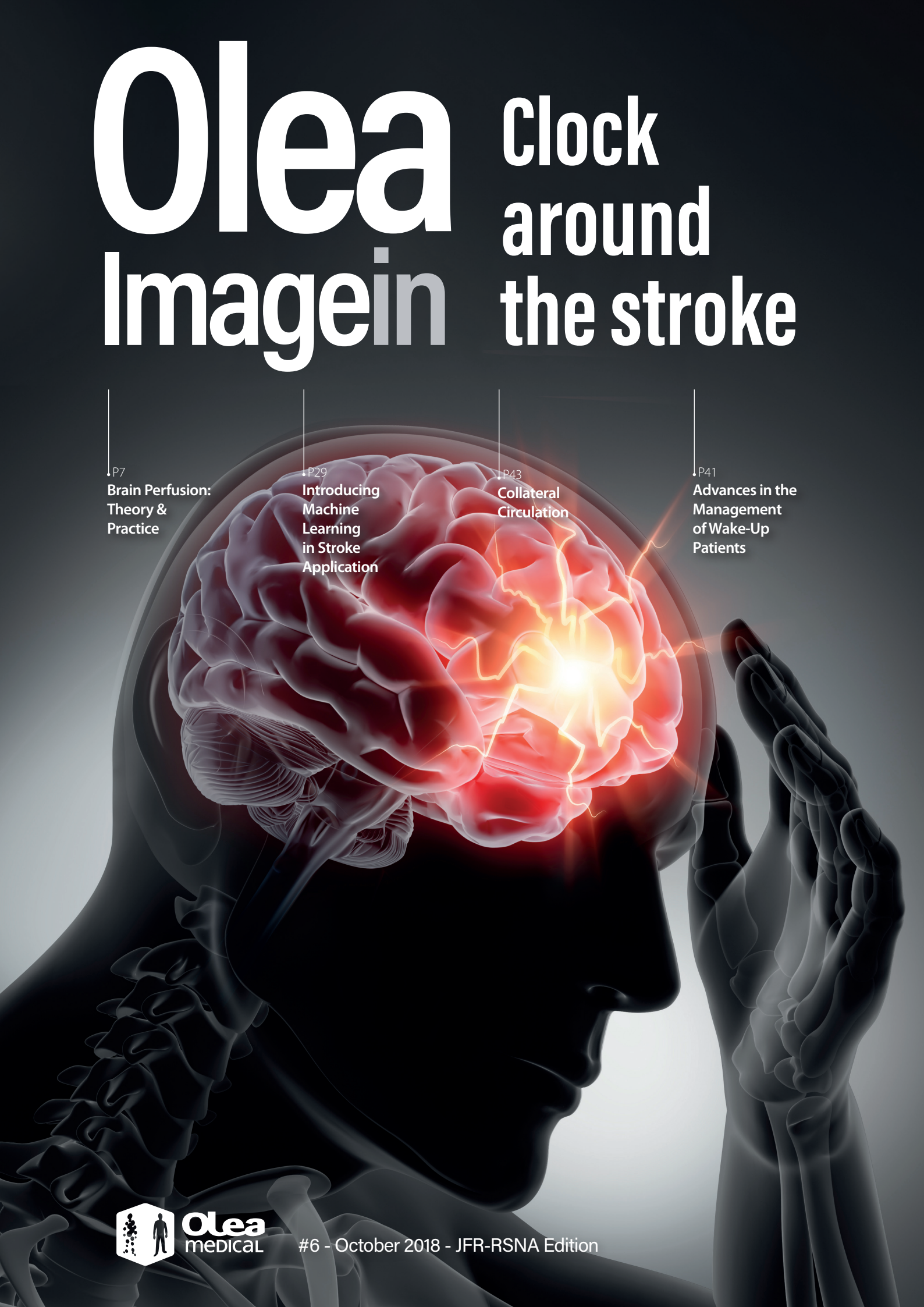
Olea Imagein

Clock around the stroke



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Director:
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Brianna Bucciarelli
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Vincent Dousset, MD, PhD
Head of the Neuroradiology Department
Pellegrin University Hospital, Bordeaux, France

Can we move from too little too late to widespread timely effective care?

In this issue, world leaders in the field present their opinions on key issues related to the ticking clock faced by every stroke patient. Ischemic stroke is the third leading causes of death in the world [1]. While a slight decrease in the incidence has been observed in the past decades thanks to preventive therapies that address major risk factors such as high blood pressure, the prevalence continues to grow with the aging population with a predicted 34% increase in total number of stroke events in the European Union between 2015 and 2035 [2]. Effective treatments available today include care in specialized stroke units, thrombolysis and mechanical thrombectomy (with about 10% of stroke patients eligible for mechanical thrombectomy). The probability of a good outcome is far superior for those patients treated with thrombectomy compared to intravenous thrombolysis, with a number needed to treat (NNT) of 2.6 for mechanical thrombectomy – meaning that for 2.6 treated patients, one will return to functional independency (defined as mRS ≤ 2) within 3 months; this compared with a NNT ranging from 8 to 14 for IV tPA alone (within the 0-3 hour and 0-4.5 hour time windows respectively) [3].
Recent trials have demonstrated the benefit of thrombectomy for all age groups even when started well beyond the initial 6 hours after stroke symptom onset [4]. However, a minority of patients with acute stroke has access to timely and effective care. For example, in 2016, 13% of stroke patients eligible for mechanical thrombectomy were treated in Europe. Effective acute stroke management requires much multidisciplinary expertise, collaboration and energy among emergency medicine specialists, neurologists, neurosurgeons, interventional and diagnostic neuroradiologists on a 24 hour, 365 day basis. Many specialized skills and resources are required to provide personalized and precise diagnostic and therapeutic care, including specialized interventional methods and materials to retrieve thrombi.

Medical teams are already overburdened and stressed... while 87% of eligible patients are not treated with the most effective currently available therapy and only one-third of optimally treated patients have a meaningful recovery. Providing timely comprehensive stroke treatment to each patient is an enormous task. How can we achieve this? First, because these treatments are cost-effective, it would be medically and economically reasonable to multiply the number of centers performing thrombolysis and mechanical thrombectomy, although the feasibility of scaling up such resources is uncertain. Second, a better definition of selection criteria for eligible patients needs to be achieved using medical imaging with CT and enhanced use of MRI. Given our current diagnostic capabilities, it is not acceptable to treat patients without stroke (false positives) and patients with stroke unlikely to benefit from thrombolysis or thrombectomy. Third, in such context, the development of teleradiology specialized for stroke may aid proper patient selection with remote guidance while patients are located at their closest primary stroke center [5]. However, considering the large and diverse stroke burden, limited resources for thrombolysis and mechanical thrombectomy, and the limitations of treatment effectiveness, more research is needed to find and develop efficient and more widely accessible solutions.

