Review

Acute Ischemic Stroke in the Clinic and the Laboratory: Targets for Translational Research

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ABSTRACT

Ischemic stroke research has enabled significant advancements in diagnosis, treatment, and management of this debilitating disease, yet challenges remain standing in the way of better patient prognoses. In this narrative review, a fictional case illustrates challenges and uncertainties that medical professionals still face – penumbra identification, lack of neuroprotective agents, side-effects of tissue plasminogen activator, dearth of molecular biomarkers, incomplete microvascular reperfusion or no-reflow, post-recanalization hyperperfusion, blood pressure management and procedural anesthetic effects. The current state of the field is broadly reviewed per topic, with the aim to introduce a broad audience (scientist and clinician alike) to recent successes in translational stroke research and pending scientific queries that are tractable for preclinical assessment. Opportunities for co-operation between clinical and experimental stroke experts are highlighted to increase the size and frequency of strides the field makes to improve our understanding of this disease and ways of treating it.

The clinic

It is 9:30 in the morning. A seasoned vascular neurologist admits a patient to the ER of a large stroke-center. Evidently, the patient – a 64-year-old woman – has suffered a stroke. She was found laying next to her bed in the early morning, at 7:30, by her husband. She went to bed at 23:30, but last seen well by her husband at 6:00, and was still well at that time. No medication used. The patient is immediately brought to the CT area. ECG shows sinus rhythm. Vital signs are OK, blood pressure (BP) is 179/94 mm Hg and the patient has a left-sided hemianopia, facial weakness, hemiparesis, dysarthria a sensory deficit and left sided sensory neglect with a NIH Stroke Scale score of 19 (Brott et al., 1989). A CT, CTA and perfusion CT is ordered and immediately carried out.

CT shows a large area with early ischemic change (ASPECTS 5) of the right hemisphere. CT angiography reveals an occlusion of the carotid top, with collaterals grade 2, and CT Perfusion shows a large core and penumbra (Fig. 1) (Barber et al., 2000). A diagnosis of ischemic stroke, likely of embolic origin, but of yet unknown source, is made.

The interruption of blood flow at the level of the proximal middle cerebral artery clearly caused the symptoms. Immediately after the results of the plain CT scan have been obtained, a thrombolytic (tenecteplase) is being given intravenously at a single dose of 0.25 mg/kg. Directly after starting thrombolytics the patient is transferred to the angio-suite for endovascular treatment (EVT). A catheter is introduced into the femoral artery, and advanced up to the site of occlusion, after which removal of the occluding thrombus with a stent retriever and aspiration is attempted. During the procedure systolic BP increases to 220/125, and analgesics and slight sedation with continuous infusion of midazolam is being given. After two attempts, the thrombo-embolus is extracted and a TICI grade 3 is reached. The thrombo-embolus comes out fragmented and partly aspirated, macroscopically it seems to consist of red blood cells but also of a yellowish substance. The patient is then transferred to a high care stroke unit. After 24 h, the patient is still not able to speak well because of dysarthria, and she has a right sided hemianopia, mild right hemiparesis of face and extremities and NIHSS has slightly improved to 16.
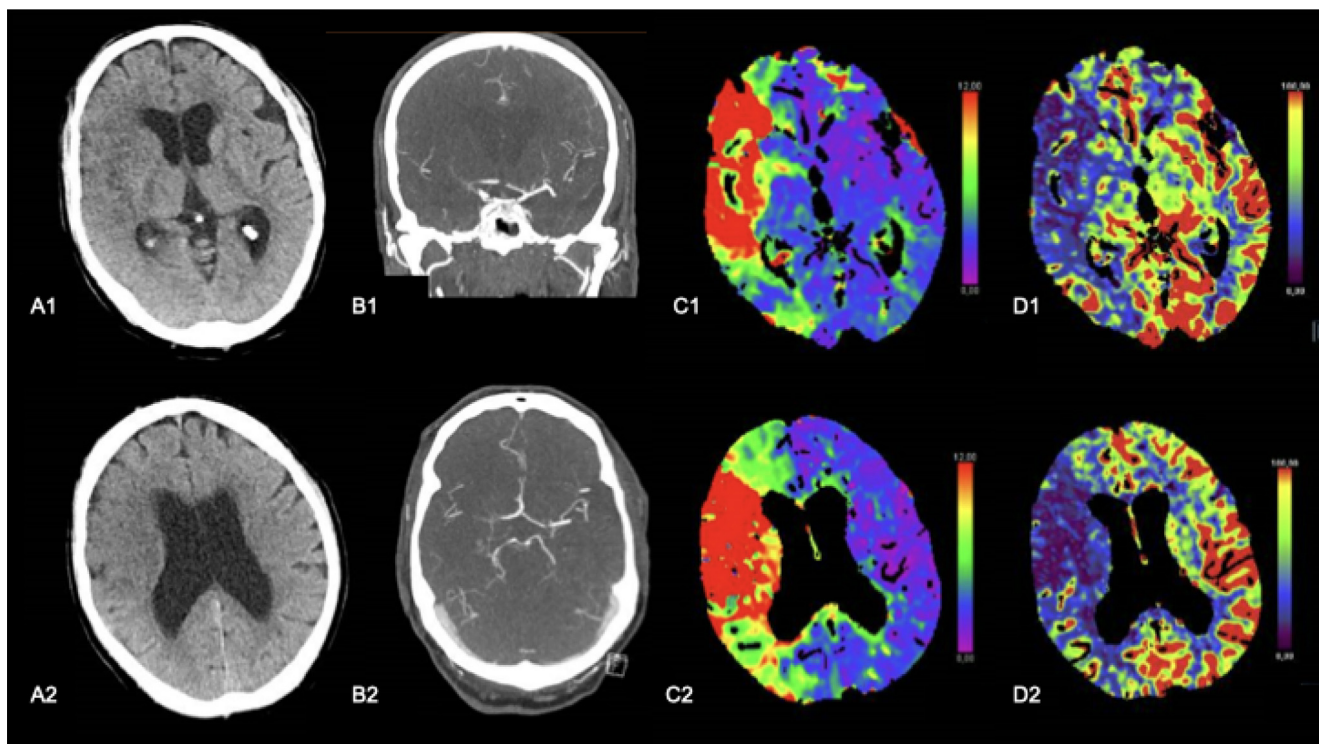
Fig. 1. Computed tomography (CT) of the head of a 64-year-old woman with acute ischemic stroke. (**A**) CT shows slightly enlarged ventricles, and a subtle hypodensity of the gray and white matter: caudate nucleus, internal capsule, insula, and a large part of the superficial distribution of the right middle cerebral artery. ASPECTS 4. (**B**) CTA shows occlusion of the top of the internal carotid artery, extending into the middle cerebral artery and the origin of the anterior cerebral artery. (**C**) Perfusion CT shows an area with prolonged T-max and a smaller area in dark blue with a low relative flow. The area with T-max > 6 s has been estimated at 177 mL, and the area with relative CBF of less than 30% is 81 mL, leaving 96 mL for the penumbra.

