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Review

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Stroke care equity in rural and remote areas - novel strategies

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Abstract

Acute stroke is one of the most common causes of disability worldwide and numbers are projected to increase. Modern and successful recanalizing treatments are available, but timely access to these treatments is most often restricted to urban populations. This disparity affects nearly half of the world's population, particularly those living in rural and remote areas, and most often affects people with indigenous background. We provide information on this disparity in acute stroke care between rural, remote, and urban areas. We discuss potential new management strategies which could facilitate the timely delivery of acute stroke care to those residents beyond the better serviced urban areas. We focus on the concept of a mobile stroke unit (MSU), especially an Air-MSU. This aircraft solution could provide an imaging capability and immediate clinical expertise via linked telemedicine to diagnose and treat acute stroke patients at the emergency site. The Air-MSU is not only envisioned to allow intravenous thrombolysis in the field but also to allow pre-hospital triage to comprehensive stroke centres through use of contrast imaging to diagnose large vessel occlusion, facilitating endovascular thrombectomy. Moreover, issues regarding optimal operating environment as well as novel imaging and diagnostic devices, which could facilitate the implementation of an Air-MSU are discussed. Innovative health care solutions are urgently needed to close the treatment gap for stroke patients living in rural and remote regions worldwide.

Keywords: Air-MSU, remote areas, stroke treatment, pre-hospital stroke management, stroke thrombolysis, thrombectomy

INTRODUCTION

Stroke and global effects

Stroke is the second most common cause of death and accounts for 12% of all deaths worldwide. Projections by World Health Organisation for 2016 to 2060 do not predict any improvement. While some areas of the world, such as America and Europe, might see a drop in their numbers, others, like Africa and Western Pacific regions are expected to face an increase in stroke deaths[1].

Currently, there are approximately 80 million stroke survivors globally, and due to population growth and aging, this number is predicted to increase dramatically. Stroke is the leading contributor (42.2%) to disability-adjusted life-years, which is the sum of years of life lost and years lived with disability. This number is also predicted to increase[2].

Despite significant advances in new therapies to treat stroke, one of the most important challenges in stroke management today is the delivery of these therapies to rural and remote areas. Access to the most effective therapies, thrombolysis or thrombectomy, for patients with acute ischaemic stroke has become a "postcode lottery." In other words, the geographical location of residence defines the available access to acute stroke, leading to an unacceptable inequity of opportunity. This applies not only to developing nations, but also to some of the wealthiest countries. Even in well-resourced regions, there are surprising problems in health care delivery and equitably to all people regardless of location. It is important to recognize that 44 % of the world's population lives in rural and remote areas with only limited access to high-quality stroke care[3]. This is often most markedly affecting those of indigenous background[4,5].

Where you live defines what you get

Delivery of the three major evidence-based acute ischaemic stroke treatments, which strongly influence mortality and disability - treatment on a stroke unit, thrombolysis in ischaemic stroke, and endovascular thrombectomy for those with large vessel occlusion - is challenging in areas with a low population density. It is known that the distance to the nearest stroke centre is a crucial factor for delivery of timely stroke treatment[6,7]. Reported times from symptom onset to admission to rural hospitals range from 5-30 h[8,9]. These pre-hospital delays have subsequently been attributed as a major driver of the very low thrombolysis rates of only 1%-6% for patients in rural areas worldwide[10-12]. This contrasts with rates of 20%-25% in metropolitan stroke centres. The decisions about the type of care and how access to acute care will be achieved is most often dominated by the question of cost efficiency rather than need. The reality is that patient numbers in these rural and remote areas are often too low to enable an economically viable service. This, together with the view that the individual preference and decision to live in rural/remote areas should not increase health care costs of the whole society, impedes process improvement.

The quality of acute stroke management varies between countries, but interestingly, also within regions of individual countries. This not only applies to middle- or low-income countries, which lack the financial resources to establish high-quality care for what is, in reality, only a few people, but also to high income countries.

