) (c) (d)

Figure 1: Subject presented with acute left hemiparesis, leg more affected than arm. Routine day one CT (a) and day 5 MRI (b) demonstrate a small haemorrhage in the left temporal lobe, away from the main area of infarction, shown on diffusion weighted MRI (c) and (d), mainly in the territory of the right anterior cerebral artery. No clinical deterioration was detected.

recruited to this human study will approximate these figures and could well provide the basis for sample size calculations for a higher phase, definitive study. Using the very "inclusive" definition of "any ICH" should maximise the chance of identifying an effect. An MRI based study [5] found evidence of some haemorrhagic transformation in up to 39.5% of patients treated with tPA up to 6 hours after symptom onset. We thus expect that our MRI substudy may yield a high event rate. ICH rates in the minocycline versus the standard care group will be compared using paired t-tests.

Our primary endpoint might be regarded as a "surrogate" for a treatment response or "proof of principle" rather than necessarily as a meaningful clinical result. This would likely require a much larger study, based upon the rates of symptomatic ICH observed in the large treatment trials of tPA.

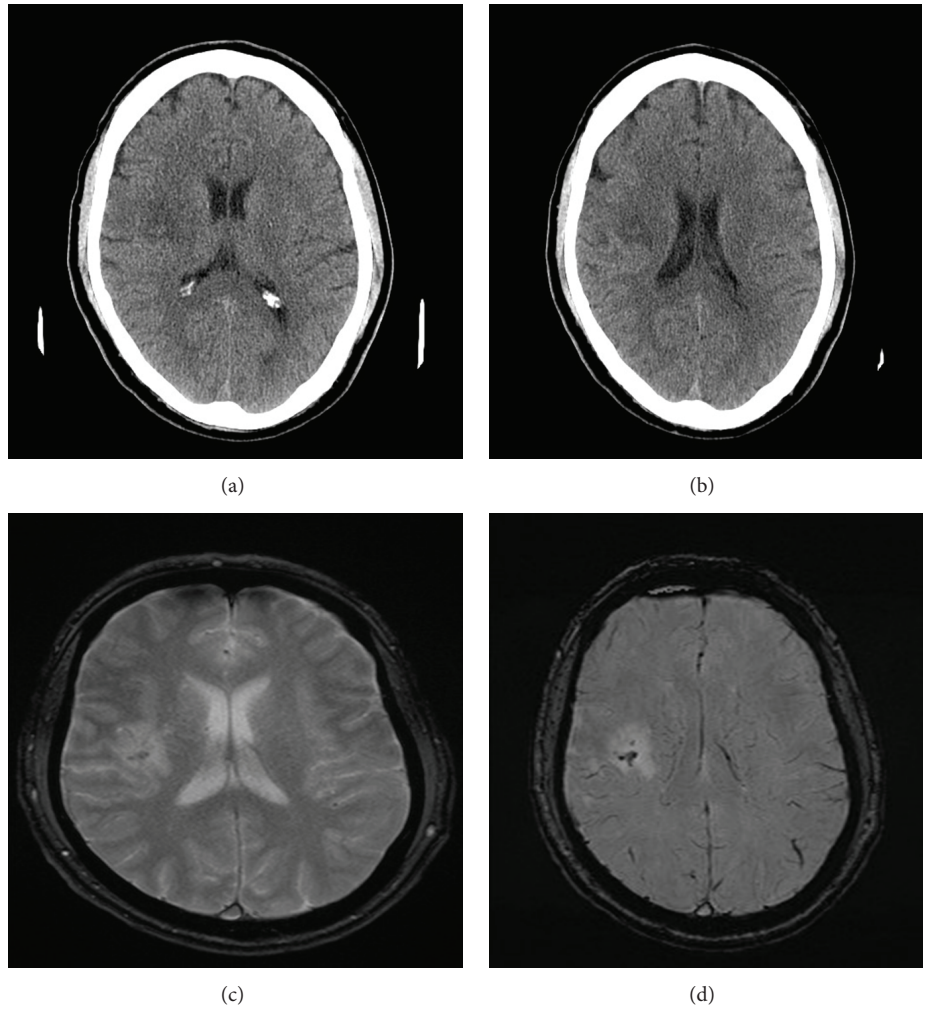
We have made some preliminary calculations of possible sample sizes based on varying rates of haemorrhagic transformation, strength of treatment effect (assuming either 25% or 50% reductions), and varying study power, presented in Table 1.

For example, if the estimated frequency of ICH is 10% and the study drug has a 50% treatment effect, a study with 80% power to show a significant effect would require 286 patients in each of the treatment and nontreatment groups. Whilst such study would not be feasible locally, it could potentially be achieved at a national level with cooperation of stroke centres around Australia and New Zealand. Our pilot human study [17] should provide more reassurance of the magnitude of a treatment effect (and hence guide sample size calculations) than the available animal data.

In the MRI substudy, where the frequency of ICH is up to 40%, 107 patents would be required. The clinical assessments have been chosen to match those used in the Perth Minocycline Stroke Study, to potentially enable pooling of results.

3. Study Duration

Patient recruitment commenced in March 2012 and is planned to continue for approximately 2 years. Approximately 70 patients per year are treated with tPA at these four centres. Allowing for patients who may be unwilling or unable to give consent for participation in a clinical trial, we conservatively estimate that 30 patients per year could potentially be enrolled, resulting in 60 patients over two years. Additional funding may be sought in the future to conduct a higher phase trial.



(a) (b) (c) (d)

Figure 2: Subject presented with mild left hemiparesis. The day one CT (a) and (b) shows a small infarct in the right subcortical white matter, with a suggestion of increased signal within the central portion. The gradient echo (c) and susceptibility weighted image (d) MRI sequences performed on day seven suggest a small amount of blood within the infarct. No clinical deterioration was detected.

Table 1: Sample size calculations table according to different treatment effects.

n for a given prevalence and reduction	Power = 75%		Power = 80%		Power = 85%		Power = 90%	
	25%	50%	25%	50%	25%	50%	25%	50%
0.04	3385	583	3891	670	4524	779	5389	928
0.06	2305	397	2649	456	3080	531	3669	632
0.08	1766	304	2030	350	2361	407	2812	484
0.10	1444	249	1660	286	1930	333	2299	396
0.20	812	140	934	161	1086	187	1293	223
0.30	619	107	711	123	827	143	985	170
0.40	542	93	623	107	724	125	862	149

4. Further Study Details

Steering Committee. The steering committee shall meet every 3 months from the commencement of the study and review procedures and any unexpected difficulties with the study.

Data Monitoring and Safety. A senior local neurologist has agreed to review safety issues and adverse events. He will review all AEs and SAEs and have access to "unblinded" data. He will notify the ethics committee accordingly regarding any safety concerns.

Trial Registration. The study has been registered with the Australian and New Zealand Clinical Trials Registry. Trial number is ACTRN12611001053910.

5. Results and Discussion

Recruitment commenced at the main tertiary site in March 2012, at one peripheral hospital site in October 2012, and screening began at two other sites from December 2012. By early January 2013, twelve subjects had been recruited, nine at the main tertiary site and three from the peripheral hospital.

At the main tertiary site, from March 2012 to December 2012, 32 patients were treated with IV tPA, but 24 were not recruited for WAIMATSS for the following reasons.

(i) Seven were unable to provide informed consent for a clinical trial.

(ii) Six proceeded to concurrent catheter angiography (five of whom underwent thrombectomy).