Enjoy your reading!

mRS: modified Rankin Scale - IV tPA: Intravenous tissue Plasminogen Activator

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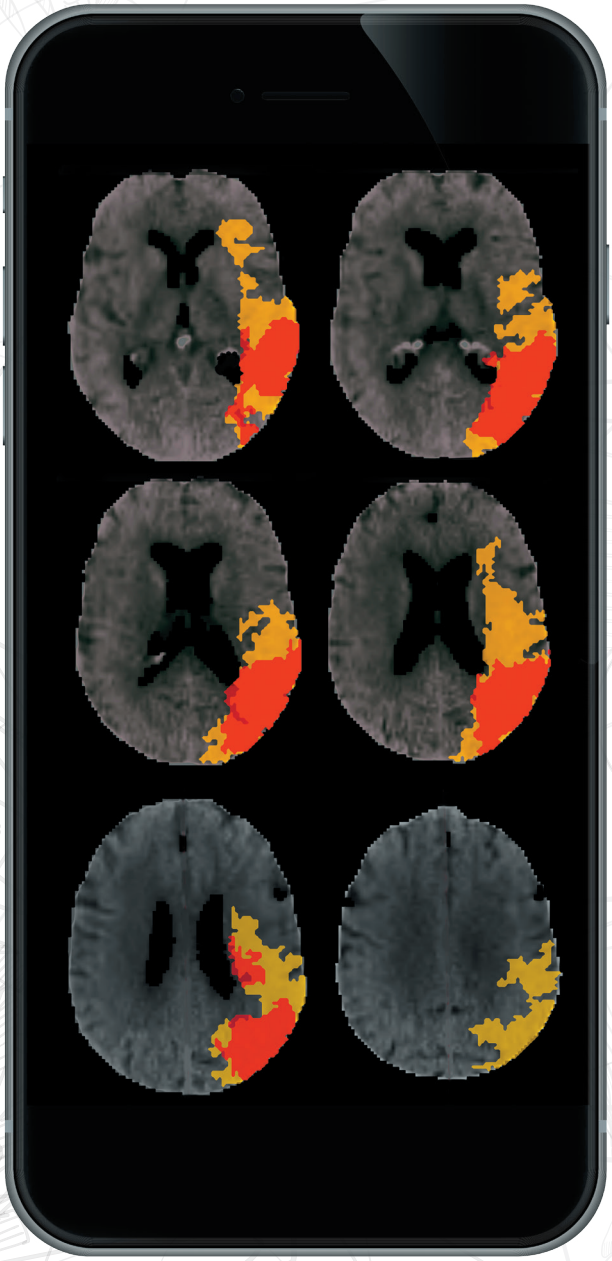

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Kambiz Nael, MD
Associate Professor of Radiology in the Division of Neuroradiology at The Icahn School of Medicine, Mount Sinai, New York, NY, USA.

Kambiz Nael is a board-certified radiologist with specialty certification in neuroradiology. Currently, he is an Associate Professor of Radiology and Director of Neuroradiology MRI, CT and Advanced Imaging at Icahn School of Medicine at Mount Sinai.

Kambiz Nael has over 100 scientific presentations and has authored or co-authored more than 60 scientific articles. His clinical and research interests include advanced neurovascular imaging and quantitative multiparametric neuroimaging approaches in the diagnosis of a variety of cerebrovascular disorders and brain and spinal neoplasms.

Kambiz Nael is a senior member of the American Society of Neuroradiology (ASNR) and also holds membership in the Radiologic Society of North America (RSNA), International Society of Magnetic Resonance Imaging in Medicine (ISMRM), Western and Eastern Neuroradiology Society (WNRS and ENRS), American Society of Head and Neck Radiology (ASHNR), and American Heart Association, Stroke Council (AHA/ASA).

"Neuroradiologists will play an increasingly important role in the diagnosis of patients with acute stroke"

Olea Imagein: How would you define the relative role of neuroradiologists and neurologists in the management of patients with acute ischemic stroke?

Kambiz Nael: I would describe it as collegial. I think neuroradiologists and stroke neurologists have been and will continue to work very closely to provide the best possible care to stroke patients. With the new clinical trials showing the significance of imaging for proper treatment selection, this mutual collaboration between neuroradiologists and stroke neurologists needs to be stronger than ever. The ultimate goal is to safely treat patients, which can be achieved by adopting a "team mentality" when both parties are contributing to the care of stroke patients.

O.I: How do you think the role of the neuroradiologist will evolve in the future?

K.N: Neuroradiologists will play an increasingly important role in the diagnosis of patients with acute stroke. Especially with widening of the treatment window, neuroradiologists can apply advanced imaging techniques to correctly identify patients who can benefit from treatment. This has implications when more patients with acute stroke can be qualified to be treated safely by proper use of advanced imaging.

O.I: What about the role of post-processing?

K.N: Post-processing needs to be accurate, quantitative and automated and the results should be reliable. There has been significant emphasis on use of CT or MR perfusion. It is crucial that we test and refine our perfusion post-processing algorithms to find the ischemic and salvageable brain tissue with high precision. This process needs to be fast and seamless. The expectation is to have the results automated and without human interaction. Stroke neurologists and interventionists need these results instantaneously to avoid treatment delay.

O.I: What is your opinion on the existing solutions?

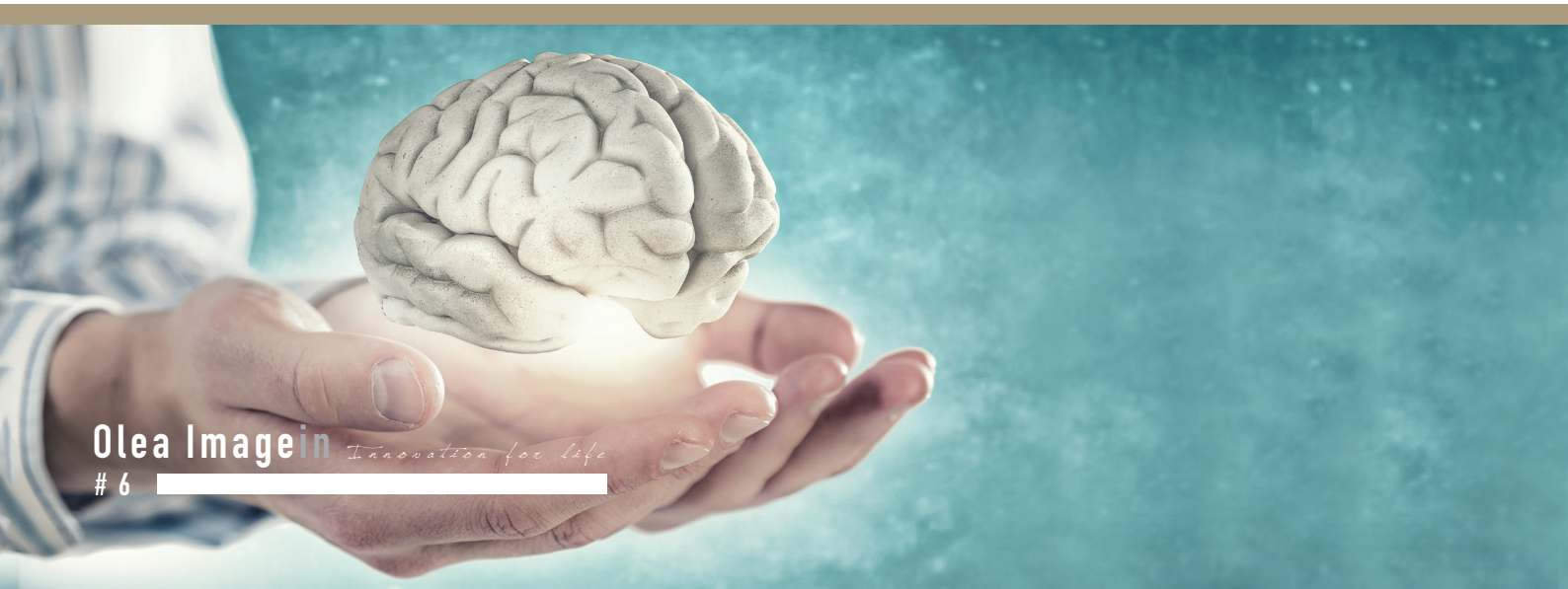
K.N: This is a work in progress. We have seen a significant increase in the number of post-processing software and automated solutions for selection of patients with ischemic stroke; in particular, since last year that treatment window has been extended up to 24 hours in properly selected patients. The accuracy and consistency of each software and inter-variability among the software platforms still need to be reconciled and we have a lot of work in front of us.

O.I: What are the expectations of expert neuroradiologists versus non expert emergency doctors?

K.N: I think the expectation should be to have the best possible information in a timely manner to make treatment decision, regardless of the expertise of physicians or where they practice. The paradigm of stroke treatment is changing rapidly with significant focus being on transfer of patients to centers with higher expertise to avoid treatment delay.

O.I: What do you think of the new stroke guidelines published at ISC 2018? What will be their impact?