Despite the success of the procedure, the neurologist is not happy. It is known from observational studies and trials that the chances of recovery to independent living with at most mild, non-disabling deficit, for this patient, are still small (Chalos et al., 2023). Furthermore, the neurologist realizes that in this patient, the etiologic and patho-physiological mechanisms that caused the stroke are not yet known. This is quite bothersome, because 1 in 20 patients experiences a recurrent stroke in the first week after EVT (Oliveira et al., 2023). Ischemic strokes in patients of advanced age are often caused by thrombo-embolism from a ruptured atherosclerotic plaque. Atherosclerotic lesions can be revealed by imaging techniques in patients, but that is still no guarantee that such a lesion, if detected, is the source of the embolism. Similarly, a large proportion of patients has atrial fibrillation. This can cause cardiac emboli, but quite often we cannot be ascertained that atrial fibrillation caused the stroke. Besides, many other causes of ischemic stroke exist. First of these is small vessel disease, or arteriolosclerosis, leading to lacunar infarctions, but this was clearly not the case in this patient (Adams Jr et al., 1993). Other causes of thrombo-embolic stroke are vasculopathies, dissections and several types of cardiac embolism. However, reflecting on the etiology that led to the vascular occlusion is only scratching the surface, and our knowledge of what happens after that is quite limited.

The neurologist's team decides to review the charts of this patient and check all the decision points, all the unknowns and uncertainties from admission to treatment. After that, they invited colleagues from the adjoining institute for experimental stroke research and discussed how their work could help improve treatment and clinical management of their patient, or at least, how their work would lead to new insights, which may act as a launchpad for new clinical trials.

The clinical team noted the following unknowns: Their patient received a tissue plasminogen activator (tPA) shortly before reperfusion. Clinical trials suggest that the effect of tPA will be almost negli-

gible in such a case, but they could not prove superiority nor non-inferiority over no thrombolytic treatment directly before EVT (Majoie et al., 2023). They are skeptical about the potential benefit of thrombolytics in this case. In accordance with guidelines, the team performed CT perfusion imaging. The perfusion images helped them to pinpoint the location of arterial occlusion, but it is now also becoming clear that restrictive selection of patients based on CTP may lead to exclusion of patients who potentially benefit from EVT, and what is defined as "core" on CTP is not always "dead neuropil". Further, patients with large cores potentially recover to a high level of functioning after EVT according to the latest clinical trials (Yoshimura et al., 2022; Huo et al., 2023; Sarraj et al., 2023). The team is at a loss how to interpret the perfusion images and wonders if time-since-onset should somehow be incorporated in their assessment of the images. The patient had some widespread atherosclerosis of the major extracranial arteries, including the carotids, without severe stenosis. It is quite likely that having diseased (major) arteries will, to some extent, contribute to poor outcome after ischemic stroke of any source. Further, the type of thrombus and its components (fibrin, platelets, red blood cells) may be important to outcome; should it influence the type of treatment given? No other treatments are being given, but now that we reperfuse, should neuro-protective agents that worked in animal studies be evaluated in experimental studies again? Blood pressure bears some relationship with treatment outcome, which fluctuated heavily during and immediately after the procedure. Relatedly, the thrombectomy procedure is usually carried out under local anesthesia, but the clinical team is aware of the conflicting results of single center randomized clinical trials, some of which suggest that procedures under general anesthesia associate with better outcomes. Also, the procedure should not be unnecessarily prolonged: would it be possible to develop a biomarker-based approach that helps establishing whether additional tissue is at risk, indicating that we should improve reperfu-

sion or simply stop the procedure? Finally, they know that in the long run, the cumulative risk of recurrent stroke increases to more than 20% in 12 years, and the cumulative risk of any vascular event in that time period increases to more than 40% (van Wijk et al., 2005). The team realizes that secondary prevention could be much more tailored and personalized if the source of thrombo-embolism could be pinpointed and characterized. They also worry about their lack of knowledge concerning the underlying cause of atherosclerosis, the effects of secondary injury caused by (neuro)inflammation and elevated intracranial pressure, and finally about when and how rehabilitation efforts lead to best obtainable functional outcome for the patient, but these issues are beyond the scope of the current paper, which focuses on the diagnosis and treatment of acute ischemic stroke.

The clinical team acknowledged that the way reperfusion treatment is now performed (coarsely) resembles what is being done in experimental animal studies: temporary occlusion of a major artery preceded or followed by a controlled intervention. The team also acknowledged that research into causes, etiology and pathophysiological mechanisms - either on a macrovascular, cellular, or molecular level - has to rely on both clinical studies and experimental investigations, *in-* and *ex vivo*.

Now that the clinical team has listed its uncertainties and unknowns, they proposed questions to the experimental group. The list is long, but not exhaustive. This is what they came up with:

Penumbra: Can imaging techniques that are currently available be further developed to help in distinguishing between neuronal tissue that can be salvaged and tissue that is beyond repair?