(iii) In four cases the investigators were not notified.

(iv) In three cases the patients declined to participate.

(v) One patient had known preexisting renal failure.

(vi) One patient was allergic to tetracycline antibiotic.

(vii) One patient probably had benign intracranial hypertension.

(viii) In one case, after review by the investigators, the patient was diagnosed as having a conversion disorder and was not invited to participate.

An amendment to the protocol was approved by the local ethics committee at the main tertiary site in November 2012 to allow for the use of informed assent given by the next of kin; it is hoped that this will allow for increased recruitment. The concurrent use of endovascular treatments such as thrombectomy has excluded 25% of tPA treated patients at the main tertiary site. The commencement of screening from December 2012 at two additional sites: one without access to interventional neuroradiology and the other where thrombectomy is used less frequently may result in increasing recruitment.

Thus far, the practical aspects of the study have run smoothly. There has been one serious adverse event: orolingual angioedema in a subject treated with tPA alone and not minocycline.

Blood products have been detected in two subjects (and the neuroradiologists remain blind to the treatment allocated to these).

In Figure 1 blood was detected on CT and MRI in a region away from the infarction.

In Figure 2 a small amount of blood was visible only on the MRI sequences. Such events will comprise the main data to enable a comparison of the treatment arms.

In summary, this pilot study draws together data from animal experiments and early human trials to explore a relatively new stroke therapy paradigm, that is, an anti-haemorrhagic transformation strategy for stroke patients treated with tPA. This is a slightly different concept to the traditional idea of trial of a neuroprotective agent in stroke. The pragmatic trial design and affordability of the study drug make this a relatively simple clinical study that could be conducted in most stroke units that offer thrombolytic therapy. Minocycline has practical advantages, including its well-established track record of safety (when used as an antibiotic), bioavailability (including orally), and the fact that it can be safely used in patients with haemorrhagic stroke. This makes it a candidate for use in the prehospital setting, without the need for imaging prior to administration. It is ease of use and inexpensiveness also make it a candidate for widespread use without concomitant thrombolytic therapy in nontertiary, rural, and even third world settings [18].

Acknowledgment

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Review Article

Detection of Paroxysmal Atrial Fibrillation in Stroke/Tia Patients

Muhib Khan[1] and Daniel J. Miller[2]

[1] *Department of Neurology, University of Massachusetts, USA*
[2] *Department of Neurology, Henry Ford Hospital, USA*

Correspondence should be addressed to Muhib Khan; muhibalamkhan@hotmail.com

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One-third of stroke and transient ischemic attack (TIA) are cryptogenic, and paroxysmal atrial fibrillation (PAF) has been suggested as a possible cause for these cryptogenic strokes. Multiple studies have recently evaluated long-term cardiac rhythm monitoring with good yield for PAF. The duration of monitoring varies between studies as well as the qualifying event definition. Moreover, the clinical significance of very brief atrial fibrillation events is unclear in the literature. This paper provides an overview of current advances in the detection of paroxysmal atrial fibrillation, the clinical and genetic factors predictive of arrhythmia detection, and the therapeutic dilemma concerning this approach.

1. Introduction

One-third of stroke and transient ischemic attack (TIA) are cryptogenic requiring additional investigation and intervention [1]. Occult paroxysmal atrial fibrillation (PAF) has been suggested as a possible cause for these cryptogenic strokes [2]. Atrial fibrillation has been long associated with high risk of stroke, but most of this knowledge is derived from patient data from chronic atrial fibrillation. It has been suggested that PAF is more prevalent than persistent atrial fibrillation in stroke and TIA patients [3]. Anticoagulation therapy initiated after detection of atrial fibrillation (AF) provides an additional 40% risk reduction of stroke as compared to antiplatelet therapy alone [4].

Therefore, it is important to diagnose AF after an ischemic stroke to provide maximal stroke prevention therapy. Current standard of care dictates an admission electrocardiogram (ECG) and at least 24 h of continuous telemetry monitoring [5]. However, brief asymptomatic paroxysmal atrial fibrillation events may remain undetected by traditional methods of screening. Recent technological advances have made it possible to perform long-term cardiac rhythm monitoring up to months or even years after a stroke.

2. Definition

Paroxysmal atrial fibrillation is not clearly defined in the literature. There is controversy over the duration and morphology of the ECG data in defining an event qualifying for atrial fibrillation. Studies evaluating the incidence of PAF in stroke and TIA patient populations have used different definitions adding confusion about the true incidence. In our paper, we have highlighted the need for a rigorous definition of paroxysmal atrial fibrillation especially in the light of widely used advanced rhythm monitoring devices.

3. Epidemiology

Atrial fibrillation prevalence is associated with age with 0.5% at 50–59 years of age increasing to 8.8% at 80–89 years [2]. PAF comprises from 25% to 60% of these cases [2]. The true incidence of PAF is unclear as most of the prevalence studies used symptomatic events, and prolonged rhythm monitoring was not available at the time on these studies. Moreover, again the variable definitions might have an impact of the incidence reported.

Table 1: Yield of long-term cardiac rhythm monitoring studies.

Study	Patient population	Duration (days)	Sample size	No. diagnosed	Percentage
Barthélémy et al. 2003 [6]	Stroke/TIA	4	28	4	14.3
Sposato et al. 2012 [7]	Stroke/TIA	5	155	21	13.5
Stahrenberg et al. 2010 [8]	Stroke/TIA	7	220	28	12.7
Jabaudon et al. 2004 [9]	Stroke/TIA	7	88	5	5.7
Tayal et al. 2008 [10]	Stroke/TIA	21	56	13	23
Miller et al. 2013 [11]	Stroke/TIA	21	156	27	17.3
Bhatt et al. 2011 [12]	Stroke/TIA	21	62	15	24
Elijovich et al. 2009 [13]	Stroke/TIA	30	20	4	20
Gaillard et al. 2010 [14]	Stroke/TIA	30	98	9	9.2
Flint et al. 2012 [15]	Stroke	30	239	29	12.1
Ziegler et al. 2010 [16]	Stroke/TIA	365	163	45	28
Total			1285	200	15.5

4. Pathophysiology

Atrial arrhythmias have varied pathophysiology ranging from rapidly discharging foci, microreentry, macroreentry, and autonomic modulation of the atria. These processes are usually due to structural abnormality within the atria. This leads to mechanical dysfunction with resultant thrombus formation in the complex, pectinate-rich structure of the left atrial appendage.

5. Natural History

Paroxysmal atrial fibrillation is a self-promoting process, and if these events are left untreated, they can progress to persistent atrial fibrillation [3]. The goal of therapy is to maintain sinus rhythm and appropriate anticoagulation [3].

6. Studies

Multiple studies have been published recently highlighting higher yield of atrial fibrillation detection with longer monitoring and newer devices [6–16]. The yield varied (5%–28%) depending on the choice of monitoring devices, study population, stroke characteristics, interval of monitoring, from stroke onset, duration of cardiac monitoring and most importantly the definition of paroxysmal atrial fibrillation. Table 1 provides a snap shot of these studies.

Most of these studies defined paroxysmal atrial fibrillation as events lasting more than 30 seconds. The 30 seconds benchmark used to describe atrial fibrillation events comes from the AHA 2006 guidelines [17]. It is unclear from the manuscript how the authors came up with the 30 seconds benchmark although they do mention that shorter events may be relevant in the right clinical setting [17]. It has been suggested that the duration of atrial fibrillation events with higher specificity can be up to 5 minutes. But then again, this higher specificity comes at the cost of lower sensitivity, and a critical balance between the two needs to be established [18].