Good examples of this are Australia and Canada, both high-income nations with the lowest population density globally (3 and 4 inhabitants/km^2 respectively). In Australia, only 3% of the acute stroke patients in rural regions are able to access a stroke unit compared to around 70% in urban regions, many of them travelling over 200 km to reach a hospital with adequate stroke care[13,14]. Further, the majority of patients living in rural areas world-wide are less likely to receive brain imaging within 24 h, carotid imaging, or consultation with a stroke physician. In Australia, most emergency retrievals are performed by the Australian Royal Flying Doctor Service (RFDS), the largest such aeromedical retrieval service world-wide, with a fleet of almost 80 aircraft. In a recent study, it was found that most retrieval locations lacked brain imaging capability, significantly delaying stroke diagnosis and treatment[15]. An unpublished analysis of access to radiological imaging in Australia shows that hospitals with computed tomography (CT) scanners are mainly located in the south-eastern coastal areas [Figure 1], leaving many areas lacking service. The lack of imaging availability in rural and remote areas directly translates to a lower number of patients receiving the modern, time sensitive stroke interventions enjoyed by urban Australians. This paucity of service intervention is particularly important in the case of endovascular treatment, one of the most effective interventions in modern medicine, which can only be performed at highly specialised stroke centres[16]. Most of these comprehensive stroke centres are located in metropolitan centres[17].

In Canada, the numbers are similar where 20% of the Canadian population lives in rural areas[18]. Only 11% of the rural hospitals in Canada are equipped with a CT scanner, and 40% of these rural hospitals are more than 300 km from a comprehensive stroke centre. Access to acute stroke service strongly depends on the area of stroke incidence. A recent geospatial analysis has shown that in some areas, such as Saskatchewan, Newfoundland, and Labrador, less than half of the population could reach a stroke centre within 3.5 h with emergency transport[19]. Not surprisingly, the 30-day stroke mortality is higher for patients treated in rural compared to urban hospitals[20,21].

This geographical inequity in acute stroke care is not a problem which is likely to improve in the near future. A recent analysis of the rural *vs.* urban disparity in stroke thrombolysis, including 914,500 acute ischaemic stroke patients in the USA, revealed that geographic disparity in alteplase use is actually increasing[22]. This emphasises the need to narrow this unacceptable gap with novel disease management ideas and strategies. While the strategies suggested in this review are being, or more likely to be, implemented in developed nations, the lessons learned may become quite relevant for developing nations.

MOBILE STROKE UNITS - A HYPERACUTE SOLUTION FOR HYPERACUTE STROKE TREATMENT

Mobile stroke units (MSU) are acute specialist ambulances, equipped with computed tomography (CT) scanners, point-of-care laboratory units, and telemedicine capabilities for interaction with experts in the hospital. They have been implemented to enable immediate diagnosis and administration of thrombolysis for eligible stroke patients directly at the emergency site[23,24]. In many countries, pre-hospital stroke diagnosis and treatment have validated this MSU concept. Randomised studies have shown that MSU-based stroke management can reduce the time to treatment and substantially increase the number of treated patients. More importantly, golden hour thrombolysis, namely treatment within the first 60 min after symptom onset, with highest chances of full recovery, is far more commonly achieved in the MSU group compared to the control group[25-27]. Indeed, a recent prospective interventional study (B-Proud) with acute ischaemic stroke patients showed that the dispatch of a MSU was significantly associated with a better clinical outcome as assessed with the modified Ranking score after 90 days[28].