Neuroprotection after reperfusion: At what point in the ischemic cascade is it worthwhile to intervene on a molecular level, i.e., with neuroprotective agents?

tPA effects: We administered tissue plasminogen activator to induce fibrinolysis. We know that tPA induces unwanted effect by activating the endothelial NMDA receptor. How can this be counteracted?

Impaired microvascular reperfusion: After re-canalization of the artery a large infarction may still develop, possibly because of impaired microvascular reperfusion. What is its cause and how can we antagonize that?

Hyperperfusion: After treatment, abnormally increased cerebral perfusion – termed hyperemia or hyperperfusion – is frequently observed after a certain amount of time. Does it cause additional damage, should we counteract it, to what extent and how?

Blood pressure and hypertension: High systolic BP is the most important risk factor for ischemic stroke and also associates with poor outcome. Clinical evidence that interventions on BP during and after EVT improves outcomes is inconclusive. What can we learn from experimental stroke studies before we embark on yet another intervention study in humans?

Anesthesia and sedation: It is likely that the agents we use have potentially favorable or unfavorable effects on microcirculation. Could experimental studies shed some light on what agents we should preferably use?

Molecular biomarkers: Is there a periprocedural biomarker available that is responsive to neuronal death and easy to obtain and interpret, that helps us assess e.g., treatment response cost-effectively during the procedure?

The experimental laboratory

Obviously, the experimental team is not able to definitively answer all the above questions from the clinic. However, as preclinical stroke researchers they have experience with translational studies to investigate (some of) these matters and they are familiar with scientific publications on these topics. Several themes central to the clinicians' pressing questions could be identified, which are outlined below. The preclinical team aimed to accommodate the clinical team in addressing their broad range of questions, succinctly introducing each theme and describe progress made in the preclinical setting. Hence, this is what the team provided as – selective and subjective – feedback:

Penumbral imaging for patient selection and prognosis: can we do better?

The original penumbra concept, prompted by seminal experiments in baboons was defined as brain tissue perfused at a level within the thresholds of functional impairment (electrical failure) but with sufficient cellular energy reserves to maintain a membrane potential (Astrup et al., 1981). Importantly, this tissue may recover if perfusion is restored in time. Identifying this "tissue-at-risk" is recommended before EVT as it can be deleterious in patients with small penumbras. As per standard protocol, our patient was imaged using non-contrast CT, first to exclude hemorrhagic stroke before treatment decision, and second to roughly estimate damaged tissue based on ASPECTS. Common practice in most countries is then to estimate the penumbra with perfusion CT, where an area of prolonged flow but normal cerebral blood volume (indicative of sustained autoregulation) should be identifiable, which is regarded as an acceptable approximation of penumbral tissue. This operationalization will include tissue both "at-risk" and under benign oligemia; it has served us well in improving door-to-groin times, but it will not provide any information on actual tissue viability. Since this method relies on incomplete information, the penumbra may be overestimated in some patients due to contrast variability from irrelevant sources (e.g., technical mishaps or so-called perfusion scotoma) which can subvert treatment expectations (Copelan et al., 2020; Abrams and Dabus, 2022). Finally, CT perfusion scans provide just a snapshot of a continuing process of progressing focal ischemia and tissue death, pathology that develops at a variable (patient-specific) pace, a probable source of over- and misinterpretation.

These shortcomings are well known, and various alternatives have been proposed to improve penumbra detection (Østergaard et al., 2013; Harston et al., 2015). One strategy that holds promise is to measure changes in physiologic parameters consequent to metabolism, such as tissue pH (Peek et al., 1989; Harston et al., 2015; Leigh et al., 2018). The rationale is that glucose metabolism in hypoxic tissue will switch from aerobic to anaerobic metabolism, with a concomitant drop in tissue pH due to regional lactate buildup. Amide proton transfer imaging, an emerging subtype of chemical exchange saturation transfer MRI, is sensitive to changes in pH and may help distinguish an "acidosis penumbra" rather than a "perfusion penumbra". With a more refined identification of the penumbra, stroke treatment could be better individualized, new avenues to experimental treatments could be opened, and patient populations normally disqualified for EVT due to time constraints may become eligible (Leigh et al., 2018). The neurologist reluctantly notes that this method entails MRI, to which the preclinical researchers acknowledge that MRI accessibility can be more troublesome at certain institutions, which is undesirable. Still, MRI has multiple advantages over CT (e.g., it is more sensitive to ischemia), while exams do not necessarily take longer than CT (Provost et al., 2019). Nevertheless, much work remains to validate pH-weighted imaging for stroke, some of which can be done preclinically; the outcome may ultimately convince interventionists to request MRI exams more often if it improves tissue outcome prediction and decision making. Lastly, it bears to mention that the penumbra paradigm is evolving over time; new ideas are constantly put forward to improve understanding and utility of the penumbra in treatment development and decision making (Østergaard et al., 2013; Leigh et al., 2018; Walther et al., 2023).

Neuroprotection after reperfusion: a brief status update

The goalposts of "neuroprotection" in ischemic stroke have been repositioned in recent years. Since the exposure of the collective failure of the translational axis that sparked a paradigm shift (O'Collins et al., 2006), stroke researchers regrouped, and the translational road-

block was identified (Endres et al., 2008). In brief, this roadblock arises from the many sources of bias in preclinical research, such as lack of randomization or blinding, poor statistical power, lack of reproduction and publication bias. These, and other issues in preclinical and clinical trials that contribute to the roadblock, have been extensively reviewed before (Dirnagl and Endres, 2014; Haupt et al., 2022). Over the years, the STAIR (Stroke Treatment Academic Industry Roundtable) has made numerous recommendations to improve validity of stroke models and the search for neuro-protective strategies in general (Saver et al., 2009). Recently introduced perspectives have proposed to shift attention towards the neurovascular unit, which is an umbrella term for components of the brain that collectively regulate cerebral blood flow in order to deliver the requisite nutrients to activated neurons (Iadecola, 2017). Importantly, usage of the word "neuroprotection" is no longer recommended on account of being ambiguous (Lyden et al., 2021). The suffix "-protection" should now be accompanied by terminology specific to which the component of the neurovascular unit is being targeted, e.g., glioprotection, vasculoprotection and neuronoprotection. Furthermore, it has been recognized that part of the failure of the translational axis could be attributable to its dogmatic adherence to testing single-target single-action molecules that intervene somewhere in the ischemic cascade – assuming such an orderly sequence of events exists. Instead, we may see an increase in multi-action multi-target (i.e., pleiotropic) strategies in the future, that could be targeted at the neurovascular unit (Lyden, 2021).