It is also to be kept in mind that most of these studies are hospital-based identification of stroke/TIA patients with prolonged rhythm monitoring at the discretion of treating physician, and the data was analyzed retrospectively. Therefore, these studies are not free from selection bias.

It has been shown that these event monitors do have a high false positive rate especially for short events. More refined software with better algorithms to filter out myopotential artifacts can increase specificity, but there is always the risk of losing the sensitivity of event detection [19].

This brings us to the question of what duration of atrial fibrillation events is predictive of a future stroke. No clear association between the duration of events and stroke risk has been established in the literature. It has been shown that even excessive supraventricular ectopic beats not constituting atrial fibrillation increase ischemic stroke and atrial fibrillation detection rates [20]. It is unclear how often these short atrial fibrillation events lead to chronic atrial fibrillation. However, it has also been noted that higher (>5.5 hours) burden of atrial fibrillation events (total duration) leads to a higher stroke risk although this total duration was extrapolated from a long duration of monitoring (>365 days) [21]. Additionally, a recent study showed increased ischemic stroke rates, as well as verified atrial fibrillation rates, in patients that were found to have subclinical atrial tachyarrhythmias of >6 mins [22].

The ongoing study CRYSTAL AF is investigating the value of longer-term monitoring with an implantable loop recorder in patients with cryptogenic stroke to identify the predictive value of these events. Moreover, both CRYSTAL AF and IMPACT trials will help us to identify the best candidates for anticoagulation [23, 24]. IMPACT is also evaluating the therapeutic intervention implied after detection of these events which is the final goal of any diagnostic evaluation in secondary stroke prevention.

7. Predictors

Multiple predictors of PAF in cryptogenic stroke patients have been proposed by these studies including diabetes, female gender, premature atrial complexes (PACs) on ECG, left atrial dilatation, left ventricular reduced ejection fraction (EF), higher stroke severity assessed by National Institute of Health Stroke Scale (NIHSS), nonlacunar anterior circulation

Table 2: Predictors of atrial fibrillation detection in patients with cryptogenic stroke.

Study	Predictors of atrial fibrillation detection
Tayal et al. 2008 [10]	Diabetes
Miller at al. 2013 [11]	Female gender
	PAC on ECG
	Left atrial dilatation
	Left ventricular EF reduction
	NIHSS
Gaillard et al. 2010 [14]	>100 PACs on 24 hr Holter
	Nonlacunar anterior circulation acute infarcts
Bhatt et al. 2011 [12]	Multiple acute infarcts
	Premature ventricular complexes

infarcts on neuroimaging, cortical infarcts on neuroimaging, and congestive heart failure [10–12, 14]. Of note, symptoms are not a significant predictor of detecting PAF as most of these events are asymptomatic [25]. Table 2 provides a synopsis of these predictors.

Most of these predictors make pathophysiological sense because of their ability to modify the atrial rhythms eventually leading to atrial fibrillation. Dilated left atrium and premature atrial complexes stand out as the most important predictors. Transthoracic echocardiogram parameters are useful in selecting the patients for prolonged monitoring in this regard [26]. Premature atrial complexes (PACs) are an important predictor, and a careful analysis of admission ECG should be performed on all stroke patients to identify these PACs for long-term monitoring selection [27].

These various predictors have been consolidated into risk assessment scoring schemes to provide a predictive model for PAF detection [28, 29]. These scores are useful tools, but clinical judgment should always be implied in selecting patients for long-term monitoring.

8. Future Direction

There is a novel concept of atrial fibrillation density which implies temporal clustering of atrial fibrillation events in a short period of time. Essentially, a patient who is monitored in the time window when most of these events are clustering has a higher probability of being detected with monitoring devices as compared to a window period when the events are not clustered. This concept again reaffirms the need to monitor these patients for longer duration [30].

The new subcutaneous implantable cardiac monitors (REVEAL) have shown potential to detect paroxysmal atrial fibrillation with higher patient compliance [31] and longer duration of monitoring. One attractive feature of this device is its MRI compatibility [32].

So far, there has been only one randomized clinical trial performed to evaluate the impact of prolonged monitoring on therapeutic decisions. The trial failed to show any benefit of long-term monitoring over routine clinical followup but the sample size of this trial was very small, and the findings need to be validated in a larger clinical study [33].

The iPhone 4S has been shown to potentially act as a monitoring device for detecting PAF and has broad worldwide implications as a method of bringing monitoring to the masses [34].

Multiple genetic polymorphisms have been implicated in pathogenesis of atrial fibrillation such as PITX2, ZFHX3, KCNN3, PRRX1, CAV1, SYNE2, FBP, HCN4, SYNPO2L, and MYOZ1.

These genes mostly encode for proteins important in the integrity of cardiac myocyte structure and normal physiology [35]. It has been noted that these genetic markers do not increase the detection yield of atrial fibrillation when added to conventional risk factors for atrial fibrillation. Further studies are needed to establish the clinical implication of genetic testing for atrial fibrillation [36].

9. Conclusions

Long-term cardiac rhythm monitoring plays an increasingly important role in determining the etiology of stroke/TIA. The widespread use of these monitors will increase the incidence of PAF, raising questions about management of these events. Future studies should focus on the optimal duration of monitoring, predictors of detecting atrial fibrillation, stroke risk pertinent to paroxysmal atrial fibrillation, and the duration of these events. There is also a need to study how often the short atrial fibrillation events lead to chronic atrial fibrillation and optimal treatment strategy, either antiplatelet or anticoagulation, in patients exhibiting brief events.

Conflict of Interests

The authors do not have any conflict of interests with the content of the paper.

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Research Article

Depression Increases Stroke Hospitalization Cost: An Analysis of 17,010 Stroke Patients in 2008 by Race and Gender

Baqar Husaini,[1] Robert Levine,[2] Linda Sharp,[3] Van Cain,[1] Meggan Novotny,[1] Pamela Hull,[4] Gail Orum,[5] Zahid Samad,[1] Uchechukwu Sampson,[4] and Majaz Moonis[6]

[1] *Tennessee State University, Nashville, TN 37209, USA*
[2] *Meharry Medical College, Nashville, TN 37208, USA*
[3] *Harbor-UCLA Medical Center, Los Angeles, CA 90095, USA*
[4] *Vanderbilt University, Nashville, TN 37203, USA*
[5] *Charles R. Drew University, Los Angeles, CA 90059, USA*
[6] *University of Massachusetts, Boston, MA 01655, USA*

Correspondence should be addressed to Baqar Husaini; bhusaini@tnstate.edu

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Objective. This analysis focuses on the effect of depression on the cost of hospitalization of stroke patients. *Methods*. Data on 17,010 stroke patients (primary diagnosis) were extracted from 2008 Tennessee Hospital Discharge Data System. Three groups of patients were compared: (1) stroke only (S^{O}, $n = 7{,}850$), (2) stroke + depression (S^{+D}, $n = 3{,}965$), and (3) stroke + other mental health diagnoses (S^{+M}, $n = 5{,}195$). *Results*. Of all adult patients, 4.3% were diagnosed with stroke. Stroke was more prevalent among blacks than whites (4.5% versus 4.2%, $P < 0.001$) and among males than females (5.1% versus 3.7%, $P < 0.001$). Nearly one-quarter of stroke patients (23.3%) were diagnosed with depression/anxiety. Hospital stroke cost was higher among depressed stroke patients (S^{+D}) compared to stroke only (S^{O}) patients ($77,864 versus $47,790, $P < 0.001$), and among S^{+D}, cost was higher for black males compared to white depressed males ($97,196 versus $88,115, $P < 0.001$). Similar racial trends in cost emerged among S^{+D} females. *Conclusion*. Depression in stroke patients is associated with increased hospitalization costs. Higher stroke cost among blacks may reflect the impact of comorbidities and the delay in care of serious health conditions. Attention to early detection of depression in stroke patients might reduce inpatient healthcare costs.