K.N: I can tell you my opinion about it when it is all set! This guideline seems to be a moving target and it has changed and been amended a few times since its original publication. But with all seriousness, I think we had a lot of new information since last year and they all need to be digested by the stroke community. Therefore, I think it is normal to have a dynamic process of adopting new information for a while, before we can finalize a standard of practice that suits most stroke centers.



Brain Perfusion: Theory & Practice

Adam Davis, MD

In 2014, Dr. Adam Davis lectured at the European Congress of Radiology (ECR) regarding the Fundamentals of Perfusion imaging of the brain. Olea Imagein asked Adam Davis to update this well-received lecture to reflect the changes in the field with the recent publication of major stroke trials.

This lecture is broken into two separate parts. The first discusses the theory and the tools of brain perfusion, where the basics and the difficulties encountered with the underlying principles of this technique as well as the solutions to these problems are discussed. In the second part, the clinical applications of brain perfusion are presented, including the literature and the guidelines, as well as the impact on clinical practice and the controversies created.

The focus of this lecture is on cerebral occlusive ischemia, however the theory and applications apply more broadly.

PART I: Theory and Tools of Brain Perfusion

Why do we use perfusion imaging? Because we want to quantify the cerebral circulation and reveal the state of tissue perfusion, in order to understand the pathophysiology of diseases such as ischemia, neoplasia or inflammation.

The clinical utility is based on two assumptions. First, we assume that the surrogate markers (iodinated contrast, gadolinium, xenon, radio nucleotide) injected into the patient imitate the circulation – a fairly safe assumption to make. Second, we assume that imaging data can be converted into meaningful physiological correlates by the models, the algorithms and the dedicated post-processing software used in every day clinical practice. This is a more challenging moment of faith.

Brain Perfusion Principles

What are the principles underlying perfusion neuroimaging? The fundamentals consist of one main measurable data, the MR signal intensity or the CT attenuation of contrast within the voxel, as a function of time. Let's focus on CT imaging. The signal S(t) is measured in two sites: in the arteries, to obtain the arterial input function (AIF), and in the parenchyma, to obtain the tissue concentration and additionally, in the veins, to determine the venous output function (VOF). There is often confusion with VOF, this latter is not used to determine the perfusion of the brain but to standardize the amplitude of the AIF in order to overcome partial volume effects. This signal needs to be converted into contrast concentration as a function of time C(t).

A simple equation is used to achieve this conversion:
C(t) = S(t) ⁄ S(baseline) x ln(K)

The contrast concentration over time C(t) is equal to the signal at a given time S(t) divided by the baseline – to provide a proportionate ratio – times the natural log of K.
We may wonder: what is K? K is a mathematical constant dependent on the contrast delivery, the angioarchitecture and the acquisition parameters. For any given patient, K is unknown. Therefore, we start with only an estimated parameter for brain perfusion. That is the reason why concentration of contrast is very difficult to quantify with accuracy in perfusion imaging. Consequently, relative values are more reliable and more transferable from case to case, from vendor to vendor, from institution to institution, from trial to trial.

Brain Perfusion Maps

Five parameters are commonly used in every day practice: time to peak (TTP), cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and time to maximum residue function (Tmax). We will define each parameter individually.

TTP

Time to peak is the simplest and the earliest commonly used parameter. It is the only one not requiring complex mathematics, since it is easily derived from the signal intensity or concentration curve. We simply start our acquisition and measure time; when the maximum concentration is reached, we have determined the time to peak, easy to obtain.
However, TTP is a time sensitive parameter; in the past, longer TTP was commonly interpreted as decreased cerebral blood flow. But that is entirely inaccurate: just because we have a delay of contrast delivery does not mean that the blood flow is decreased, or that the tissue is under-perfused and at risk of infarction; it only means that blood is arriving there later. We can have perfectly adequate collaterals and a longer time to peak: adequate collateral flow by necessity has an elongated TTP. So, this early measure, used for many years, has been pretty much abandoned.

CBV

Cerebral blood volume, expressed in ml/100g tissue, is a very important index almost daily used. CBV requires the least complicated mathematics, it is simply the area under the first pass concentration-time curve – basically the integral of C(t) – and the most reproducible parameter across software vendors. A simple mathematical equation and reproducible?

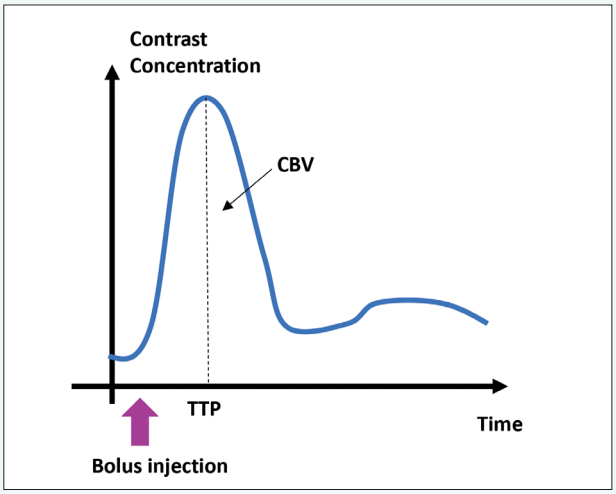


Figure 1: Typical concentration-time curve

We might say: this is easy! Unfortunately, it is not. There are problems associated with using CBV to determine perfusion.

If we consider a typical concentration curve (Figure 1), we observe that the signal increases and then decreases as time progresses. At the end, it does not return to zero. Why? Because of recirculation. We never get to the end of the contrast-concentration curve because contrast has already passed through the circulatory system and new blood is coming in; this recirculation corrupts the end of the curve. So, how can we measure the area under the curve, if we don't know where the curve ends? What manufacturers do is to estimate the end of the curve, usually by drawing a line just prior to the arterial recirculation – the second bump in the contrast time curve. So now we have a problem: we are approximating the volume beneath the concentration curve to determine the CBV. However, there is another way to estimate CBV. It can be calculated using the entire area under the concentration curve normalized by the AIF one. This method is implemented in Olea Sphere® and allows to overcome this issue.

An additional problem is that there is no one correct place to define reliable perfusion. The concentration curves normally differ depending upon what part of the brain is measured; therefore, there are multiple concentration curves that define what the normal state is. Their shape will be different in the artery, the gray matter or the white matter.

Why is this important for the determination of the CBV? Because typical perfusion protocols truncate C(t) so that tissue with delayed or slow flow has an artificially smaller area under the curve. As we can see from the diagram on Figure 2, when we measure the arterial input function, i.e. the contrast in the artery, we say: here is the end of the curve, we will stop it here. But the tissue concentration is continuing to decrease. That delay is the reason why we underestimate the CBV every time. It is because of the natural and physiologic delay within the brain, the tissues and the arteries.

This fact is important because of the way we think about CBV. The common paradigm that people work with is that as cerebral blood flow decreases, auto-regulation induces vasodilatation to compensate. This phenomenon increases CBV to maintain CBF so that delivery of oxygen and metabolites remains adequate. But if CBF continues to decrease, it drops beyond the capacity of auto-regulation and vasodilatation to compensate; as a consequence, CBF starts to fall off and CBV drops. That CBV dropping has been interpreted for many years as a marker for infarction [1-3]. The problem is that we underestimate CBV routinely, which causes erroneous diagnosis for infarction. In summary, CBV was our first problem: we were using an erroneous marker.

The parameter we have traditionally used to determine infarction, CBV, is partly if not entirely inaccurate.