Does that mean the quest for "neuroprotection" is back at square one? One more reason for translational failure worth highlighting, which was also acknowledged by STAIR, is the persistent historical mismatch between preclinical and clinical trial designs testing a particular strategy (Dirnagl and Endres, 2014). At the bench, experimental treatments were often applied in models with perfect recanalization rates (which is expected when using e.g., the intraluminal filament model (Sutherland et al., 2016)) while before EVT, far fewer patients were likely to achieve complete recanalization, yet treatments were administered, and hypotheses were tested regardless. Now that EVT has been cemented as the most effective recanalization therapy and becoming increasingly available, the role of reperfusion efficacy in disease outcome is better understood by physicians and researchers. Reviewing this mismatch has begged the question whether certain "neuroprotection" strategies are candidate for reassessment, particularly those that are safe and easy to implement at the bedside or during procedures (Lourbopoulos et al., 2021; Lyden, 2021; Xu et al., 2023).

One example for a candidate is isobaric hyperoxia, the therapeutic administration of a gas mix with high oxygen content at normal barometric pressure (i.e., one atmosphere). For many years, hyperoxia has been tested successfully in preclinical studies (Liu et al., 2006; Singhal, 2006, 2007), but failed clinically several times over (Singhal et al., 2005; Shi et al., 2016; Roffe et al., 2017). Recently, a single-center blinded and randomized clinical pilot trial compared isobaric hyperoxia (4-h 100% O_2 through a face mask) combined with EVT to EVT alone. It was found that the infarct volume was smaller at 24–48 h, and that the modified Rankin Score was reduced at 90 days in the treatment arm (Li et al., 2022). It is interesting to note that in these trials where hyperoxia failed, it was not an adjunct to recanalization therapy. One could therefore speculate that some minimum degree of reperfusion is a requirement for certain therapeutic strategies to work, as any potential beneficial effect will be futile if brain cells cannot be sustained (by blood flow) in the long term. While it was emphasized that the sample size of this proof-of-concept trial was small – results need to be reproduced by larger multi-center trials – it inspires optimism, albeit cautiously.

Side effects of tPA that can interfere with treatment outcome

Even though EVT is being cemented as the new gold standard for large vessel occlusions, tPA is still indispensable in many situations of distal occlusion and frequently applied in some combination with EVT. After nearly 30 years of thrombolytic therapy with tPA, our understanding of this molecule has evolved from "simply" a protease to a protease and cytokine with multifaceted side-effects on various substrates or receptors in the CNS, including endothelial cells, neurons, and various glial cells (Docagne et al., 2015; Vivien, 2017). Indeed, a well-known detrimental side-effect of tPA is overactivation of NMDA receptors, which has been reported to induce excitatory neuronal death (Nicole et al., 2001). However, the agonistic effects of tPA on this receptor have been a matter of debate (Matys and Strickland, 2003). For example, therapeutic effects that reduce cell death that depend on the NMDA receptor have been reported (Lebeurrier et al., 2005; Wu et al., 2013a, 2013b). These observations indicate yet more work is needed to further disentangle the role of tPA on neuronal signaling and excitotoxicity. It may be of particular interest to prevent tPA from interacting with NMDA receptors, and it is expected animal models will continue to play a vital role in this endeavor.

Another relevant side-effect is the tPA-associated risk of bleeding and edema through actions on astrocytes and endothelial cells that damage BBB integrity (Kassner et al., 2009; Yepes et al., 2009). Several mechanisms may contribute to this process, which are likely exacerbated by metabolic stress induced by the primary ischemic process. In the endothelial cells, tPA promotes synthesis of metalloproteinases, which in turn contribute to BBB permeability and possibly hemorrhagic transformation (Wang et al., 2003; Suzuki et al., 2009). Our understanding of the actions of tPA on the BBB can provide new avenues through which risk of hemorrhagic transformation can be mitigated (Vivien, 2017). Advances in the fields of nanomedicine and nanomaterials may enable new drug delivery processes that counteract some of the unwanted effects of tPA in the future (Parvez et al., 2022).

Molecular biomarkers that may inform on treatment response

Another concept that can improve patient management and is amenable for preclinical assessment, given the effect interventions can have on CNS substrates or molecules (see above), are molecular biomarkers. These constitute measurable indicators in stroke that provide information on e.g., the stroke subtype or severity of the accident, which would aid stroke diagnosis, prognosis, and development of therapeutic strategies (Ramiro et al., 2018). Hopefully, pathologically deregulated molecules could also be meaningful therapeutic targets to address the urgent need for treatments. For example, in patients it has been demonstrated that low circulating levels of a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) associate with a poor response to recanalization therapies, both after tPA treatment and EVT (Bustamante et al., 2018). Furthermore, levels of inflammatory biomarkers (such as IL-6 and copeptin) have shown remarkable predictive value for outcomes, more so than clinical variables (De Marchis et al., 2013). With respect to our patient, in addition to facilitating predictions about overall outcomes, blood-borne biomarkers that could provide information about the origin of certain complications that lead to poor outcomes would be highly welcome developments (Bustamante et al., 2016). Preclinical research has contributed to this process in several ways.