1. Background

Between 20% and 60% of stroke patients are diagnosed with depression/anxiety [1], and these are often newly diagnosed in stroke patients both during hospitalization and up to 3 years after discharge [1–20]. Depression is associated with longer institutionalization and poorer rehabilitation outcomes [21, 22]. Further, depression is more often diagnosed for females and white stroke patients [23, 24], and it is correlated with higher rates of suicidal ideation and stroke mortality [25–27]. Depression increases the risk of stroke [28] as well as increased healthcare costs [29–34]. As these and other stroke related factors are evaluated, understanding their impact on healthcare cost is necessary for better management, improved therapeutic outcomes, and reduced healthcare cost.

2. Depression and Healthcare Cost

Several studies have reported the effect of depression/anxiety on healthcare costs. For example, while female Medicare patients had a higher prevalence of depression and higher use of outpatient services, inpatient hospital costs for male patients were 47% higher compared to females ($15,060 versus $10,240, $P < 0.001$) [30]. In another study, the medical cost of depressed patients was 54% higher compared to nondepressed patients [34]. While higher cost among stroke

patients is associated with greater number of readmissions, longer hospitalizations, and greater number of outpatient visits compared to a control group without depression, evidence is sparse about whether these costs vary by race and gender.

In this study of Tennessee stroke patients ($n = 17,010$), we examine two issues: (1) prevalence of depression among stroke patients by race and gender and (2) the effect of depression on total hospitalization cost in 2008 by race and gender.

3. Methods

3.1. Data. We obtained inpatient discharge data from the 2008 Tennessee Hospital Discharge Data System (HDDS) compiled by The Tennessee Department of Health's (TDH) Division of Health Statistics. All hospitals licensed by the TDH are required by law to report patient-level discharge information. Data are reported on a uniform billing form developed by the National Uniform Billing Committee. Diagnoses in the administrative files are given by the attending physicians (according to the ICD-9 codes), and it is unclear what tests are used in arriving at those diagnoses. Further, these diagnoses appear only when the patient is treated for those conditions in the hospital. We extracted data on primary diagnosis of stroke (ICD-9 codes of 430–438) along with the secondary diagnoses of depression/anxiety (ICD-9 codes 296.2—major depressive disorder, single episode, 292.3—major depressive disorder, recurrent episode, 3000.4—neurotic depression, 309.0—brief depressive reaction, 309.1—prolonged depressive reaction, 311—depressive disorder, not elsewhere classified, and 300—anxiety states, hysteria, phobic disorders, and neurotic depression) for blacks and whites since they constitute 97% of Tennessee population. Since there is a high overlap in symptoms of depression and anxiety ranging from 48% to 74% [37, 38], we combined the diagnoses for depression and anxiety as a single variable for our analysis. Data extraction on stroke patients included sex, age, race, days of hospitalization, number of re-admissions, and costs associated with stroke treatment as well as the total hospital charges for the entire year of 2008 when the patient was readmitted for illnesses other than stroke. Extracted data also included co-morbidities such as atrial fibrillation, hypertension, diabetes, cholesterol, and cardiovascular events such as heart attacks. The stroke sample included whites (82%) and females (55%), and the average age in the sample was 70 years. Stroke rates were age adjusted per 2000 US population.

3.2. Statistical Analysis. Analysis of variance compared the average hospitalization costs [39] for three groups of stroke patients: (1) stroke only (S^O, $n = 7,850$), (2) stroke + depression/anxiety (S^{+D}, $n = 3,965$), and (3) stroke + other mental diagnoses (S^{+M}, $n = 5,195$). The Fisher exact test was used for comparison of healthcare cost and prevalence of comorbidities by race and sex. Percentages of stroke diagnoses were compared using Pearson's Chi-squared test with Yates' correction for continuity, and odd ratios (ORs) were obtained through logistic regression analyses, which controlled for age, sex, hypertension, diabetes, cholesterol, and atrial fibrillation. A probability value of $P < 0.05$ was the accepted threshold for statistical significance.

4. Results

4.1. Prevalence of Stroke, Depression, Comorbidities, and Healthcare Cost. Our analysis showed that 17,010 patients (4.3% of all 400, 235 adult patients) had a primary diagnosis of stroke with an age-adjusted prevalence rate of 370.6 per 100 K. Stroke was higher among blacks compared to whites (4.5% versus 4.2%, resp., $P < 0.0001$; prevalence rates of 517.1 versus 322.0, resp.; OR = 1.31, 95% CI = 1.26–1.36 after controlling for risk factors, Table 1). Stroke was more prevalent among males than females (5.1% versus 3.7%, $P < 0.0001$; rates of 374.1 versus 369.2 per 100 K; OR = 1.22, 95% CI = 1.18–1.25). Further, stroke was more common among black males compared to white males (5.8% versus 5.0%, $P < 0.001$; prevalence rates of 532.3 versus 351.0 per 100 K; OR = 1.31, 95% CI = 1.23–1.39) and among black females compared to white females (3.9% versus 3.7%, $P < 0.02$; prevalence rates of 505.7 versus 298.9 per 100 K; OR = 1.29, 95% CI = 1.22–1.37). Nearly one-quarter of stroke patients were depressed/anxious (23.3%). Depression among stroke patients was higher among whites than blacks (25.1% versus 15.2%, $P < 0.001$) and among females than males (27.5% versus 18.3%, $P < 0.001$).

Table 1 shows that nearly 20% (3,402 of 17,010) of stroke patients had congestive heart failure (CHF) and 4% had experienced heart attacks (MI). Coronary heart disease (CHD) was also more prevalent among the stroke patients (39% overall, 41% among whites versus 30% among blacks). Other stroke co-morbidities varied by race and sex. Hypertension (92%) and diabetes (45%) were more prevalent among blacks and atrial fibrillation (32%) and high cholesterol (17%) were more prevalent among white patients.

Table 1 further shows that treatment cost associated with stroke only (S^o) was higher among blacks as compared to whites ($41,370 versus $30,215, $P < 0.001$, a difference of 36.9%). This cost difference also exists when the average annual costs for the entire year of 2008 is examined for patients without stroke. Here again, nonstroke black patients compared to nonstroke white patients had higher 2008 cost ($45,892 versus $40,376, $P < 0.001$), partly due to longer hospitalization for black patients (8.6 days for blacks versus 7.3 days for whites, $P < 0.001$). The cost differential remained intact when the comparisons are made simply for stroke cost ($74,338 for blacks versus $55,884 for whites, $P < 0.001$) or the cost for the entire year of 2008 with multiple readmissions ($74,338 for blacks versus $55,884 for whites, $P < 0.001$). Similar trends for stroke cost emerged for black males ($74,006 versus $59,403, $P < 0.001$) and for black females ($74,589 versus $52,877, $P < 0.001$). Again, higher costs among blacks reflected higher comorbidities and longer hospitalizations for blacks than whites. Thus, black stroke patients (due to high comorbidities and longer hospitalization) cost 62% more than nonstroke black peers ($74,338 versus $45,892, a difference of $28,446) and more

Table 1: Age-adjusted stroke rates and characteristics by race and gender in 2008 ($n = 17,010$).