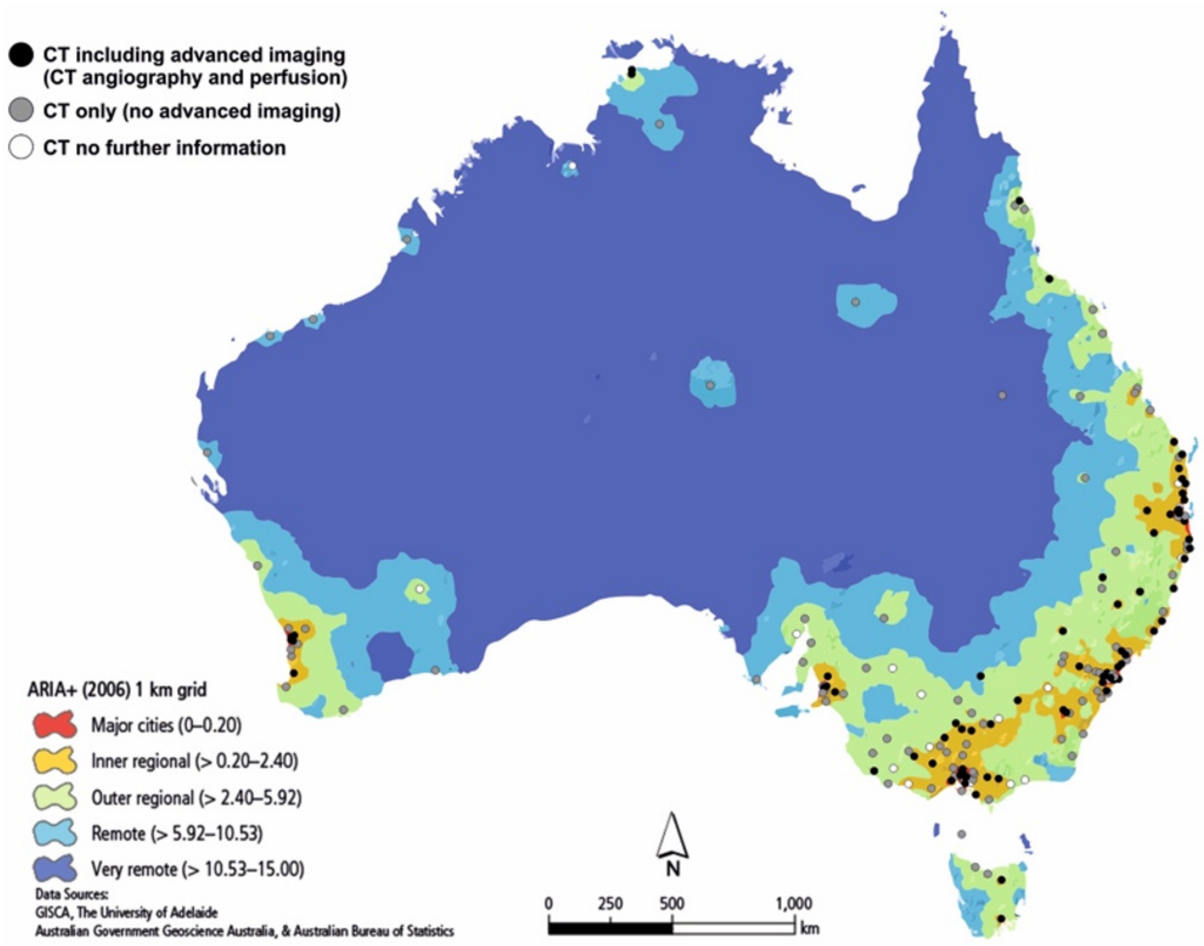

Figure 1. Example of access to stroke imaging in Australia. Hospitals with multi-modal computed tomography (CT) imaging availability are indicated by black circles. Grey circles represent hospitals with non-contrast CT scans possibility only. Imaging is mainly available in the area of higher population density in the south east of the country.

In addition, with the possibility to perform a CT angiography directly at the emergency site, MSUs have the potential for diagnosis-based triage decision-making at the emergency site[25,29]. Correct triage allows patients to be delivered much faster to centres where catheter-based treatment for thrombectomy for large vessel occlusion can be carried out. This can positively impact their clinical outcome.

DEVELOPMENT OF AN AIR-MSU - A POTENTIAL SOLUTION FOR RURAL AND REMOTE STROKE TREATMENT ACCESS?

The concept of using a MSU for stroke assessment with optimised triage and treatment initiation at the emergency site could represent a novel acute stroke management strategy for rural and remote areas. The concept would need adjustment for these areas to match the need for a timely access to hyperacute care. The implementation of the MSU concept in an aircraft might represent an alternative way to deliver acute stroke care to underserviced areas.

