Ischaemic stroke and ST-segment elevation myocardial infarction: fast-track single-stop approach

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Introduction

Acute ischaemic stroke (AIS) is a devastating disease associated with high morbidity and mortality, ranking 2nd single most common cause of death in Europe1 and 4th cause of death in the USA.2 Based on the 2014 American Heart Association statistic, 795 000 US Americans experienced a stroke annually, 87% related to ischaemic, and 10% to haemorraghic events with 3% related to sub-arachnoidal bleeding.3 According to the current guidelines, systemic fibrinolysis is reserved for patients treated within 3 h after the onset of ischaemic symptoms (recommendation I/A) or within 3–4.5 h after the onset of achaemic symptoms (recommendation I/B). Intra-arterial fibrinolysis is recommended for patients who are not candidates for systemic fibrinolysis within 6 h after the onset of ischaemic symptoms (recommendation I/B). Mechanical thrombectomy is reserved for patients who have contraindications for systemic fibrinolysis (recommendation IIa/C) or as a rescue procedure in patients with large-artery occlusion who have not responded to intravenous fibrinolysis (recommendation IIb/B). The usefulness of (primary) intracranial angioplasty and/or stenting is considered ‘not well established’, and if these techniques are employed they should be used in context of clinical trials (IIb/C); however, these 2013 guidelines lag behind the current evidence (see below).3

Utilization of revascularization therapy in patients with AIS is low; < 5% of all patients admitted with AIS receive systemic fibrinolysis and the use of catheter-based therapy is even less.4 In contrast, according to the guidelines the vast majority of patients with ST-segment elevation myocardial infarction (STEMI) receive primary percutaneous coronary intervention (PCI) defined as percutaneous catheter intervention in the setting of STEMI, without previous fibrinolysis’ as a first-line treatment ‘provided it can be performed in a timely manner in high volume PCI centers with experienced operators and 24-hour, 7-day catheterization laboratory activation;5 conditioned on availability of PCI centers.

Here, we briefly compare the interventional approach to AIS and STEMI and suggest a novel fast-track approach to AIS management.

Ischaemia and reperfusion tissue damage and salvage

The degree and extent of the ischaemic and reperfusion tissue injury of an organ depends on factors such as the duration of ischaemia, metabolic rate, status of collaterals, and preconditioning.6 Based on experimental evidence largely obtained in rodents in brain tissue, three critical levels of cerebral blood flow (CBF) reduction have been defined; first, ca. 70–80% of normal CBF, corresponding to 50–55 mL/100 g/min inhibition of protein synthesis occurs; second, ca. 50% of normal CBF, corresponding to ca. 35 mL/100 g/min, lactic acidosis, and cytotoxic oedema develop; third critical, ca. 30% of normal CBF, corresponding to ca. 20 mL/100 g/min, depletion of adenosine-tri-phosphate, and breakdown of metabolism and functions occur. With reperfusion, the initial transient hyperperfusion is followed by prolonged hypoperfusion partly due to the no-reflow phenomenon. The ischaemia-reperfusion state is accompanied by progressive microvascular-cellular damage. Based on the degree of CBF reduction the necrotic core (CBF < 10 mL/100 g/min; irreversible brain tissue damage) and ischaemic penumbra (CBF > 20 mL/100 g/min; functional reversible brain tissue damage) can be differentiated (for review, see Ref. 7). The current perfusion computed tomography (CT) allows reliable distinction between penumbra and ischemic core.8

The penumbra represents tissue at risk susceptible to the dynamic ischaemia-reperfusion injury (IRI); the key determinant of the width of the therapeutic window. Ischaemia-reperfusion injury is typically associated with transient hyperperfusion, no-reflow, loss of autoregulation, disruption of the blood–brain barrier (BBB), formation of cytotoxic (intracellular) and vasogenic (extracellular) parenchymal oedema and risk of haemorrhagic transformation...
and other phenomena, all related to the activation of the complex biological cascades (for review, see Ref. 9). Thus, while the ischaemic penumbra corresponds to the maximum potentially salvageable brain tissue at a given point of time (moving target of interventions) the maximum tissue salvage is rarely achieved due to progressive character of IRI, and in case of intervention the risk of procedure-related injury. In addition, the ultimate tissue salvage shall depend on modifying individual factors; foremost individually highly variable availability and efficacy of primary and secondary collateralars,\textsuperscript{10,11} but also reactivity of brain tissue’s neuro-immune-endocrine systems, pre-strokes status, ischaemic preconditioning, and topography of the lesion.\textsuperscript{12,13}