Variables	WF $n = 7495$	WM $n = 6405$	BF $n = 1773$	BM $n = 1337$	Total $n = 17,010$	Any stroke blacks $n = 3110$	Blacks no stroke $n = 65,595$	Any stroke whites $n = 13,900$	Whites no stroke $n = 317,630$
Stroke rate per 100 K	298.9	351.0	505.7	532.3	370.6	517.1	—	322.0	—
Age	73	69	64	61	70	63	49	77	57
MI%	3.8	4.2	3.6	5.3[+]	4.1	4.3	3.1	4.0	4.4[*]
CHF%	19.5	17.9	20.1	21.3[*]	19.1	20.6[*]	14.5[*]	18.7	13.6
CHD%	31.7[*]	31.4	23.6	24.3	38.9	29.8	17.5	41.0	25.8[*]
At fib%	32[*]	31	24	24	30	24	13.0	32[*]	18.6[*]
Hyp%	85	84	92	92[*]	86	92[*]	54	84.5	52
Diabetes%	31	36	47[*]	42	36	45[*]	27.4	34	22.7
Chol%	15.8	17.3[*]	11.3	13.4	15.7	12.2	5.1	16.5[*]	8.2[*]
Dep/anx%	29.7[*]	19.8	18.3	11.0	23.3	15.2	10.7	25.1[*]	21.4[*]
Number of readmissions	1.11	1.12	1.13	1.13	1.12	1.13	1.6	1.11	1.5
Hop stk day	5.0	5.1	7.1	7.3	5.4	7.2[*]	—	5.0	—
Tot hos day	11.3	11.7	15.7	15.4	12.2	15.6[*]	8.6[*]	11.5	7.3
Average ischemic $	27,071	30,904	43,074[*]	38,710	31,460	41,120[*]	—	28,833	—
Average hemo. $	45,852	50,017	69,796[*]	60,586	51,211	64,643[*]	—	48,246	—
Average Total stroke $[+]	29,238	31,359	41,207	41,586[*]	32,255	41,370[*]	—	30,215	—
All 2008 admis $	52,877	59,403	74,589	74,006	59,259	74,338	45,892[*]	55,884	40,376

[+]Average cost for all strokes combined includes cost associated with ischemic + hemorrhagic + unspecified strokes + TIA; # is average number of admissions/hospital days; CHF: congestive heart failure; CHD: coronary heart disease; all costs are reported in averages. Average of all total 2008 cost includes cost combined for all admissions in 2008.

[*]Fisher's exact test differences are significant between nonstroke black and white patients at $P < 0.001$.

than 80% of the cost for white nonstroke patients ($74,338 versus $40,376). Comparable race and gender differences also existed in costs associated with ischemic or hemorrhagic stroke (see Table 1). In summary, black patients had higher costs associated with hospitalizations compared to white patients no matter how the costs were examined.

4.2. Effect of Depression on Hospital Cost for Stroke. We examined cost and associated co-morbidities including Charlson Index of comorbidity for three stroke groups including: (1) patients with stroke only (S^O); (2) patients with stroke + depression (S^{+D}); (3) stroke patients with other mental diagnoses (S^{+M}). Within each stroke category, we compared cost and associated factors by race and gender. Table 2 shows that the average healthcare cost was nearly 63% higher for stroke patients with S^{+D} compared to S^O ($77,864 versus $47,790, $P < 0.001$, a difference of 63%) or S^{+D} compared to S^{+M} ($77,864 versus $62,387, $P < 0.001$, a difference of 24.8%). Clearly, these data show that depression among stroke patients is associated with higher hospital costs compared with stroke patients who have other mental illnesses.

Table 2 provides costs and comorbidities data for three groups of stroke patients, further illustrating that both stroke prevalence and annual costs were higher among blacks, and the race-sex differences are made evident. Among depressed stroke patients (S^{+D}), black males had higher annual hospital charges compared to white males ($97,196 versus $88,115, $P < 0.001$), in part due to longer hospital stays compared to white males (24.6 versus 20.2, $P < 0.001$). Similarly, black S^{+D} females had higher cost compared to white S^{+D} females ($95,269 versus $68,184, $P < 0.001$). For black males, the higher cost cannot be attributed to depression/anxiety as only 11% of black males had a diagnosis of depression; the higher cost here appears to reflect complexities (denoted by a higher Charlson comorbidity index) that develop from co-morbid conditions such as higher prevalence of hypertension and diabetes. Similar race and gender trends also existed for black males and females across S^{+M} and S^O groups of patients.

5. Comments

Previous studies on healthcare cost have reported substantially higher cost (54% higher) for patients with cardiovascular disease (CVD) and stroke in association with depression and anxiety [31–34]. Our analyses show that depression and anxiety among Tennessee stroke patients is associated with a 63% increase in the annual hospital care cost. Further, our findings of higher cost for depressed stroke patients, especially among women, are consistent with those reported previously [34]. Since depression can be considered as an independent risk factor for CVD [40, 41] and since women outnumber men in the population (as well as in our S^{+D} group—54% versus 46%), costs attributable to depression

Table 2: Three stroke group cost by race and gender, 2008.

	Stroke only S°, n = 7,850; age = 71; entire 2008 cost = $47,790				Stroke + Dep S^{+D}, n = 3,965; age = 68; entire 2008 cost = $77,864*				Stroke + other ment S^{+M}, n = 5,195; age = 69; entire 2008 cost = $62,387			
	WF	WM	BF	BM	WF	WM	BF	BM	WF	WM	BF	BM
Mean age	75	71	64	61	71	67	62	61	73	67	65	61
HTN%	84	83	91	91	87	89	96	93	83	83	91	92
Diabetes%	31	36	48	47	34	42	55	48	30	32	42	36
CHF%	17	15	17	21	23	25	26	29	20	19	22	20
MI%	2.9	3.3	3.4	3.5	4.4	6.5	3.4	7.5	5.0	4.2	4.1	6.4
Atrial fibrillation	31*	30	22	23	32	36	24	31	32*	30	26	24
Hospital days	8.1	7.8	12.7	12.8	15.7	20.2	21.9	24.6	11.6	12.2	16.9	15.6
Number of Admissions	1.7	1.7	1.9	1.8	3.0	3.6	2.9	3.2	2.2	2.1	2.3	2.3
Comorb Index^{++}	1.4	1.5	1.7	1.9*	1.6	1.9	2.1	2.3*	1.7	1.8	1.9*	1.7
Total stroke cost combined $	27,601	28,926	39,500	40,866*	31,369	32,488	39,482*	37,773	29,630	34,209	44,914*	43,140
Annual cost for all 2008 admissions $	42,329	46,210	63,072	64,622*	68,184	88,115	95,269	97,196*	53,575	61,155	80,849*	77,076

*Differences significant at $P < 0.001$; $^{++}$Charlson Comorbidity Index—higher score denote greater number of comorbid conditions.

may be reduced by early diagnosis and treatment of depression. The stroke patients in our sample had higher prevalence of both hypertension (more than 80%) and diabetes (more than 35%). Addressing depression and reducing risk factors through preventive programs [42] could substantially reduce the morbidity, mortality, and healthcare costs associated with stroke [42, 43].