As an extension of the specialist care the RFDS delivers in Australia, discussions about an Air-MSU have evolved recently[30]. The concept involves an airplane or helicopter Air-MSU equipped identically to a MSU road ambulance with multimodal imaging capabilities, a point-of-care laboratory, and a telemedicine connection to a stroke specialised centre so that stroke patients in remote regions could obtain diagnosis and treatment at the emergency site. The large Victorian Stroke Telemedicine project, a state-wide programme to establish access to acute stroke thrombolysis in non-specialised regional hospitals has demonstrated that the delivery of acute remote stroke specialist support can be safely implemented[31].

The advantage of a helicopter solution is the potential for rapid activation (no runway needed) and the direct landing possibilities on hospital helipads. A fixed-wing aircraft, however, would be able to cover a much wider area of approximately 5000 km in radius with a shorter flying time.

There are different settings in which such an Air-MSU could be beneficial and it can be assumed that the daily operation of such an Air-MSU would need to have a high level of flexibility, mainly because constant changes are likely to occur in the setting depending on the actual emergency call and situation on scene. An Air-MSU could be used in a similar way to a road MSU as a first responding ambulance directly dispatched to the patient. The team would then function as first emergency medical team for the patient, independent of the actual medical condition. The disadvantage of this arrangement is that the crew is then locked into the current event and therefore might not be available for other even more deserving calls. For example, a stroke patient who may be suitable for early therapeutic intervention appears while the current call turns out to be a stroke-mimic.

Alternatively, the Air-MSU could operate in a rendezvous system and meet the patients en-route once a first local emergency medical service crew has clinically confirmed the stroke diagnosis. This setting is dependent on the availability of the local emergency medical service and might vary from day to day. The advantage is not only that the diagnosis accuracy of the stroke call is higher for the Air-MSU team but also that there would be additional help available to manage a difficult scene.

In both scenarios an acute stroke treatment with intravenous thrombolysis, could be initiated at the emergency site, saving crucial time for the patient.

A third scenario would be an inter-hospital transfer of patients from local hospitals/health care centres to stroke specialised centres. A recent publication of the RFDS stroke retrieval calls in rural Australia describes more than 1700 retrieval flights for acute stroke patients in a period of 4 years with a median flight distance of 291 km per patient and a median transfer time of 238 min. The subtype of the stroke was not categorised for most of these patients as CT scanners were not available[32] so that a specific therapy such as intravenous thrombolysis could not be started. Most of these transfers were time consuming with an attendant delay such that patients were usually outside their treatment time window once arriving at the stroke centre[15]. In this situation, the Air-MSU could provide immediate stroke diagnostic assessment and treatment initiation before transferring the patient to the required level of stroke care.

However, all these scenarios depend on an accurate direct dispatch of the Air-MSU and the first team involved to develop a likely working diagnosis of an acute stroke including treatment eligibility. This is one of the significant hurdles in the delivery of acute stroke care, as well as in standard stroke management. Inappropriate activation of a specialised stroke team reduces its targeted capacity for those likely to benefit. This is even more relevant when the specialised stroke team has long distances to travel for patient retrieval as would be the case with an Air-MSU approach. Hence, an appropriate implementation of such a novel system of care would require an optimised pathway to identify relevant patients. This would include an embedded, country- and region-specific education programme, not only for the dispatch centres, but also for the local emergency medical service, healthcare centres and every other link in the chain. Specialised training may include the implementation of specific stroke dispatch criteria, dispatch call monitoring[33], telemedicine to triage cases prior to activation and use of more accurate stroke scales[34]. The challenge should ideally be nation-wide and involve government with initiatives such as "calling stroke a national priority"[35].

Another main hurdle in the implementation of an Air-MSU for acute stroke care in geographically large, underserviced areas is the significant development necessary to integrate a CT scanner on board a flying ambulance. Alternate imaging devices for diagnosis and differentiation of the different stroke subtypes should, therefore, be considered and may be equally advantageous in acute stroke management.