Necrotic core and ischaemic penumbra in AIS correspond to myocardial necrosis and myocardium at risk in STEMI patients. Experimental data obtained in dogs suggested that myocardium subjected to coronary blood flow (CoBF) reduction even down to ca. 30 mL/100 g/min (normal CoBF ca. 110 mL/100 g/min) may be salvageable. Following complete sudden occlusion of a coronary artery irreversible myocardial ischaemic injury develops within 20 min in the inner layer of the myocardium and proceeds in a wave-like fashion towards the epicardium to be completed within up to 3–4 h. Brief periods of myocardial ischaemia may be associated with prolonged dysfunctional yet reversible states such as stunning and hibernation. Similar to AIS salvage of the myocardium at risk in STEMI is limited due to IRI and risk of procedure-related factors (for review, see Refs. 14,15).

Although both, AIS and STEMI, are caused by sudden complete arterial blockage important differences exist. First, AIS are mostly caused by distal emboli\textsuperscript{16} while STEMIls are typically caused by local thrombi,\textsuperscript{17} the former with highly different material composition\textsuperscript{18,19} affecting the site and distribution of embolization\textsuperscript{20} and possible differences in the fibrinolytic and mechanical properties, not yet studied. Second, damage to BBB is far more detrimental, particularly due to the formation of vasogenic parenchymal oedema and risk of intra-parenchymal haemorrhage\textsuperscript{21,22} compared with the frequently less deleterious endothelial myocardial damage.\textsuperscript{23} Third, the collateral networks of the brain are more efficient compared with those of the myocardium.\textsuperscript{24–27} Fourth, in the brain the topography and the size of the ischaemic lesion determine the outcome and prognosis (for review see Ref. 28) while in the myocardium largely the size alone is decisive determinant of prognosis in STEMI patients.\textsuperscript{29,30} For the outcome of interventional treatment particularly in AIS patients, the presence of the individual modifying factors (see above) appears also critical.

Reperfusion interventions

In patients with AIS systemic fibrinolysis was firmly established based on the National Institute of Neurological Disorders and Stroke (NINDS)\textsuperscript{31} and the European Cooperative Acute Stroke Study (ECASS)\textsuperscript{32} trials in mid-1990th after initially promising\textsuperscript{33} yet later rather disappointing results.\textsuperscript{34–36} Despite benefits of intra-arterial fibrinolysis\textsuperscript{37,38} has remained second-line treatment based on current guidelines.\textsuperscript{3} To achieve mechanical revascularization initially balloon angioplasty\textsuperscript{39} and stenting\textsuperscript{40} were employed. Subsequently, intracranial blood clot removal have been marketed\textsuperscript{41} and tested in clinical trials with positive\textsuperscript{42–45} and negative\textsuperscript{46–48} results. However, in recent carefully designed randomized trials clear benefits of mechanical thrombectomy over standard care have been demonstrated (Figure 1).\textsuperscript{49–51} Figure 2A–C provides an example of a successful revascularization of the right middle cerebral artery using the stent-retriever technology.

In patients with STEMI systemic fibrinolysis was introduced in 1970th\textsuperscript{52} and in 1980th firmly clinically established following a series of successful early trials.\textsuperscript{53,54} Although proven effective\textsuperscript{55,56} intra-coronary fibrinolysis has been subsequently largely abandoned because cumbersome without offering clear benefits over the systemic application. Following introduction for emergency cases\textsuperscript{57,58} balloon angioplasty has proven superior to systemic fibrinolysis in numerous randomized trials\textsuperscript{59–61} only to be later replaced by stenting.\textsuperscript{62–64} Nevertheless, scientific discussions regarding the optimum interventional strategy in acute STEMI settings concerning issues such as timing of stenting\textsuperscript{65} and use of thrombus aspiration\textsuperscript{66} are still ongoing. Figure 3 demonstrates the timeline of interventional therapy in AIS and STEMI settings.