Molecular biomarker assays can be performed at different levels (e.g., transcription, proteomic) and samples may originate from various sources (bodily fluids such as plasma or CSF (Montaner et al., 2020)). In rats, the CSF proteome in the hyper-acute phase of experimental stroke has been described before and 30 min after filament-induced MCA occlusion. Cerebral ischemia acutely increased the levels of hundreds of proteins in the rat cerebrospinal fluid (Simats et al., 2018). From these, seven promising candidates were selected and studied in blood samples from patients with ischemic stroke (taken < 6 h after symptom onset) and controls. Creatine kinase B-type (CKB), calcium-calmodulin-dependent protein kinase II subunit-α (CaMK2B) and uridine monophosphatase-cytidine

monophosphate kinase (CMPK) showed promise as biomarkers of functional stroke outcome. However, despite the long search among the thousands of molecules that are altered during pathological processes of stroke, no valuable indicator has been adopted by the clinic yet. It is unlikely that we can single out a molecular marker able to adequately predict stroke subtype or outcome, since ischemic stroke is a heterogeneous disease that involves countless of pathological processes and thus even more molecules that participate in the ischemic cascade. Instead, a better strategy may be to adopt a multi-level approach to identify and choose a set of the best candidates that are involved in a pathological process. For example, a collection of biomarkers that may be particularly informative on the status of the cerebrovascular unit has already been proposed (Steliga et al., 2020). Experimental stroke research is likely to become increasingly important in the identification of biomarkers and the development of therapeutic strategies that try to intervene on a molecular level.

Incomplete microvascular reperfusion from mice to man

Incomplete microvascular reperfusion (IMR) refers to incomplete restoration of flow in the microvascular bed despite successful opening of the occluded artery, which may be amenable to treatment. The experimental team were reminded of the patient's charts, which show a retrieved but partially fragmented thrombus. Conceivably, a partially disintegrated thrombus can be a source of clot fragments (microemboli) that are thought to be a contributing factor to IMR (Dalkara and Arsava, 2012). As discussed above, IMR concerns the functioning of the neurovascular unit, and may also be of attractive to explore for biomarkers. The experimental team notes that relevant literature can be somewhat tricky to navigate, as two terms – "no-reflow" and "incomplete microvascular reperfusion" – have been used interchangeably to describe this process, despite earlier suggestion to disambiguate the two (Dalkara and Arsava, 2012). No distinction will be made here for the sake of brevity.

The history of IMR/no-reflow is long and has been extensively reviewed before (Dalkara and Arsava, 2012). Recent developments of super-resolution microscopy techniques have enabled new discoveries in preclinical studies of IMR/no-reflow. Desilles *et al* employed intravital microscopy to show that leukocyte aggregation and micro thrombosis develop shortly after filament-induced transient ischemic stroke (Desilles et al., 2018). Erdener and colleagues have shown that flow of red blood cells repeatedly halts and resumes after reperfusion in the penumbra, like temporary traffic jams, which they have called "dynamic flow stalling". The number and duration of stalls could be modulated by depleting neutrophils (Erdener et al., 2020). El Amki and colleagues, by inducing experimental stroke of thrombotic origin in mice, have similarly shown that reperfusion by a thrombolytic is incomplete and attributable to neutrophils (El Amki et al., 2020). Yet another putative source for IMR/no-reflow are capillary pericytes, mural cells that are present along the endothelial walls of capillary vessels. In a week-long serial two-photon microscopy study on mice, it was found that the majority of pericytes within field-of-view constrict acutely after ischemia–reperfusion and hamper blood flow, yet these pericytes do survive and may be amenable to treatment (Shrouder et al., 2023). These findings are important steps forward as they demonstrate that causes and consequences of IMR can be studied *in vivo* at the microvascular level using experimental techniques, which will benefit the development of new therapeutic strategies to counteract this process.

While IMR/no-reflow used to be an obscure topic and mostly confined to the laboratory, the age of recanalization therapy and the subsequent observation of "futile recanalization" – poor outcome despite successful recanalization – has kindled clinical interest. Neuroimaging techniques that probe cerebral perfusion have enabled investigation of this hypothesis in clinical samples (van der Knaap et al., 2024). However, it is important to remain prudent. Recent systematic reviews

attempted to determine the incidence of impaired reperfusion after successful recanalization with different results: one group estimated no-reflow at 29% (Mujanovic et al., 2023), while another group used more stringent recanalization criteria arrived at near-zero figures (0–9.1%) (ter Schiphorst et al., 2024). Both groups noted that operational definitions of IMR/no-reflow are widely inconsistent between articles, creating confusion regarding the true incidence of IMR/no-reflow. While a reduction of cerebral blood flow (CBF) on perfusion maps is often used as a surrogate for IMR/no-reflow, it is not a validated clinical neuroradiological marker and likely a major source of inconsistency. Additionally, there has been an excellent and sobering discussion on the risks of relying on inadequate definitions of successful recanalization (i.e., by relying outdated recanalization grade scales), and other confounds that can bias CBF downward to create false impressions of IMR/no-reflow in patients, to which the reader is referred (ter Schiphorst et al., 2024).

Even though incidence, causes and consequences of IMR/no-reflow are not fully understood, it has not kept basic scientists and clinicians from attempting to alleviate them. Intravenous alteplase was administered to counteract downstream thrombosis in a rat model of filament-induced ischemia–reperfusion, which improved reperfusion and ameliorated post-stroke outcomes (Desilles et al., 2015). Clinically, adjunct thrombolytic treatment in EVT has also been employed, albeit in different paradigms, with mixed results: preliminary evidence from the CHOICE trial, where intra-arterial alteplase was given after successful thrombectomy, indicate that functional outcome may improve after 90 days (Renú et al., 2022). In a smaller single-center trial, intra-arterial tenecteplase was administered after first attempt of EVT regardless of recanalization status, with statistically insignificant results (Zhao et al., 2023). Lastly, the MR CLEAN-MED trial employed a very different paradigm: it investigated safety and efficacy of adjunct acetylsalicylic acid and unfractionated heparin − to antagonize two potential causes of IMR: platelet aggregation and neutrophil extracellular traps, respectively − but this trial was stopped prematurely due to increased risk of symptomatic intracranial hemorrhage and absence of an effect on functional outcome (van der Steen et al., 2022).