The average healthcare cost among blacks compared to whites were higher regardless of whether the stroke was hemorrhagic or ischemic (hemorrhagic cost—$64,643 versus $48,246 $P < 0.001$; ischemic cost—$41,120 versus $28,833, $P < 0.001$). These higher costs remained intact when total stroke costs (combined ischemic+hemorrhagic+unspecified stroke + TIA) were compared between blacks and whites ($41,370 versus $30,215, $P < 0.001$), particularly black males compared to white males ($41,586 versus $31,359, $P < 0.001$). The same cost pattern emerges when the annual cost for the entire 2008 year was combined (blacks had higher annual cost compared to whites: $74,338 versus $55,884, $P < 0.001$, Table 1) and when racial comparisons for nonstroke patients were made. These differences suggest that blacks with chronic conditions may seek medical services later in the progression of their disease and that this late entry to care [44, 45] may require more services and longer hospitalization as is evident in our data (16 days for black patients compared to 12 days for white patients, Table 1). Further, the higher cost among black males may in part exist because previous studies suggest that they are more likely to drop out of behavioral and pharmacological therapies [46] which in turn leads to more complications and readmissions (re-admissions are higher among blacks—see Table 1).

The lower overall cost of care among women (particularly white women) compared to men may result from a number of factors including that women, in general, seek professional help earlier on in the development of their illness compared to men [47, 48] and this alone may reduce complications and hence reduce length of hospitalization and cost [47–49]. In order to impact CVD end points among women, depression/anxiety must be treated both as independent risk factors for preventing CVD and for reducing cost in females with known CVD [50].

Finally, Our findings of higher hospitalization cost of stroke is associated with depression and anxiety that consistently appear as a co-morbid condition requiring greater attention in managing healthcare cost. Findings of higher cost and greater utilization of services, though scantly reported (see Table 3 below), nonetheless are supportive of monitoring ways to contain higher treatment cost associated with stroke and other major events.

6. Limitations

The administrative hospital discharge files do not provide clinical data regarding severity/duration of diseases, test results, or cost of pharmacological treatment provided. Further, these administrative files do not provide itemized cost, and hence it is impossible to determine the cost of pharmacological treatment for depression/anxiety for any patient. The administrative data only include the total cost for the entire hospital stay, number of admissions, and sometimes within the total cost per admission, the cost associated with major procedures such as CABG. In addition to the primary diagnosis, these administrative files provide data on secondary diagnoses (i.e., co-morbidities) only when treatment is provided for those conditions. These administrative files lack clinical details of diagnoses or co-morbid conditions which may shed additional light on racial and gender differences in healthcare cost. Our data are from a single state and for only one year (2008), and as such they may not reflect outcomes from other geographic areas/regions. Finally, based on this

Table 3: Increased medical care costs of stroke associated with depression. Recent peer-reviewed publications.

First author and year	Country	Type of study	Participants	Results	Conclusions
Bhattarai et al., [35] 2012	UK	Population-based cohort	299,912 participants, ages 30 to 100 years	14% of male and 26% of female stroke patients with single morbidity had comorbid depression; patients with concurrent diabetes, CHD, and stroke had a very high prevalence of depression (men 23% and women 49%)	Compared to those with no morbidity, depression was associated with higher rates of healthcare utilization and increased costs at any level of morbidity.
Sicras et al., [36] 2008	Spain	Cross-sectional, retrospective	2,266 stroke patients	Females (OR 2.1), obesity (OR 1.1), and neuropathy (OR 2.2) were significantly associated with depressive disorder in stroke patients	Adjusted total costs of depressive disorder were higher in most components, euro 2, −37.55 versus euro 1,498.24 ($P < 0.001$). Medication drugs accounted for 73.4% of the total costs.
Jia et al., [29] 2006	USA	National cohort	5,825 Department of Veterans Affairs patients with stroke	41% of the sample had poststroke depression	After adjusting for patient demographic and clinical factors, patients with stroke and poststroke depression had significantly $P < 0.0001$, more hospitalization, outpatient visits, and longer length of stays, 12 months after stroke compared with patients with stroke but no poststroke depression

cross-sectional data, we were unable to differentiate prestroke depression from poststroke depression. However, in either case, the association of stroke with depression in our study seems to contribute to increased hospital stay, greater comorbidities, and significantly greater cost of healthcare.

7. Conclusion

Stroke patients with depression/anxiety have significantly higher healthcare costs compared to those with stroke only (i.e., without depression/anxiety) or those with other mental health diagnoses. Based on the patterns reported here, greater attention to prevent comorbidities and early detection of depression in stroke patients are all promising interventions aimed at reducing inpatient healthcare costs while improving overall care, with the greatest opportunities for improved health and cost savings in the black male population. Analytic epidemiologic studies are needed to examine whether the higher healthcare costs among blacks exist due to delays in seeking treatment and/or poor access to services, leading to more complex problems and longer hospitalizations. Additionally, research is needed to determine whether aggressive treatment of depressed patients that have suffered stroke might reduce the overall costs of stroke care.

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Clinical Study

Playing Piano Can Improve Upper Extremity Function after Stroke: Case Studies

Myriam Villeneuve[1,2] and Anouk Lamontagne[1,2]

[1] *School of Physical and Occupational Therapy, McGill University, Montreal, QC, Canada H3A OG4*
[2] *Feil and Oberfeld Research Centre, Jewish Rehabilitation Hospital, Research Site of the Montreal Center for Interdisciplinary Research in Rehabilitation (CRIR), 3205 Place Alton-Goldbloom, Laval, QC, Canada H7V 1R2*

Correspondence should be addressed to Anouk Lamontagne; anouk.lamontagne@mcgill.ca

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Music-supported therapy (MST) is an innovative approach that was shown to improve manual dexterity in acute stroke survivors. The feasibility of such intervention in chronic stroke survivors and its longer-term benefits, however, remain unknown. The objective of this pilot study was to estimate the short- and long-term effects of a 3-week piano training program on upper extremity function in persons with chronic stroke. A multiple pre-post sequential design was used, with measurements taken at baseline ($week_0$, $week_3$), prior to ($week_6$) and after the intervention ($week_9$), and at 3-week follow-up ($week_{12}$). Three persons with stroke participated in the 3-week piano training program that combined structured piano lessons to home practice program. The songs, played on an electronic keyboard, involved all 5 digits of the affected hand and were displayed using a user-friendly MIDI program. After intervention, all the three participants showed improvements in their fine (nine hole peg test) and gross (box and block test) manual dexterity, as well as in the functional use of the upper extremity (Jebsen hand function test). Improvements were maintained at follow-up. These preliminary results support the feasibility of using an MST approach that combines structured lessons to home practice to improve upper extremity function in chronic stroke.

1. Introduction

Persistent contralateral motor impairments are common following a stroke. It is estimated that 80% to 95% of patients experience sensorimotor upper extremity impairments as well as activity and participation limitations, which persist beyond 6 months after stroke onset [1]. This is a major concern as in order to manage daily activities, chronic stroke survivors often use nonoptimal compensation strategies that can lead to a pattern of learned disuse of the paretic arm and further exacerbate the level of disability. Existing therapies that aim at improving upper extremity function show modest to moderate improvements [2], possibly due to insufficient training intensity [3] and lack of adherence. It was also shown that well beyond the optimal recovery window that occurs within the first 6 months after a stroke, rehabilitation still has the potential to induce neurological and functional changes [4, 5]. There is a need to develop and implement interventions that will meet the patient's interests to actively engage them during and beyond the supervised rehabilitation period so that long-term improvements in upper extremity function can be achieved.