Technical aspects

The need of embolus retrieval in AIS settings makes the use of dedicated devices such as the clot retrieval stents (see Appendix) mandatory. Retrievable stents are delivered via micro-catheters frequently requiring co-axial support catheters for safe delivery. Balloon dilatation or stenting are usually not required. To restore patency several thrombectomy passages are usually needed. The main technical challenges consist in dealing with tortuosities and
complex lesions such as long dissections, tandems, and complex carotid-T lesions. In some cases, general anaesthesia (GA) may be needed. Acute stroke intervention without GA has two main advantages: (i) short door-to-groin puncture time (GA causes usually 20–60 min delays) and (ii) possibly also better outcomes (due to shorter delays and avoidance of GA risks). Patients undergoing mechanical thrombectomy should receive systemic fibrinolysis prior to the intervention based on current guidelines (3).

In STEMI cases conventional instrumentation including over-the-wire balloon catheters or micro-catheters, dilatation balloon and stent are employed. The use of adjunct pharmacological agents, thrombus aspiration catheters, covered stents or thrombo-embolic protection umbrellas remains optional. While potentially beneficial, residual role of systemic fibrinolytic treatment concerns patients in whom PCI cannot be delivered within 90–120 min based on current guidelines.5

**Metrics**

To assure the quality of the catheter-based treatments standard of therapy have been developed for both, AIS72 and STEMI, settings. Thrombolysis in cerebral infarction flow grades IIb/III and thrombolysis in myocardial infarction flow grades, respectively, represent the targets in AIS73–76 and STEMI interventions.77,78 The AIS and STEMI interventions are usually performed by neuro-interventional radiologists and interventional cardiologists, respectively. While the training requirements for AIS treatments have not yet been internationally established, for STEMI treatments they have been defined.79,80

**Rationale for the streamlined fast-track single-stop approach**

Rationale for the streamlined fast-track single-stop approach is based on five main precepts. First, recent evidence suggests better clinical outcome in AIS patients treated by mechanical thrombectomy compared with the current approach.49–51 This advantage should be further explored and exploited. Second, duration of ischemia represents the key determinant of the severity of the resulting IRI and the opportunity of the therapeutic window.81 The symptom onset-to-revascularization time and even more pressingly the door-to-revascularization time must be dramatically reduced. Third, new data confirms the critical importance of individual factors, predominantly the status of the collateral networks, significantly modifying the viability of brain tissue.10,11 Therefore, determination of the therapeutic window should be based on individual criteria including the status of collaterals. Fourth, broad interventional expertise within the cardiology community is available, and could be activated, provided an extensive dedicated training build upon the existing procedural skills developed in carotid artery stenting.82 Fifth, logistics and regional catheterization laboratory networks providing 24/7 services are available and could be potentially modified to accommodate a second tier.

**Opportunities to meet**

Based on experience, the onset of symptoms-to-door time accounts for ca. 40% and the ‘door-to-revascularization time’ accounts for ca. 60% of the entire time span, i.e. ‘symptom-to-revascularization time’. In the latter, the time required for diagnostics accounts for ca. 40% and that for therapy ca. 60%. To shorten the ‘symptoms-to-door time’...
Figure 3  Timeline, interventional Therapy in STEMI and ischemic stroke patients, 1976–2015 (see also references).
time' community alert and public awareness must be improved. To shorten the 'door-to-revascularization time', diagnostics and therapy can be merged, operators and interdisciplinary teams can be trained, and continuous quality control and strict logistics concerning all professionals involved can be introduced and maintained.

With the emergence of the new imaging technology employing rotational angiography allowing CT-like 3D-image reconstruction comparable information with conventional CT may be acquired in a single step process including high-resolution cerebral angiograms. In addition, while imaging is taking place in the angiography suite, the operator may proceed with mechanical thrombectomy with no further delay. More specifically, during a single/double 200° rotation ~800 images are acquired. The raw digital data set with a spatial resolution of 0.103 mm²/voxel (down to 0.01 mm²/voxel) and grey scale resolution of 5 HU (down to 3HU) is reconstructed using a dedicated cone-beam reconstruction algorithm to generate high-resolution images of the brain parenchyma and brain vessels. Depending on the analytical software tools anatomic or functional perfusion images can be calculated allowing CT-like definition of ischaemic and/or haemorrhagic brain tissues, cerebral perfusion, and cerebral extra- and intracranial (lepto-meningeal) collaterals. Image acquisition and image reconstruction time for the entire data set are ~12–20 and ~30 s, respectively. On-site imaging with immediate interventional option should clearly reduce the 'groin-puncture to revascularization time'. In addition, and equally importantly, the suitability of individual patients and individual target sites and target lesions for the interventional approach can be determined in real-time on-site.