The experimental team concludes that, despite the unrelenting push for therapies against IMR/no-reflow, interventions are still far away. The body of literature is vast and incomplete, and our understanding of the incidence, causes and consequences of IMR/no-reflow is still limited. Similarly, results from failed clinical trials remind us of how delicate the (post-stroke) brain is. Going forward, it is expected that cross-validation of hypoperfusion measured by translational neuroradiological imaging (i.e., CT or MRI) with super-resolution techniques or post-mortem brain assays in animal models of stroke is going to play a role in verifying IMR/no-reflow (ter Schiphorst et al., 2024).

The prognostic value of hyperperfusion after recanalization

While incomplete restoration of perfusion may be of primary concern after EVT, clinical and preclinical imaging studies have shown that the magnitude cerebral hemodynamics can swing the other way after revascularization. When a hemodynamic index such as CBF exceeds 100% of a certain reference value (Sundt et al., 1982), it is referred to as hyperperfusion. The discovery of hyperperfusion in a patient after recanalization therapy can be alarming – it is a feared complication after carotid artery stenting (Huibers et al., 2018) – but the prognostic value of hyperperfusion after acute ischemic stroke is still unclear. Hyperperfusion, as an imaging marker, has been associated with favorable, neutral or detrimental outcome (van der Knaap et al., 2024). The hypothesis that hyperperfusion could be beneficial under some circumstances is not new (Marchal et al., 1999), but has garnered interest in recent years, likely due to increased data availability now that perfusion imaging techniques are ubiquitous in stroke centers. The literature may suggest that the prognostic value of hyper-

perfusion is an intricate function of several factors (van der Knaap et al., 2024), and a brief update is provided below.

The *time course* of hyperperfusion after EVT may be relevant, i.e., hyperperfusion may have different prognostic value depending on whether it occurs "*early*" after recanalization (~24 h) or "*late*", for example after several days. We propose this hypothetical time frame to offer some support in explaining the hyperperfusion time course, but the definition is clearly arbitrary; what constitutes "early" or "late" differs on a case-by-case basis. Regardless, various clinical accounts exist that associate CBF hyperperfusion detected at 24 h post-stroke to improved outcome (Bivard et al., 2013, 2014; Bhaskar et al., 2017; Lu et al., 2021; Potreck et al., 2021; Luijten et al., 2023; Rosso et al., 2023). Some preclinical evidence supports this notion, suggesting that lesion size and location (Heiss et al., 1997; Wegener et al., 2013), as well as occlusion duration (Heiss et al., 1997; Shen et al., 2011) are factors that mediate the time course and magnitude of hyperperfusion. Conversely, associations between hemorrhagic transformation – a feared complication of ischemic infarction – and hyperperfusion have been detected, which could be particularly relevant when they occur "*late*" after recanalization (Yu et al., 2015; Okazaki et al., 2017). Recently, several other pieces were added to the puzzle. In a prospective clinical MRI study, it was found that CBF overshoot measured "*very early*" (2–6 h) after EVT associated with increased lesion size measured at 24 h (Luby et al., 2023). These findings were corroborated by an experimental stroke study in rats that found increased CBF, measured 30 min after recanalization, associated with lesion growth and worsened functional outcome four days later (Franx et al., 2024a). These MRI studies suggest that increased CBF can be deleterious if detected within hours after recanalization. Interestingly, experimental neuroimaging in a mouse model of ischemic stroke has shown that leptomeningeal collaterals, pial anastomotic vessels that join terminal cortical brancher of major cerebral arteries along the surface of the brain, may play an important role in mediating this response (Binder et al., 2024). Using three different mouse strains with certain genetic predisposition for quality of leptomeningeal collateral perfusion, it was shown that immediately after thrombolysis, mice with good collaterals exhibited a relatively gradual reperfusion response, whereas mice with poor collaterals suffered an excessive perfusion response and constriction of distal arterial vessels compared to other mouse strains. This excessive perfusion response associated to detrimental outcomes such as increased lesion size, with similar relationships being found in a separate patient cohort, demonstrating that poor leptomeningeal collateral anatomy can result in rapid, deleterious reperfusion and suboptimal recovery (Binder et al., 2024). Clearly, the timing of hyperperfusion is relevant, and may reflect different underlying pathomechanisms depending on the time of first occurence.

Another potentially relevant component of hyperperfusion is *spatial location*, that is, whether it emerges intra- or *peri*-lesionally. Again, the waters are rather murky: clinically it was reported that perilesional hyperperfusion is favorable at 24 h post stroke (Bhaskar et al., 2017). One patient study probed hyperperfused perilesional areas at 24 h with magnetic resonance spectroscopy and found signs of increased cellular metabolism (Bivard et al., 2014). Yet there are also reports that hyperperfusion, detected both intra- and *peri*-lesionally at 24 h, associates with improvement (Luijten et al., 2023; Rosso et al., 2023) Preclinically, hyperperfusion in areas that proceed to infarction often also seem to overlap with tissue that recovers (Wang et al., 2002; Lee et al., 2004). However, it may also be considered that knowledge of the spatial location of hyperperfusion (viz. the stroke lesion) holds little explanatory value, especially if follow-up imaging is not performed. Rather, hyperperfusion could also be considered an epiphenomenon, consequent to a certain underlying tissue state. Longitudinally quantifying the metabolic status of hyperperfused (peri)lesional stroke tissue would enable better characterization of hyperperfusion and what it means for clinical trajectory.

Taken together, there is much conflicting information on the implications of post-recanalization hyperperfusion, and much remains unknown. Here we discussed timing and spatial location, but other factors may also be relevant, such as magnitude of the overshoot and occlusion severity that precedes it. Regarding the question if and how hyperperfusion should be counteracted, it is paramount to first understand the disease process one tries to target – where, when, and how is hyperperfusion detrimental – before trying to intervene. Here lies great potential for translational modeling studies, since many of the readout parameters relevant to the elucidation of hyperperfusion (e.g., tissue-level outcome measures) cannot be obtained in patients because they require invasive procedures. Promising strategies to modulate hyperperfusion, for example in the subacute (late) phase, entail BP management to keep CBF within safe limits (Claassen et al., 2021; Nogueira et al., 2022). Recent clinical studies suggest that BP management can be personalized. By continuous observation of changes in pressure and various cerebral autoregulation indices, it seems possible to derive a range wherein cerebral autoregulation performs optimally and protects the brain from additional hypo- or hyperperfusion related injury (Petersen et al., 2019, 2020). The importance and potential of BP management is discussed further below.