We have known this for quite a while. Several papers looked at cerebral volume and concluded this may not be a parameter we should be using as our marker of infarction. A study by Campbell et al. [4] concluded: *"In contrast to previous reports, CBF corresponded with the acute diffusion-weighted imaging (note: our gold standard in infarction) lesion better than CBV, although no single threshold avoids detection of false-positive regions in unaffected white matter. This relates to low signal-to-noise ratio in CTP maps and emphasizes the need for optimized post-processing".*

In another paper by Bivard et al. [5], the authors looked at a comprehensive analysis of this issue and said: *"A double core threshold with a delay time (Tmax) of more than 2 seconds and cerebral blood flow less than 40% provided the most accurate definition of the infarct core".* This was so significant that the authors felt compelled to add: *"These findings mark a departure from the previous widely accepted view that CBV is best used to define infarct core. Of course, very low CBV is indicative of infarction, but no single threshold accurately defined the infarct core compared with CBF thresholds".*

More recent articles also confirmed this finding. In 2016, Lin et al. [6] wrote: *"With a delay time of greater than 3 seconds and a delay-corrected CBF set at less than 30%, CT perfusion resulted in a nonsignificant difference compared with MR imaging in the volume of the entire ischemic region and the ischemic core".* This helped to confirm that a double parameter threshold was the best to compare to the gold standard MRI.

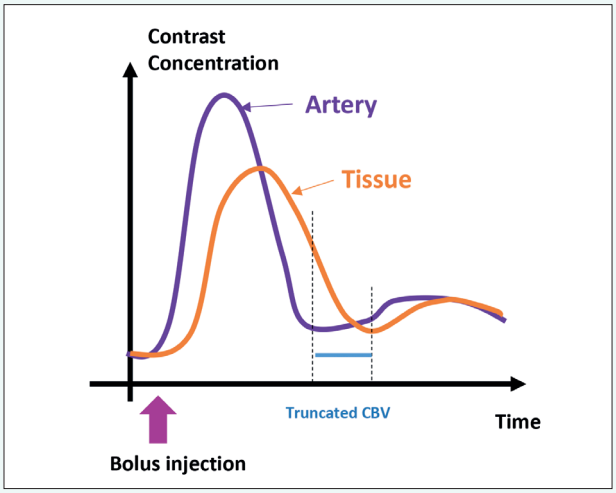


Figure 2: Tissue vs. artery concentration-time curves

CBF

That takes us to cerebral blood flow and an obvious question: if we are looking at areas of infarction that have low CBF, then why don't we just simply measure CBF?

CBF may be determined in the most simplistic way: as the concentration curve increases in a voxel C(t), the blood flow represents the slope of the initial curve. If the signal intensity rises quickly as a function of time, there would be a steep slope indicating a high value of CBF. Ideally, we would want a rapid, well-defined compact contrast bolus to pass through the vasculature, in order to best mimic the blood flow. However, the appearance of the contrast within the voxel is actually not an accurate representation for practical clinical imaging. There are many factors that affect the overall appearance of that curve including the type of contrast, the injection rate, the injection volume, the angioarchitecture (stenosis and collaterals) and the intravenous mixing.

A study from Coursey et al. [7] examined the concentration curves produced using different injection rates. At 8 cc/sec, a much more rapid upslope and a higher peak were observed than at 4 cc/sec, for the same patient (as illustrated on Figure 3). The injection rate therefore has an impact on the concentration curve independent of the true blood flow. The upslope is mostly due to the progressive accumulation of contrast in the blood pool during the injection which then continuously flows into the voxel. We are not measuring blood flow, we are measuring injection rate.

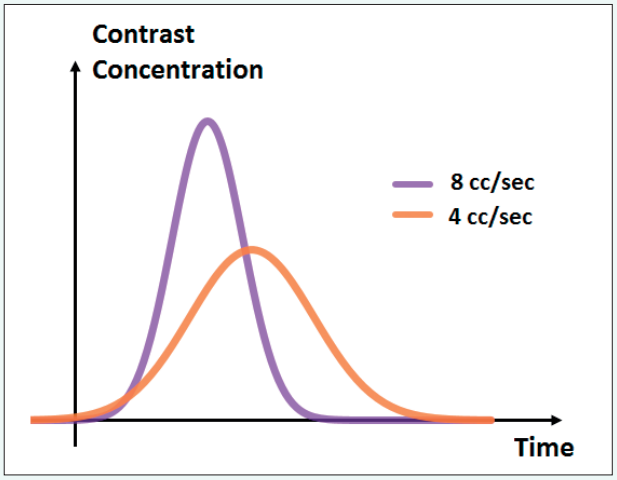


Figure 3: Concentration-time curves obtained using different injection rates

The same can be noticed for the viscosity of the contrast. Mahnken et al. [8] measured time-enhancement curves for contrast agents at different viscosities: the slopes were different, steeper for low viscosity and a little slower for high viscosity, which could be interpreted as increased or decreased blood flow, respectively. But the blood flow has not changed, we have just changed the viscosity of the contrast material.

So it brings us to a natural question: how do we more accurately determine the initial slope of the curve to derive the CBF? The answer is by abandoning this technique entirely, since there are better ways to determine the CBF.

Introducing advanced mathematics to better estimate hemodynamic parameters

Let's take a step back and discuss the residue function. This is a term that is not commonly heard, but it is a really important concept to know in order to understand the parameter Tmax. Theoretically, the best way to determine blood flow would be to instantly deliver the contrast to the voxel, see how large a signal is created and then watch it disperse as the blood washes out, much like throwing a handful of powdered chalk into a stream would indicate to you how much water is there by the dilution of your chalk and whether the water is moving slowly or rapidly. The amount of signal intensity and its diminution would then be a direct reflection of the CBF. That is exactly what the mathematical algorithms assume is happening. We use (de)convolution methods to solve for this, to try to mimic this theoretical process.

(De)convolution algorithms solve complex equations and we use them to convert concentration-time curves within the tissue and the artery into meaningful clinical parameters. These mathematical operations use two functions to solve for a third function – a modified version of one of the original functions. Convolution algorithms take one function, and translate it (or move it) through the second function over time, resulting in a third function that reflects the area of overlap between these two functions (Figure 4).

After measuring 1 – the arterial input function (AIF), i.e. the signal intensity in the arteries over time, and 2 – the contrast signal in the tissue over time C(t), we use the deconvolution methods to give us the residue function (Figure 5).

Theoretically, the residue function is a curve representing the instantaneous signal of contrast within the voxel, the impulse, as well as the washout of the contrast within that voxel. With the residue function, we are able to determine CBF, the time to maximum of the residue function (Tmax) and the mean transit time (MTT).

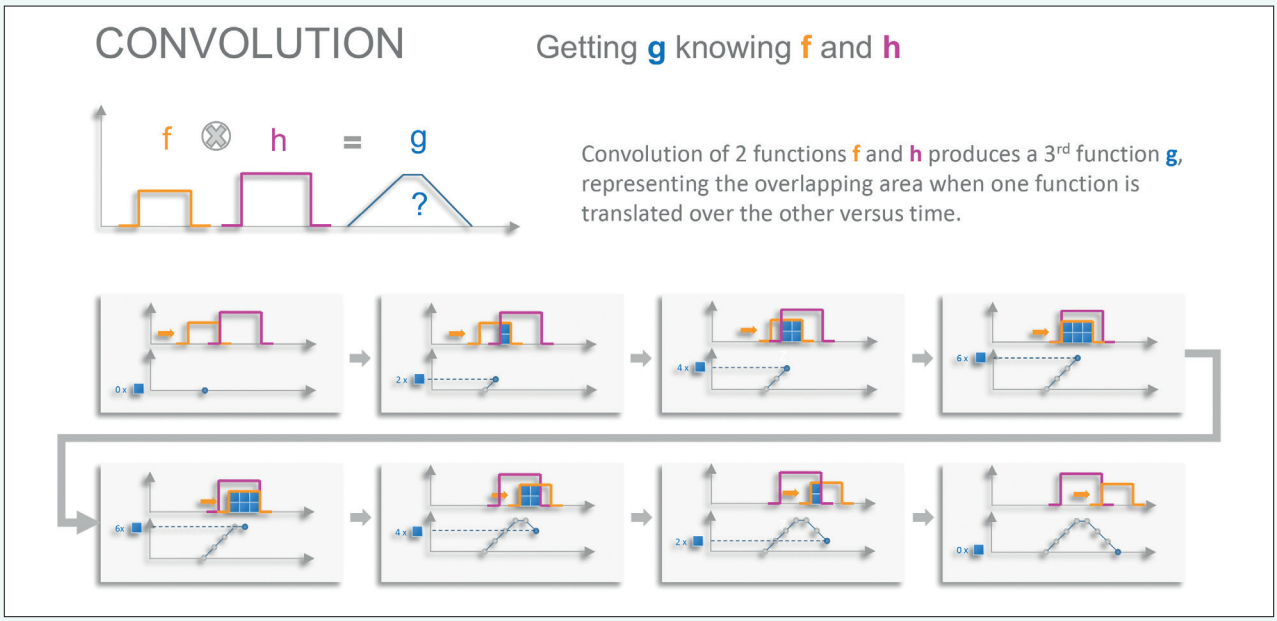


Figure 4: Understanding how convolution product works

Indeed, the height of the impulse of the residue function is the CBF; the time it takes from the beginning of the acquisition to that impulse is the Time to maximum of the residue function (Tmax); and the weighted average of the area under the curve is the MTT.