The 'groin puncture-to-revascularization time' can be shortened by improving the devices and by dedicated training of the operators. Technological progress depends on industrial efforts and is to be expected. Dedicated curriculum to train operators to perform intracranial interventions limited to the treatments of AIS would need to be discussed in interdisciplinary forum and based on consensus developed and established. According to the anecdotal evidence from the UK between April 2013 and March 2014, a total of 295 procedures in 21 hospitals were registered.84 This low number of procedures would prevent adequate training of sufficient number of operators regardless of specific background. Data from interventional cardiology provide unequivocal evidence for significant relationship between procedural volumes performed by individual operators and by their institutions.85 Because intracranial interventions belong arguably to the most advanced and technically demanding catheter-based cardiovascular interventions only expert operators regardless of specific training background shall receive procedural privileges.

Increasing availability of hybrid-theaters86 designed for interdisciplinary use of cardiovascular specialists, frequently equipped with the rotational angiography, represent the ideal hosting environment for interventional management of stroke patients. Single-stop diagnostic and, when indicated, interventional therapy represents the most advanced workflow to date. The current practice of interdisciplinary collaboration exemplified by heart teams5 provides promising guide to form teams of AIS experts.

Open issues

Comprehensive management of patients with AIS requires 24/7 availability of interdisciplinary teams of specialists with complementary expertise. The required core expertise includes neurologists, neuro-radiologists, interventionists, anaesthesiologists, intensive care specialists, and neuro-surgeons. Development of functioning interdisciplinary teams shall be one of the key determinants of success of the streamlined fast-track single-stop strategy and sensible approach to deal with upcoming, potentially controversial issues shall be required.

Streamlined fast-track single-stop approach established within the framework of comprehensive stroke management and care shall require 24/7 availability of interdisciplinary teams, increased utilization of interventional procedures, greater need for post-procedural intensive and post-stroke care. Cost calculation shall become critical issue to assure long-term costs of this new kind of AIS treatment. Finally, to improve outcomes better understanding of the pathophysiology and the time-course of IRI shall be required not as an end to itself but mainly to improve selection criteria for interventional therapy and to assess the procedural risk of individual patients.

Summary

Current management of patients with AIS relies primarily on conservative approach. Suggested streamlined fast-track single-stop approach should expedite the workflow and improve clinical outcomes. Given the broadly available interventional cardiology expertise cardiologist should play an active and sensible role in the development of new interventional concepts of care of patients with acute ischaemic stroke.

Appendix

Marketed and CE-certified stent-retrievers for mechanical intracranial thrombectomy

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>CE certificate</th>
<th>Main features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trevo ProVue</td>
<td>Stryker Neurovascular, Fremont, U.S.A.</td>
<td>October 16, 2012</td>
<td>Self-expanding, non-detachable, nitinol, closed cell design, 3 x 20 mm, 4 x 20 mm, 6 x 25 mm</td>
</tr>
<tr>
<td>pReset/pReset LITE</td>
<td>Phenox, Bochum, Germany</td>
<td>May 13, 2014</td>
<td>Self-expanding, non-detachable, nitinol, closed cell design, 3 x 20 mm, 4 x 20 mm</td>
</tr>
<tr>
<td>Solitaire™ FR/ Solitaire™ 2</td>
<td>Covidien, Mansfield U.S.A. (since January 2015 Medtronic, Minneapolis, U.S.A.)</td>
<td>September 9, 2009/ March 13, 2013</td>
<td>Self-expanding, non-detachable, nitinol, closed cell, open slit (parametric) design, 4 x 15 mm, 4 x 20 mm, 6 x 20 mm, 6 x 30 mm</td>
</tr>
</tbody>
</table>
References


54. Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI).