Music-supported therapy (MST) is an innovative approach that has been shown to yield larger improvements in fine and gross motor dexterity compared to conventional rehabilitation and constraint-induced movement therapy in acute stroke survivors [6]. MST was also shown to yield enhanced motor skills and neuroplastic changes of auditory-motor network in chronic stroke participants [7]. In addition to integrating key principles of motor learning and providing instantaneous auditory feedback on performance, the rapid establishment of auditory-motor coupling during music playing would underlie the efficacy of MST [7, 8]. Such coupling can be observed within 20 minutes of musical training and is largely enhanced after 5 weeks of training in nonmusicians [9]. Existing MST

Table 1: Initial participant characteristics.

	Participant 1	Participant 2	Participant 3
Age (years)	60	67	58
Gender (male/female)	Male	Male	Male
Time since stroke (months)	9	10	16
Side of stroke (left/right)	Right	Left	Right
Type of stroke (ischemic/hemorrhage)	Ischemic	Ischemic	Hemorrhage
CMSA arm/hand score (max = 7)	3/3	3/3	4/5
Piano experience (years)	0	0	0
Handedness	Right	Right*	Left*

*Affected hand is the dominant hand; CMSA: Chedoke-McMaster Stroke Assessment.

programs, however, involve 5 days/week of training and may be difficult to implement in an outpatient and community rehabilitation settings. Furthermore, no previous MST program has focused on finger movement accuracy, timing, and speed, which are important determinants of finger coordination. We have developed, using a user-friendly computerized piano program, a piano training paradigm that provides feedback on note accuracy, timing and speed while allowing participants to progress through finger sequences of increasing complexity. The purpose of this study was to investigate the feasibility of an individually tailored piano training intervention that targeted finger movement coordination and combined structured piano lessons to home practice. The specific objective was to estimate the short-term and retention effects of a 3-week piano training program on manual dexterity, finger movement coordination, and functional use of upper extremity in persons with chronic stroke.

2. Methods

Three male participants with a mild to moderate deficits of upper extremity motor function due to a first supratentorial chronic stroke (6 to 24 months duration) in the middle cerebral artery territory were recruited after being discharged from rehabilitation (Table 1). Participants had (1) some capacity of dissociation of upper extremity movements as reflected by scores of 3 to 6 on the arm and hand components of the Chedoke-McMaster Stroke Assessment and (2) the ability to follow simple instructions. They had corrected to normal vision and were free of visual field defects (Goldman perimetry), hemineglect (<6 omissions, Bell's test), and cognitive deficits (scores > 23, Montreal Cognitive Assessment). None had musical experience. The study was approved by the Ethics Committee of the Centre for Interdisciplinary Research in Rehabilitation (CRIR), and informed consent was obtained from each participant.

Subjects participated in a step-by-step musical training consisting of three individual 1-hour sessions per week for 3 consecutive weeks, for a total of 9 sessions. The individual sessions were complemented with a home program consisting of biweekly piano exercises of 30 min duration. Synthesia, an MIDI piano program, was used to program and display the musical pieces played by the participants on the electronic piano keyboard (Yamaha P155) during the training sessions. The musical pieces involved all 5 fingers of the paretic hand, and participants were cued to press the piano key(s) indicated by the visual stimuli (illuminated, blue dot) presented on the computer screen. Nine musical pieces were created and were introduced to the participants in an increasing order of difficulty: (1) *simple*, or "following notes" involving movements of consecutive fingers; (2) *intermediate,* or third, fourth, and fifth intervals involving movements of nonconsecutive fingers; and (3) *complex,* which involves chords, that is 2 fingers played at the same time. Within each musical piece, the participants started at a tempo of 30 bpm. When reaching a note accuracy and timing score of 80%, as measured in Synthesia, the tempo increased by steps of 10% until reaching a tempo of 60 bpm. Home piano exercises were executed on a roll up flexible piano (Hand Roll Piano 61 K).

Changes in fine motor (nine hole peg test (NHPT)) and gross motor dexterity (box and block test (BBT)) were measured at multiple baseline time points ($week_0$, $week_3$), immediately prior to ($week_6$) and after the intervention ($week_9$), and at a 3-week follow-up ($week_{12}$). The Jebsen hand function Test (JHFT), which reflects the functional use of the hand, is time-consuming and was administered only at pre- and post-intervention, as well as follow-up. Piano performance measures, including timing and note accuracy, were collected with Synthesia throughout the training sessions. Participants recorded their home practice duration and frequency in a logbook.

3. Results

All participants showed improvements in note accuracy and timing accuracy within and across the training sessions. Participant 3 completed 3 musical pieces and the two others completed 5 pieces during the 3-week intervention. They progressed through finger sequences of increasing complexity, involving movements of consecutive fingers followed by movements of nonconsecutive fingers (intervals). Each musical piece started at 30 bpm and were practiced on an average of 25 times over 2 to 3 training sessions before reaching a note accuracy > 80% at 60 bpm. When considering a tempo of 60 bpm, the duration of musical pieces also increased from 17 s to 48 s (participants no. 1 and no. 2) and

from 17 s to 32.5 s (participant no. 3) between the first and last training session.

A mean increase of 6 blocks (range: 4–10 blocks) and a mean reduction of 24.8 s (16–31 s) were observed on the BBT and NHPT, respectively, between pre- and post-intervention (Figure 1). At variance, little variations were observed between baseline measurements at $week_0$ (BBT = 23.3; NHPT = 139.2 s) and $week_3$ (BBT = 24.7; NHPT = 134.8 s) and pre-intervention (BBT = 23.7; NHPT = 138.1 s). None of the participants were able to complete the writing subtest of the JHFT. The 3 participants, however, showed larger scores on all other subtests of the JHFT at post-intervention compared to pre-intervention, with mean increments ranging from 36.2% to 44.2% (Figure 1). Post-intervention scores for the BBT, NHPT, and JHFT were maintained at the 3-week follow-up. Average home practice duration was 50 minutes per session, which exceeded the 30 minutes practice time required. All participants reported enjoying the piano training program, and they all expressed the desire to continue piano lessons after their participation in the study. No adverse reactions to the intervention were reported, with the exception of one participant (no. 2) displaying occasional "hand stiffness" typical of spasticity during the intervention, as well as a fatigue described as a "general fatigue" after the training sessions. The stiffness was going away with frequent breaks, and the fatigue resolved within a few hours after the sessions.

4. Discussion

This case study is, to our knowledge, the first to report the immediate and retention effects of a structured piano training program combined to home practice in chronic stroke survivors. Improvements in fine and gross manual dexterity, as well as in the functional use of the hand, were observed in all three participants immediately after, but also at the 3-week follow-up. These changes were accompanied by improvements in the speed of execution, as well as in the timing accuracy and note accuracy for each musical piece. Such positive training effects are especially remarkable, considering that participants involved in this study were suffering from a chronic stroke and were exposed to an intervention of short duration. Similar improvements in manual dexterity were observed in a 3-week MST program involving piano and drum pad playing in acute stroke survivors [6], although changes in fine dexterity in the present study (NHPT: +24.8 s) do appear to exceed those reported in the combined drum-piano MST paradigm (NHPT: +13 s). Present results contrast, however, with findings from a case report involving the combined drum pad and piano playing intervention in chronic stroke survivors, where no changes on the NHPT and BBT were observed following the intervention [10]. We hypothesize that the impact on manual dexterity observed in the present study is attributed to the intensity and specificity of the piano exercises that were specifically designed to target dissociated and coordinated finger movements, with an emphasis on note and timing accuracy, as well as speed of execution. Rich feedback was provided to the participants throughout the supervised training session using a computerized program that provided knowledge of performance (note accuracy and timing) and knowledge of result (final speed and error score).