Tmax

Tmax is an important parameter to understand and utilize. It is not a true physiologic value, it is a theoretical construct reflecting the bolus arrival time from the artery to the parenchyma. Increased Tmax is thought to represent a delayed and diminished collateral circulation. It is easier to assess than CBF, because it is expressed in seconds and there is no white/grey matter differences. In common use, the increase of Tmax will correlate with the final infarct volume. Tmax higher than 4 to 6 seconds has often been defined as the penumbra [9-12], but there is considerable variability in the literature.

Tmax is important because it has been used in all major stroke intervention trials (DEFUSE 1,2&3, EPITHET, MR RESCUE, EXTEND-IA) [12-17] as an indicator of penumbra and infarction.

Tmax, like other parameters, is strongly influenced by signal to noise ratio, so that there is an inherent inaccuracy in the measurement. Tmax has not been shown to correlate 100% accurately with the ultimate infarct. It is therefore an excellent indicator, but not a perfect one.

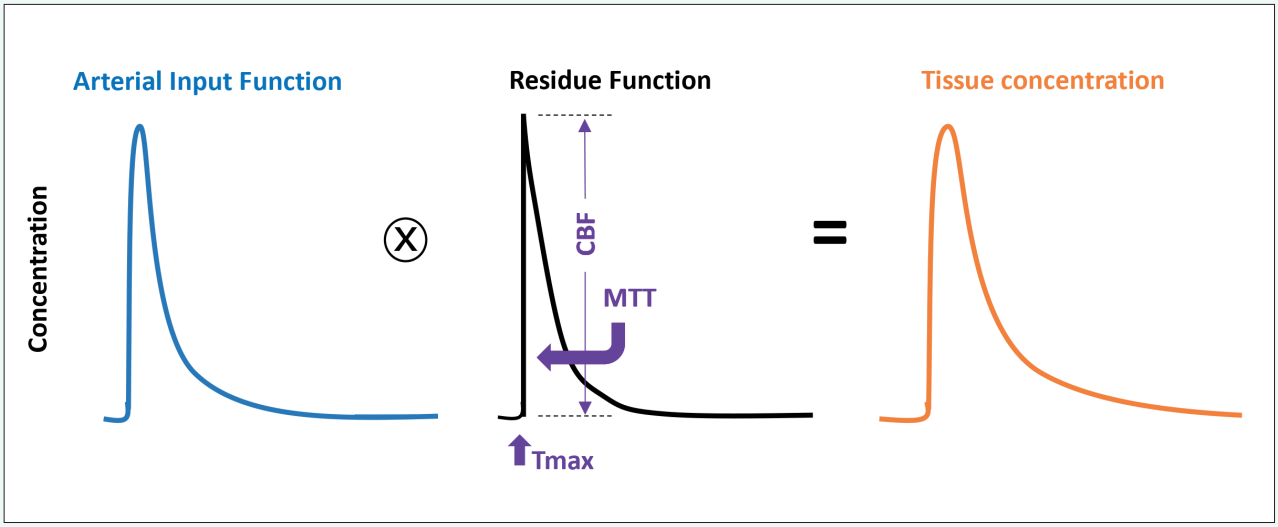


Figure 5: Tissue concentration-time curve as a convolution of the AIF with the residue function

MTT

Mean transit time is basically the average time that the blood remains in the tissue. It is often thought to represent the microvascular/capillary circulation. It can be derived directly from the concentration-time curve and the determined CBV and CBF, but we know that they are corrupted by the injection kinetics; therefore, MTT is calculated as the weighted average of the area under the curve of the residue function down slope (Figure 6).

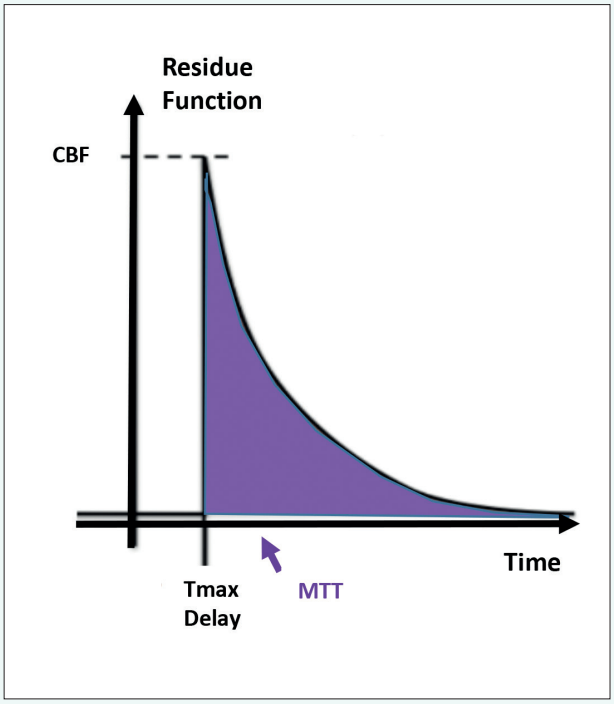


Figure 6: Residue function with CBF, Tmax and MTT parameters. Adapted from [18]

Increased MTT has been interpreted as representing longer flow to the tissue, thus reduced CBF or elevated CBV, since MTT is simply CBV divided by CBF. Therefore, MTT, just like Tmax, has been thought to identify tissue at risk for infarct, or ischemic penumbra. It is a sensitive and conspicuous parameter, and is simply expressed in seconds, eliminating gray and white matter differences. The deconvolution is [to some degree] time insensitive, so that there is diminished artifact with delayed contrast. Nevertheless, like any parameter, delayed flow through the tissue does not necessarily indicate risk for infarction. MTT is also influenced by other factors that degrade our assessment like signal to noise ratio.

Accuracy of Brain Perfusion

So here we are. We have just discussed the parameters most frequently cited during clinical perfusion neuroimaging. How well are we doing with them?

One clinical study from Kudo et al. [19] measured perfusion and ischemic thresholds using 5 different commercial software to post-process CTP data from 10 stroke patients. They determined infarct size for these 5 different vendors. For CBF and MTT ratios, the sizes of infarct determined varied and depended upon which vendor software was utilized. The values that we have come to rely on to indicate whether tissue is infarcted or not is entirely dependent upon the software we are using! How does one make a decision in this context?

This result is not a surprise. In an article from Kamalian et al. [20] considering real clinical material, the authors mentioned that *"the optimal absolute CBF thresholds were 4.7, 5.4 and 10 ml/100g/min using three available commercial software*

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packages. The corresponding optimal normalized thresholds for infarct were 84%, 72% and 68% reductions in CBF as compared with the contralateral hemisphere". Once again, same patient data in 3 different software programs produces 3 different results.

What are the consequences of these uncertainties, these differences in accuracies between different software vendors in the determination of the thresholds for infarction and penumbra? This was such a significant and serious matter that in 2012, Dr. Ramon Gilberto Gonzales said at the ASFNR referring to a Massachusetts General Hospital stroke consensus study: *"There is no advantage of CT perfusion in the evaluation of stroke. It is unreliable for determining infarct core"* [21]. This was a significant problem, which sent the entire stroke community into disarray, because the fundamental underlying clinical parameters that we were using in CT perfusion for stroke were questioned as being unreliable and unhelpful in our daily clinical practice.