Blood pressure and hypertension; prognostic factors before and after reperfusion

Increased BP in ischemic stroke, either as a symptom or a comorbid cardiovascular condition, has received limited attention from experimental stroke labs. The acute BP rise in the event of ischemic stroke has multitudes of potential causes, such as damage to brain structures that participate in BP regulation or activation of sympathetic hyperactivation of the adrenomedullary pathway consequent to the ischemic event (Jansen et al., 1988; Olsson et al., 1992; Qureshi, 2008). Symptomatic increases in BP associate with the likelihood of adverse events, but through what mechanism is unclear (Mulder et al., 2017; Malhotra et al., 2019; Samuels et al., 2023). In fact, what little investigation of BP that has been conducted in animal models indicates that mild increases in BP could help protect the brain (Ji et al., 2009), though it should be noted that these experiments were performed under general anesthesia (which lowers BP), and it is conceivable that mild BP elevations help sustain blood flow to the penumbra (Ji et al., 2009). What effect severely variable BP has on progression of brain damage in an ischemic event is currently not known, possibly because BP is not easily controlled in rodents (especially mice), which are typical experimental stroke research subjects. Recently however, a model of ischemia–reperfusion in New Zealand White rabbits has been proposed that offers convenient manipulation of blood flow, facilitated by a relative large size of the arterial lumen of this strain (Alexander et al., 2023). This reproducible model may be able to shed new light on the effects of BP on ischemic stroke outcomes.

On the other hand, an increased BP could be the result of undiagnosed conditions such as hypertension (Toyoda et al., 2006), which becomes more common as age increases (Hauer et al., 2017). Common methods to study hypertension in stroke include salt-rich dieting or using genetically hypertensive models such as the Wistar-Kyoto Spontaneously Hypertensive Rat (SHR). Such experimental stroke studies have demonstrated striking effects of hypertension on stroke outcomes. For example, it has been shown in SHR that innate immune responses to ischemia are altered, leading to increased infiltration of leukocytes that correlated with infarct size (Möller et al., 2015). Furthermore, experimental stroke studies have provided a wealth of information on the effects of hypertension on cerebral circulation during and after ischemia (Cipolla et al., 2018). Translational models of ischemia–reperfusion have demonstrated deficient flow restoration in SHRs compared to controls (Kang et al., 2014; Cipolla et al., 2017). Given that reperfusion therapy is grounded in the idea that

reperfusion is the best solution to ischemia, this relationship may be relevant to the lack of efficacy in patients with hypertension. In fact, it has been known for many years that therapeutic strategies are less effective in stroke models that include hypertension (O'Collins et al., 2013). Conceivably, approaches that protect the brain following a stroke require successful restoration of blood flow in both models and patients, and the potential connection between underlying vascular conditions and inadequate blood flow restoration could shed light on why some treatments are destined to fail from the outset. It will be crucial to confirm this in patient populations with hypertension. Naturally, while hypertension may be the cardinal vascular risk factor in ischemic stroke (Hankey, 2020), there are other important vascular comorbidities that hamper prognoses could not be covered here, such as diabetes mellitus (Venkat et al., 2017) and hyperglycemia (Ferrari et al., 2022). Preclinical treatment methods that address the combined impact of neurological and vascular conditions (comorbidity) in acute ischemic stroke are highly anticipated (Gąsecki et al., 2020; Lyden, 2021).

The impact of anesthesia and sedation on treatment outcomes

Reperfusion therapy is typically combined with some form of periprocedural anesthesia, from light conscious sedation to complete general anesthesia (GA). Anesthesia is inextricably linked to stroke outcome, not in the least because it almost always has an effect on BP. GA is often motivated to guarantee patient immobility, pain management or airway protection (Anastasian, 2014). Since the advent of EVT, the question whether conscious sedation or GA should take preference has gained considerable interest, which is reflected by multiple randomized controlled trials of GA versus conscious sedation that have been concluded or are currently ongoing. Two *meta*-analyses have shown that GA-assisted stroke treatment associates with higher rates of disability and mortality compared to non-GA controls (Brinjikji et al., 2017; Campbell et al., 2018). However, another *meta*-analysis of seven single-center randomozed controlled trials that randomized EVT patients to GA or non-GA treatment found improved recanalization rates and functional outcomes associated with GA (Campbell et al., 2023). The evidence for benefit of either conscious sedation or GA in EVT is therefore mixed. This is in rather stark contrast to preclinical data: here, a *meta*-analysis of experimental stroke studies has found a robust protective effect for various anesthetics on lesion size (Archer et al., 2017).

Several comments can be made in light of this discrepancy. Historically, the most studied subject in biomedical research is a healthy young adult male lab animal (Beery and Zucker, 2011). Apart from species, the context wherein stroke is modeled is vastly different from the target population in the clinic, which is usually aged, contains both sexes and comorbidity is often involved. It is now well-accepted that young healthy male animal do not adequately represent the patient population affected by stroke, and results from this model may have low external validity in some respects. In line with this, the abovementioned *meta*-analysis undertook a *post-hoc* analysis, albeit with limited data, to elucidate the effect of anesthetics on female and comorbid models of stroke (Archer et al., 2017). The conclusion, with certain reservations, was that therapeutic effects of GA failed in female, aged and comorbid animals. Future experimental stroke studies may focus on replication and elucidate in a more diverse preclinical sample (e.g., different species, aged and/or comorbid subjects, etc., following the STAIR recommendations). These results can be used to spur clinical investigations to improve possible therapeutic effects of certain GA classes that fail in subsets of patients (Lyden et al., 2021). Other outstanding questions that could be answered in a preclinical setting include whether GA or conscious sedation is more beneficial in the context of recanalization therapy. This task will be challenging, since the best experimental contrast in such a study would be a treatment group – anesthetized – compared to awake stroke conditions.