ALTERNATIVE STROKE ASSESSMENT OPTIONS - AN ALTERNATIVE TO A CT SCANNER

In recent years intensive research has been undertaken to investigate new, lightweight, portable, and affordable devices with the aim of making a fast and accurate on-site diagnosis. Pilot protypes of devices being currently developed aim to reduce weight from around 500 kg to 50-100 kg. Many of these are newly developed imaging devices with a focus on identification of intracranial changes after brain trauma, such as subdural haematoma or deterioration due to brain edema hours to days after stroke symptom onset, when structural changes are more easily detectable[36]. Only few devices have been developed which have the potential to differentiate ischaemic *vs.* haemorrhagic strokes within the first hour after symptom onset. This differentiation is the most critical goal, given that administration of thrombolysis could be catastrophic in intracerebral haemorrhage. One of these is using a microwave technique, which can detect changes in the electrical properties of brain tissue due to change in blood flow, water content, and temperature with a high sensitivity. In early clinical tests, the ability of microwaves to differentiate haemorrhagic stroke from ischaemic stroke was described with an area under the curve of 0.85-0.88[37]. Further research is necessary to increase the understanding and the potential area of usage for this novel diagnostic strategy and as to whether the sensitivity and specificity are high enough for clinicians to confidently exclude the presence of blood to enable thrombolysis remains to be seen.

The CT scanner currently used in most mobile stroke units weighs at least 500 kg. There is the potential for the development of light-weight portable CT scanners using novel, non-thermionic nanotube technology. This allows miniaturization of the scanner and has no moving parts. This is another exciting research avenue for road and air transport platforms, to serve rural and remote populations[38].

It is well known that intracranial large vessel occlusions can be visualized with a transcranial ultrasound technique[39]. Special ultrasound devices combining artificial intelligence, robotics, and automated cerebral ultrasound are under development to enable an operator-independent tool to identify acute stroke[40]. Mobile transcranial ultrasound has been shown to identify an acute anterior large vessel occlusion stroke with a sensitivity of 78% and specificity of 98%[41].

Specific biomarker analysis is an alternative point-of-care blood test, which could be an ideal tool for a pre-hospital stroke assessment. The STROKECheck device uses the identification of the biomarkers GFAP, RBP-4, and NT-proBNP to differentiate ischaemic stroke including large vessel occlusion from haemorrhagic strokes and stroke mimics. The device is currently being investigated in a pre-hospital trial (Biomarkers for Initiating Onsite and Faster Ambulance Stroke Therapies, Bio-FAST, ClinicalTrials.gov Identifier: NCT04612218) in southern Europe. First results of 90 participants showed that 84% of ischaemic stroke patients could be identified with the biomarker device without incorrect identification of intracerebral haemorrhage[42]. Table 1 gives a summary of the above mentioned novel diagnostic tool with available evidence and ongoing clinical trials.

Table 1. Novel stroke diagnostic tools for stroke diagnosis in the hyperacute phase