The same author [21] commented that part of this problem had to do so with contrast-to-noise ratio (CNR), and concluded that CT perfusion has a much lower CNR (<1) than Diffusion-weighted MRI (>8). This means that the imaging contrast difference between abnormal and normal tissue is negligible.

This is completely correct. Figure 7 shows a CT of a patient with a left MCA territory acute infarct. Using American College of Radiology criteria and appropriately placed regions of interest, we can see that within the area of basal ganglia, we have a CNR of 1 for the infarct relative to the normal side (left image), and within the centrum semi-ovale only 0.5 (right image).

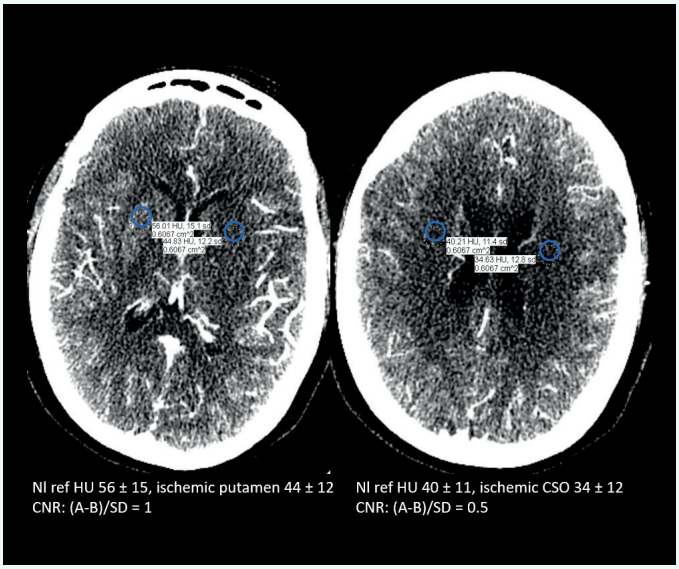

Figure 7: CNR of CTP images, calculated as the difference between the ROI values within normal tissue and within the ischemic area divided by the standard deviation (SD) of the ischemic ROI value

This problem of noise during CT perfusion is directly related to our desire and our need to reduce the radiation dose to the patient.

We will tolerate the greatest amount of noise and image degradation that still allows us to make a determination of the area of ischemia. Lower radiation dose increases patient safety but it is important to remember that it is in direct opposition to image quality.

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Brain Perfusion Improvements

After reviewing the basic principles of brain perfusion, the question is: how can we improve on this? Let's go back to basics. We know the two measurements that we can utilize: the concentration over time in the feeding arteries and within the parenchymal voxels. These are our hard data. How do we make them more accurate? There are several things that we can do to improve our results.

Local AIF

First, we can measure the arterial input function (AIF) locally instead of globally. Global uses a single value, typically near the skull base, distant from the tissue we are interested in; this introduces delay that corrupts the data. Local means the artery used is closer to the tissue of interest: the curve becomes more relevant since it is closer to reflecting the blood flow characteristics from the smallest arteriole / capillary to the tissue – the true value that we are actually interested in. Local AIF reduces time delay due to normal physiology, dispersion and collateral flow.

When post-processing a cerebral perfusion study, we locate the marker on one of the arteries of the brain, this becomes our AIF. When choosing a single artery we typically choose a single vessel at the skull base and try to avoid volume averaging. The problem is that there is a long delay between the flow at that artery and the more distal tissue, and we know that this delay is problematic, because delay cuts off the end of the curve and poorly represents the truer hemodynamics between the smallest arterioles / capillaries and the parenchyma. A better way of doing it might be to consider lots of arterial input functions, all over the brain, producing an average value that is closer to the tissue, so that our AIF matches more closely the kind of artery that we want to utilize..

This technique of measuring local AIF is implemented into Olea Sphere® software. In Figure 8, we can see multiple areas of the MCA bilaterally being measured, some quite distal in the MCA territories. Now, we have a more ideal arterial input function that reflects what is going on in the entire brain. Multiple sites of distal arteries give us less delay and more accurate results.

Does this make a difference? Absolutely. Willats et al. [22] looked at MR perfusion imaging for cerebral infarction first using a global AIF, second using a local AIF. They compared the results with the ultimate infarct on MR Diffusion and found that the local AIF more closely approximated the final infarct size while global AIF grossly overestimated the size. The authors concluded that *"local AIF methods were found to reduce the amount of residual dispersion in the perfusion maps compared with the conventional GAIF analysis. [Local AIF] methods can better characterize the severity and extent of any perfusion deficit"*.

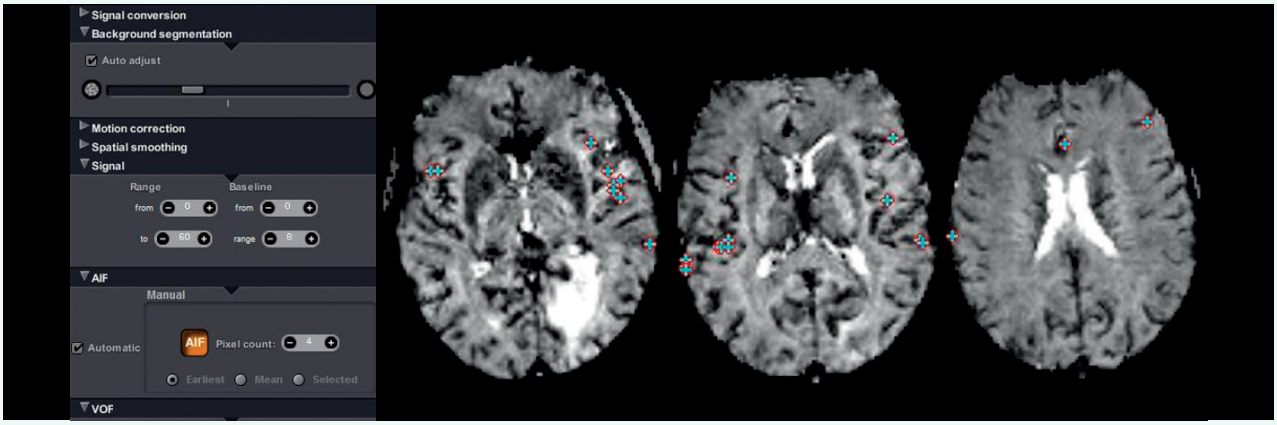

Figure 8: AIF selection in Olea Sphere® software

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SVD Algorithms

Secondly, we can use better mathematical algorithms. Ultimately, it boils down to the deconvolution algorithms that we discussed earlier. The best of these algorithms are time-insensitive: they diminish the differences in arrival time of the bolus at different voxels. Singular value decomposition (SVD) deconvolution methods such as circulant (cSVD) or oscillating (oSVD) are time-insensitive and better at generating a result closer to the ultimate ischemic threshold.

Not all SVD methods create the same results. Indeed, Figure 9 shows the estimated versus true value of blood flow from a phantom testing, with three SVD deconvolution methods, and highlights that time-insensitive oSVD is not perfect, but it is certainly more accurate than sSVD and cSVD. oSVD has a better predictive potential among the SVD methods.