However, GA is often necessary in preclinical stroke to ensure animal wellbeing during microsurgery and sometimes to enable in-vivo imaging, and established awake stroke models that allow controllable ischemia–reperfusion of proximal feeding arteries not needing any anesthesia whatsoever − are currently lacking. While it is possible to induce awake stroke, e.g. by photo-thrombosis or a laser-induced occlusion of a distal pial vessel. (Lu et al., 2014; Seto et al., 2014; Balbi et al., 2017; Sunil et al., 2020; Brunner et al., 2023), the effect of anesthesia outcome after controlled reperfusion cannot be studied in these models. Alternatively, it may be more realistic for preclinical stroke studies to investigate the effect profiles of typical GA agents used in the clinic, such as volatile gas or propofol, both of which are recommended for recanalization procedures (Navarro and Kofke, 2021). This seems especially relevant in light of emerging retrospective patient studies reporting possible differential effects of either class on clinical outcomes (Diprose et al., 2021; Crimmins et al., 2022), for which a potential mode-of-action was recently revealed with MRI in a rodent model of ischemia–reperfusion (Franx et al., 2024b).

Discussion

Here the local experimental team has provided a broad overview of proceedings in basic/translational stroke research. Evidently, the experimental team was not able to fully answer all queries, partially because in-depth discussion had to be sacrificed in favor of accommodating the breadth of the initial array of questions asked by the clinical team. Other relevant matters such as sex effects were not included but these are reviewed and discussed elsewhere (Ahnstedt et al., 2016; Chalos et al., 2019). Topics such as the penumbra, neuroprotection and the ischemic cascade have a longstanding tradition in preclinical stroke research. As indicated by questions from the neurologist, these subjects remain relevant, but may be viewed again from a different angle, i.e., the perspective of recanalization therapies. Furthermore, inquiries from the clinic highlight the need for more information on topics that are not well represented in translational stroke research, such as the effect of (peri)procedural blood pressure variability on outcomes. Other subjects, such as atherosclerosis, are intensively investigated in the realm of cardiovascular research but less so in experimental stroke. Collecting and integrating knowledge of atherosclerosis in the context of ischemic stroke would certainly benefit from a multi-disciplinary approach.

The clinical and experimental team agree that, for effective translation of findings between bench and bedside, it is vital to understand what aspects are exactly modeled, including stroke model characteristics and study design certain design wherein a model is used. Then, it is integral that conditions are consistent between the lab and clinical settings. As discussed above, the application of isobaric oxygen as a possible adjunct in endovascular treatment, which was previously clinically investigated in *any* ischemic stroke patient as opposed to recanalized ones, has made this abundantly clear (Li et al., 2022). However, certain limitations of translational stroke modeling should also be acknowledged. As indicated above, anesthesia is currently a vital part of procedural workflows, though it has confounding effects on stroke outcome if not properly controlled (Hoffmann et al., 2016). Even more important is the fact that patients are awake when they suffer the effects of stroke, at least before arrival at the stroke center. This does not invalidate translational stroke experiments, but highlights the importance of study design, where effects of anesthesia in experimental groups are balanced against one another. For the advancement of stroke modeling, and elucidation of anesthetic effects on disease outcomes, the development of awake ischemia–reperfusion models, where a vascular occlusion can reproducibly be induced and lifted in a controlled manner, will be high priority.

There are several other components of the translational axis that deserve special attention in light of the present discussion. As per

the STAIR guidelines, not only is it recommended to test novel therapeutics in aged or comorbid models to overcome the translational roadblock, the conditions that these models recapitulate provide valuable insight into why the brain is more susceptible to ischemia and its consequences (Lyden et al., 2021). As discussed above, the effects of hypertension can be investigated in the lab using transgenic, genetic, or induced hypertension models. Aged models are highly relevant as well, because age is the most important non-modifiable risk factor for occurrence and outcome of stroke (Wafa et al., 2020), but certain stroke induction methods may be precluded depending on the procedure. For example, the filament model may fail in aged models because animals will have grown too large, and their vasculature will become increasingly brittle, which increases the likelihood of complications (Candelario-Jalil and Paul, 2021). Nevertheless, we anticipate important insights from studies that incorporate factors of comorbidity. These models may prove indispensable to spur new research in subgroups of patients that respond differently (poorly) to stroke or stroke treatment. Furthermore, demonstration of stroke mechanisms or potential treatment efficacies in the gyrencephalic brain, e.g., in large animal models, can bolster our understanding of pathophysiology and interventions. Benefits and considerations of approaches that entail large animal models were recently reviewed elsewhere (Taha et al., 2022).

To conclude, in this overview we have highlighted questions arising from the clinical stroke settings and multiple lines of translational evidence from experimental stroke studies with potential to satisfy clinically relevant inquiry. While we can describe what to expect from translational research, it may be far more important to realize how to get there, which places emphasis on the importance of continuous discourse between clinicians and basic/translational scientists to identify questions or topics that require scientific attention. Sometimes, this means renovation: old evidence should be considered in a different or new light (new-found relevance of incomplete microvascular reperfusion in the context of EVT is an example of this), and importantly, the applicability of an occlusion-reperfusion animal model to modern clinical practice. On the other hand, basic scientists may take cues from the clinic and innovate to push the field forward, which may be found in e.g., the development of awake stroke models. Nevertheless, the speed and efficiency at which the experimental stroke field develops will depend on whether clinical and basic scientists are able to cooperate, intensify their dialogue and integrate their disciplines.

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Bart Franx: Writing – original draft, Writing – review & editing. **Rick M. Dijkhuizen:** Writing – original draft, Writing – review & editing. **Diederik W.J. Dippel:** Visualization, Writing – original draft, Writing – review & editing.

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