Device	Mode of action/aim	Evidence	Pro/Cons	Ref.
Lightweight CT scanner	- Non-thermionic nanotube technology - Differentiation of ischaemic *vs.* haemorrhagic stroke *vs.* stroke mimic	- No clinical data available	- Detection of other brain diseases possible - May be able to include perfusion imaging - Possibly more expensive	[38]
Microwave technique	- Detects dielectric contrast between tissues (in stroke: contrast between blood and grey and white matter) - Differentiation of ischaemic *vs.* haemorrhagic stroke	- Early clinical studies: area under the curve of 0.85-0.88 - Phase II/III trial: "Mobile Microwave-based Diagnosis and Monitoring of Stroke: on the Road Towards Improved Stroke Triage and Care, Including Prehospital Initiation of Thrombolytic Treatment," currently recruiting, completion expected Feb 2022	- Identification of stroke mimicking diseases not possible - Low cost - No perfusion imaging	[37] MODS trial: ClinicalTrials.gov Identifier: NCT04257149
Mobile transcranial ultrasound including robotics and artificial intelligence	- Ultrasound detection of occlusion signal - Differentiation of large vessel occlusion ischaemic stroke	- Sensitivity of 78% and specificity of 98%	- No stand-alone diagnostic tool	[40-41]
Blood biomarker: glial fibrillary acidic protein (GFAP), retinol binding protein (RBP-4) and NT-proBNP[4]	- Blood point of care test - Differentiation of ischaemic *vs.* haemorrhagic stroke (*vs.* stroke mimic)	- First results STROKECheck device (GFAP, RBP-4, NT-proBNP), Bio-FAST trial): 84% of ischaemic stroke patients could be identified	- Accuracy in early hours after symptom onset unclear	[42] Bio-FAST trial: ClinicalTrials.gov Identifier: NCT04612218
		- GFAP: meta-analysis (1297 participants) with sensitivity of 0.756 (95%CI: 0.630-0.849), specificity of 0.945 (95%CI: 0.858-0.980), and subgroup time from symptom onset to GFAP measurement of 0-60 (235 participants); sensitivity ranges from 0.00 (95%CI: 0.00-0.97) to 0.89 (95%CI: 0.65-0.99), and specificity from 0.94 (95%CI: 0.83-0.99) to 1.00 (95%CI: 0.83-1.00)		[43]
		- GFAP + RBP-4: patients with ICH who had RBP4 < 48.75 microg/mL and GFAP > 0.07 ng/mL: sensitivity = 32%, specificity = 100%		[44]
		- Open label non-randomised, prospective, pre-hospital trial: "Prehospital Advanced Diagnostics and Treatment of Acute Stroke" to define cut-off values for GFAP and RBP4		Treat-NASPP: ClinicalTrials.gov Identifier: NCT03158259Formularende

MODS: Mobile Microwave-based Diagnosis and Monitoring of Stroke: on the Road Towards Improved Stroke Triage and Care, Including Prehospital Initiation of Thrombolytic Treatment; GFAP: glial fibrillary acidic protein; RBP-4: retinol binding protein; NT-proBNP: N-terminal pro B-type natriuretic peptide; Treat-NASPP: Prehospital Advanced Diagnostics and Treatment of Acute Stroke.

If alternative therapeutic devices shall find a place in acute stroke diagnosis in future, it is likely that several different technologies will need to be combined to allow a more precise diagnosis. However, all of these devices are likely to be small and light enough to be easily transported to acute stroke patients in rural and remote areas, enabling faster diagnosis and timely initiation of treatment.

CONCLUSION

Patients with stroke in rural and remote areas around the world have an unacceptable inequity in access to acute treatment compared to their urban counterparts. New approaches are urgently needed to overcome this service delivery gap. The concept of an Air-MSU "bringing the stroke treatment to the patient" and linked to telemedicine services may be a novel solution to allow diagnosis of stroke patients at the emergency site. This is likely to facilitate faster triage and initiation of acute stroke treatment. The mobility and flexibility of the Air-MSU concept may present a superior strategy to the more obvious and traditional approach of overcoming tyranny of distance by establishing more on-site stroke capable health care facilities. The development of novel diagnostic imaging and diagnostic tools may help reduce the cost of implementation of an Air-MSU service. While early implementation is more likely in developed countries, and further research is needed to understand the optimal technical and clinical settings, lessons learned may later become important for developing nations. Also, careful cost benefit analysis for the individual settings will be needed, which not only addresses the overall benefits but also the question of availability of resources, costs of implementation, and financial sustainability, which are crucial factors for most countries worldwide.

DECLARATIONS

Authors' contributions

Wrote drafts of the manuscript, conceptualized ideas, provided inputs for all aspects of the manuscript preparation and of the scientific content and reviewed the manuscript: Walter S, Easton D, Schwarz M, Zhao H, Davis SM, Donnan GA

Conceptualized ideas, edited and critically reviewed and discussed the manuscript: Fassbender K, Gardiner FW, Langenberg F, Dos Santos A, Bil C, Fox K, Bishop L, Coote S, Middleton S, Bladin C

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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