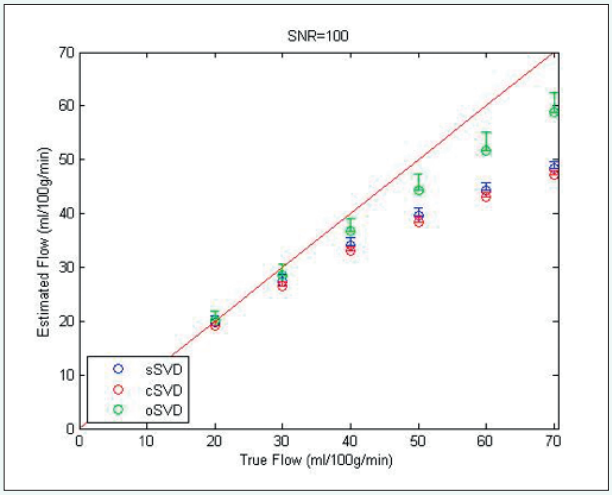

Figure 9: Comparison of sSVD (blue), cSVD (red) and oSVD (green) results using phantom data

The imaging noise contained in our studies, as well as motion and other factors that degrade image quality, introduce errors and uncertainties in the measurements. In Figure 10, the dotted line represents digital phantom data true measurement; and the blue line is the SVD determination. Both residue function and concentration curve over or under fit

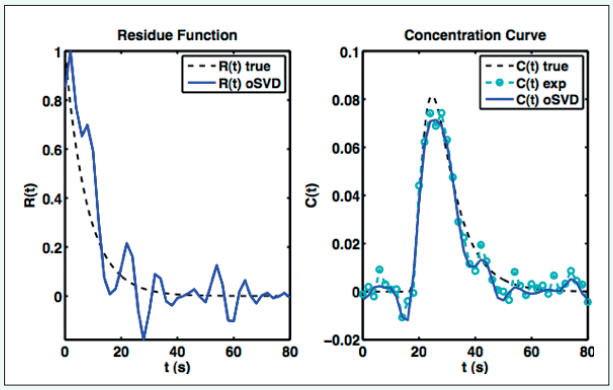

Figure 10: Residue function and concentration curve from oSVD (blue lines) compared to true curves (dotted line) using digital phantom data. Adapted from [23]

the true curves at certain points: SVD values oscillate around the true values, so that the concentration curve is a little bit short.

This is because the SVD method is sensitive to noise. When we image, we have noise. When we introduce noise to imaging, we introduce uncertainties. And when we introduce uncertainties, we introduce oscillations – and we are not exactly sure where the true value is.

Bayesian algorithm

Is there a better way of doing it? Yes. That is where Bayesian models come in.

Bayes theorem is a maximum likelihood theorem [23,24]. It is a probabilistic method using assumptions on prior knowledge of flow, as well as models of microvasculature. Bayesian model assumes that all motion, all natural occurrences happen on a smooth undulating incrementally increasing or decreasing acceleration. The waves within the ocean move in a gradually accelerating and decelerating fashion. Blood flow doesn't suddenly move from one velocity to another, it gradually increases and then decreases in speed. This Bayesian model assumes that the same is exactly happening in our brain perfusion.

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This algorithm preconditions data in order to more closely approximate what we believe would be the accurate results. Bayesian method produces better correlations with true values than the traditional SVD methods and, importantly, a greater accuracy at the extremes of measurement (Figure 11). In stroke, we are measuring parameters that are low flow or low volume. A greater accuracy with noisy data – low signal to noise – produces a better differentiation between normal and pathological states.

Figure 11 shows again a digital phantom, where true values are in dotted black, oSVD values in blue, and Bayesian values (called "New Algorithm") in red. Regarding the residue function (left), Bayesian values closely fit the true data. As for the concentration curve (right), we can see that Bayesian curve is much sharper, and fits the true curve a little bit better. The fit is more accurate with less over and under fitting.

This was clinically confirmed in a paper presented by Dr. Kambiz Nael at ASNR in 2017 [25]. Both cSVD and Bayesian measurements for infarct size were determined and compared with the results of MRI Diffusion. Bayesian methods still over or under estimated the ultimate infarct volume, however the degree of overestimation or underestimation was significantly less than cSVD, resulting in a more accurate determination of the area of infarction.

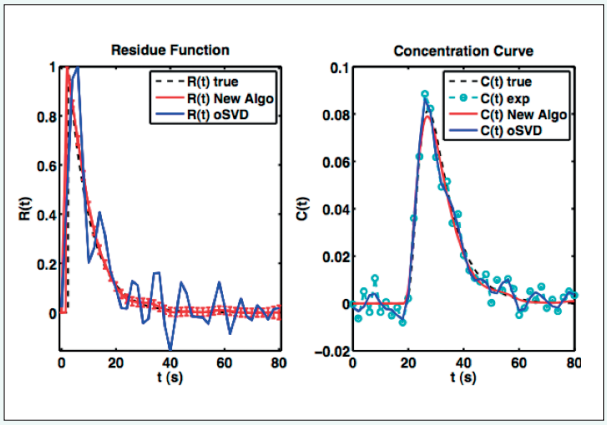

Figure 11: Residue function and concentration curve from oSVD (blue lines) and Bayesian (red lines) compared to true curves (dotted line) using digital phantom data [23]

New index: Delay

The third thing we can do is use different parameters. Bayesian method provides more accurate calculation for CBF, the index that correlates more closely with infarct. But it also allows us to calculate the arterial tissue delay. This can be thought as the Bayesian correlate for Time to maximum residue function (Tmax), i.e. the time between the arrival of the AIF and the tissue concentration. This is a truer measurement of circulation delay, less affected by those parameters that degrade SVD Tmax.

Scan the entire brain

Also, we can scan the entire brain. This may seem an obvious thing to do, but it was really not the common clinical practice for many of the last several decades. Because of the limitations of the CT technique, until now we have only been examining small volumes of brain during perfusion imaging, perhaps 4 to 6 cm of brain parenchyma during the CT study. This limited anatomic range resulted in inaccurate CT assessments.

In a study by Lin et al. [26] published in 2016, the authors demonstrated that when we measure less than 8 cm of brain tissue in the range of the scan, the sensitivity of measurement decreases markedly – for both patients without recanalization (for penumbra) and patients with complete recanalization (for infarct core). When larger volumes were scanned, the sensitivity and specificity of CT perfusion as compared with MRI Diffusion was approximately 80% and 90%, respectively. It is important to remember that these values need to be considered with caution because it is sometimes difficult to compare a CT and MR scan, for several reasons: differences in spatial orientation of the study, resolution, volume averaging, as well as the fact that these studies are being acquired at two different times. When the patient presents, a scan is performed which is likely very different in ischemic extent than the images obtained 24 hours later when the patient may have had medical support such as oxygenation, fluids and other parameters to improve circulation. So, there is an inherent difficulty in comparing an acute CT perfusion study with a delayed MRI study.

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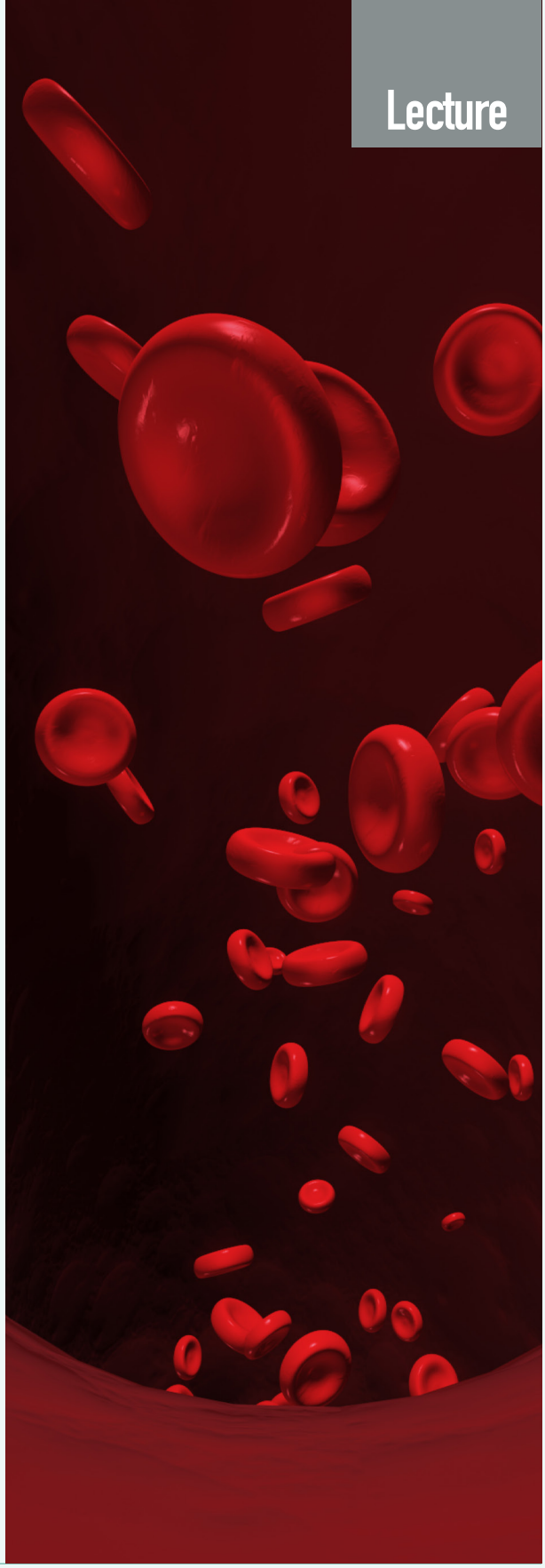
But regardless, the authors proved that sensitivity and specificity of CT perfusion – when larger areas of brain parenchyma were scanned – were fairly consistent utilizing different thresholds. They concluded that *"whole-brain CT perfusion is as accurate as MR imaging in measuring the ischemic penumbra and core, and outperforms limited-coverage CT perfusion in this manner. These are important messages for the use of CT perfusion in clinical practice"*. They added that *"CT perfusion and MRI are interchangeable applications"*.