Comparison of present training effects with other existing upper extremity interventions in chronic stroke such as constraint-induced movement therapy is difficult, due to the use of different outcome measures and inclusion of participants with different characteristics. Present findings, however, can be interpreted in the light of the smallest real differences, or true changes, for the BBT (6 blocks) and the NHPT (32.8 s) [11]. Despite of their chronic stage, our participants either approached (nos. 1 and 3) or exceeded (no. 2) the smallest real difference on the BBT. Similarly, one participant (no. 1) almost reached the smallest real difference for the NHPT while the two others made more modest gains. These observations suggest that MST has the potential to yield real improvements in upper extremity function in chronic stroke participants with different levels of hand and arm motor recovery. The presence of an enhanced functional use of the upper extremity post-intervention also suggests that a better coordination of finger movements can impact on the upper extremity as a whole, and may be a prime target for rehabilitation. Finally, the persistence of positive effects at follow-up further indicates that improvements can be maintained even after the cessation of the training. Compared to other therapies such as constraint-induced movement therapy MST may be less time consuming and labor intensive. It has the potential to be safely self-managed and pursued well beyond the rehabilitation period, such that gains can be maintained or further enhanced.

MST relies on key principles of motor learning, including repeated and task-specific practice as well as the involvement of multisensory feedback, which gives instantaneous knowledge of result and performance. It would further take advantage of a rapid establishment of auditorimotor coactivation induced by the musical training [8], while engaging the participants in an individually tailored and rewarding program. Participant's remarkable adherence to the home practice sessions, which led to practice times beyond expectations, indicates high levels of motivation. This motivation, as well as a perception of being engaged in an enjoyable, socially valued leisure activity, are factors that may help patients pursuing musical lessons beyond the usual rehabilitation time frame.

The small sample size in this pilot study limits the generalization of results. Present results, however, support the feasibility of MST in chronic stroke and provide useful information that can be used to generate further hypotheses and design larger intervention studies. Longer-term benefits of the training on upper extremity function and quality of life should also be investigated.

5. Conclusion

This study provides preliminary evidence indicating that a piano training program combined to home practice is feasible and can lead to meaningful improvements in manual

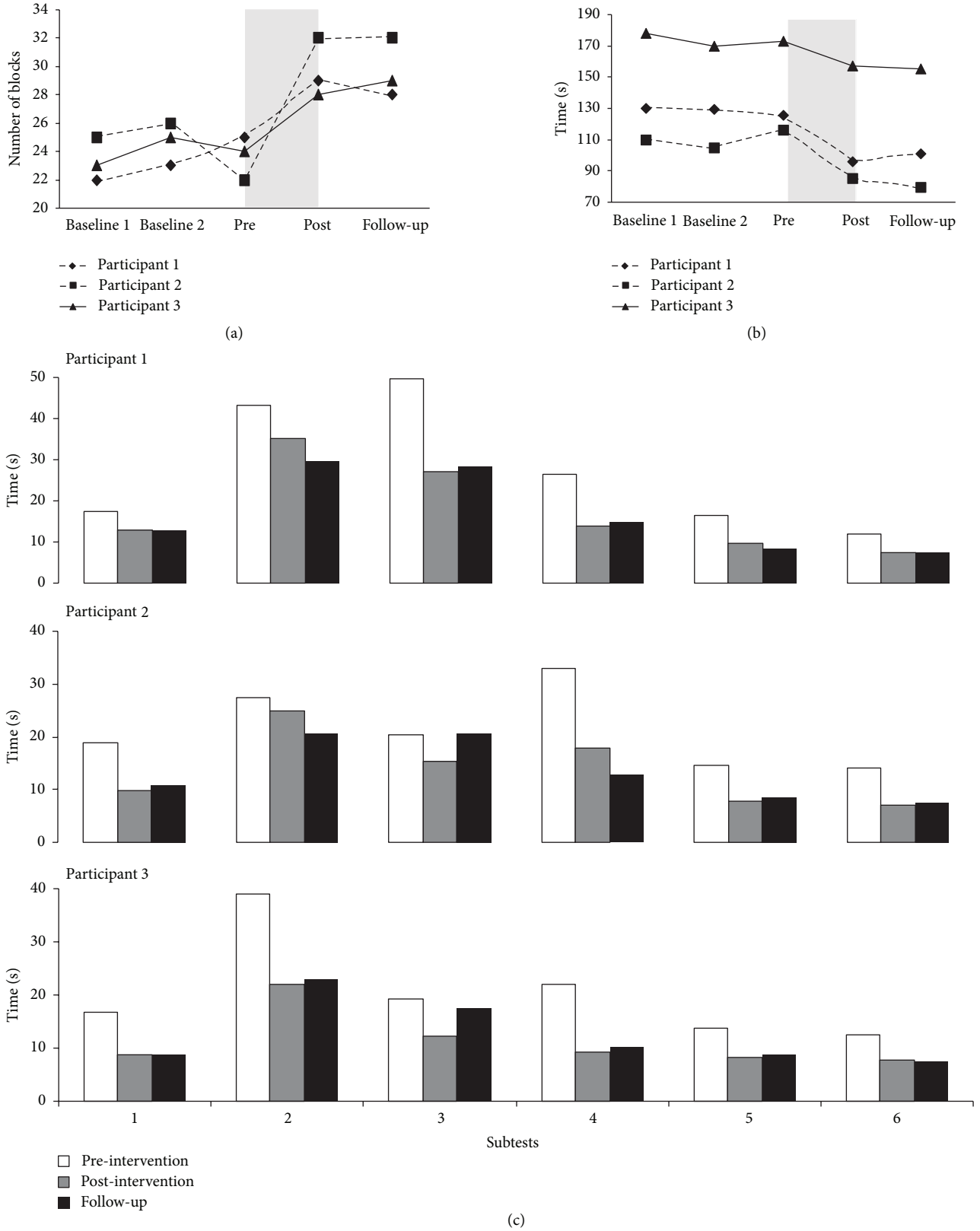

Figure 1: Scores of the three participants at different time points on the box and block test (a), nine hole peg test (b), and the Jebsen hand function test (c). For the box and block test, the scores represent the maximum number of blocks transported from one box to the other in 60 seconds. For the nine hole peg test, the time required to place and remove nine dowels into a nine holes is represented. For the Jebsen hand function test, the time required to complete the following subtests is shown: (1) simulating page turning; (2) lifting small common objects; (3) simulated feeding; (4) stacking checkers; (5) lifting large, light objects; (6) lifting large, heavy objects.

dexterity, finger movement coordination, and functional use of upper extremity in chronic stroke survivors. For the first time, it was also demonstrated that MST training effects are maintained at a 3-week follow-up. This unique intervention, which targeted finger movement coordination, engaged the participants in an individually tailored and highly motivating program. It has the potential to be self-managed and pursued on the long term, outside the rehabilitation setting, and lead to further and sustainable improvements in upper extremity function.

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