Automated CT perfusion thresholds

The last thing that we can do to improve our results is to use automated CT perfusion thresholds to accurately assess infarct and penumbra volumes.

This was a very hard lesson to learn for many radiologists, including myself who have read numerous clinical perfusion studies, and thought we were pretty accurate in interpreting the quality of color maps in order to diagnose the area of infarct and diminished perfusion in a particular patient. What we have learned is that computer-generated thresholds for determining infarct and penumbra are significantly more accurate than human radiologists interpreting qualitative color maps. Computer-generated maps using threshold values are mandatory to make an accurate interpretation. More importantly, we now have the ability to automatically generate these perfusion studies 24 hours / 7 days a week without having human participation, making them much more readily available and applicable for stroke care.

This was confirmed in a study performed by Dehkharghani et al. [27]; the authors found that the automated analysis of CT perfusion studies in stroke patients was easily and quickly obtained, in about 3 minutes, and the automated analysis of core and hypoperfusion outperformed the radiologist qualitative analysis. This automated analysis provides an accurate assessment of infarct and penumbra on a per voxel basis, and that is very important since it is a more accurate way of looking at the perfusion data for any individualized patient.



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PART II: CT Perfusion Clinical Applications

Trending ideas

Let's move to the second part of this lecture and look at the clinical application of perfusion imaging. Where are we? What is the current state of the art of CT perfusion, regarding those patients who present at less than 6 hours or more than 6 hours?

The trending ideas within the stroke community are that: 1- Non-contrast CT (NCCT) alone or NCCT with CT angiography (CTA) is sufficient for imaging evaluation; 2- Time is the most important determinant for therapeutic decisions; 3- Given a new neurologic deficit, early presentation, a negative head CT, and a documented large vessel occlusion by CTA, all patients should undergo thrombectomy; 4- CTA collateral score provides equivalent information to perfusion imaging for the assessment of infarct and penumbra. Unfortunately, none of these are true.

Here is the take-home point: the clinical presentation, the non-contrast study, the demonstration of an occlusion, do not give the complete story regarding the perfusion status and the viability of the parenchyma or give the information that you need in order to make a treatment decision.

This is not a surprising conclusion. In a study from Zhu et al. [28], the areas of infarction and penumbra in successive patients presenting at various time intervals, from 0.5 hours to up to 32 hours, were measured. What could be noticed from these 165 patients with MCA M1 or ICA terminations occlusions, is that the amount of tissue that is infarcted or the area of ischemic penumbra were extraordinary variable over time. There is no consistent or predictable relationship between infarction and penumbra given the time of patient presentation. The authors concluded that *"PCT penumbral information could not be inferred from clinical, NCT and CTA data, or various combinations thereof. [...] For the same site of occlusion, the volume of penumbra was highly variable for a set volume of infarct".*

Therefore, time of presentation and proximal vessel occlusion do not provide a therapeutic mandate, they only indicate that thrombectomy should be considered. So, other than a non-contrast head CT and the patient's neurologic status, what really matters when deciding to do therapy? The first is the volume and location of irreversible ischemic injury (infarct); the second is the volume and eloquence of salvageable ischemic tissue (penumbra). In order to determine those two regions, CT perfusion or the combination of MR diffusion and perfusion is required.

In the recent stroke trials (MR CLEAN, REVASCAT, ESCAPE, SWIFT PRIME, EXTEND-IA, THERAPY) [29-33,17], we could see that when perfusion imaging was used at a greater extent to determine patient selection, a corresponding increase in good outcome in those patients was observed. Similarly, the percentage of risk reduction improved with increasing the use of perfusion for patient selection; and unexpectedly, the amount of time of presentation to treatment was less in the studies that utilized perfusion imaging, contrary to what people believed – that perfusion imaging would increase the amount of time and delay treatment.

The DAWN and DEFUSE 3 trials [34,12] demonstrated that the time window for thrombectomy was greater than had been previously understood, and that thrombectomy could be effective from 16 hours to 24 hours. Both used imaging as an inclusion criteria, CT perfusion or MR diffusion. While DAWN only required infarct size to be limited, DEFUSE 3 required demonstration of salvageable tissue via an infarct / penumbra "mismatch".

Thrombectomy with caution

There is an idea within the stroke community that there is a 'no Downside' argument. The argument that perfusion imaging simply eliminates patients who might have done better than expected. They argue that since perfusion imaging has very little complication, why deny patients the potential benefit of attempted thrombectomy? Furthermore, the endovascular trials showed that there is no risk to treatment – no difference in adverse outcome for the treatment group? However, this is not true.

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All of the recent major trials indicated that there is a morbidity associated with thrombectomy. The MR CLEAN trial [29] showed that new ischemic stroke, which are areas of infarction within the brain that are outside of the initial areas that were affected, were reported for 5.6% of treated patients versus 0.4% of control patients. Additionally, in the MR CLEAN trial, there was a procedural complication rate of 11.2%. These were serious complications, i.e. areas of new infarction, vessel dissection or vessel perforation. The EXTEND-IA trial [17] demonstrated a complication rate of 9% with 6% being infarct in a new territory. The DEFUSE 3 trial [12] showed a 2% procedural complication rate, however no new stroke was reported. Therefore, thrombectomy itself is not exactly a benign procedure, there is serious risk from performing thrombectomy. It should be performed in a more informed fashion, fairly weighing the potential benefit (salvaging penumbra – hypoperfused territory that has not infarcted) with the risk of the procedure.

Can CT perfusion help us to identify those patients who will benefit from thrombectomy? The answer is yes. We know this from the recent stroke trials, but we have actually always known this. There are numerous previous studies that have shown that perfusion imaging can help us with patient selection. As an example, in a study from Turk et al. [35] published in 2013, the patients were divided into 2 groups: treated before 8 hours and after 8 hours, with specific inclusion criteria. The authors found that when utilizing CT perfusion as guide for patient selection, there was no difference in outcome between the 2 groups. They concluded that there were *"similar rates of good functional outcome and intracranial hemorrhage in patients with ischemic stroke when endovascular treatment was performed based on CT perfusion selection rather than time-guided selection".*

Collateral circulation

So, what is perfusion telling us? What is the underlying physiology that perfusion imaging is demonstrating that allows us to stratify patients? It is really the adequacy of collateral circulation to non-infarcted parenchyma at risk.

The answer of course is yes, and we have known this for quite a while. A study from Kucinski et al. [36] published over 15 years ago indicated that collateral circulation is the underlying physiologic parameter that determines the patient outcome. They found that the degree of collateral flow was the only independent predictor of a favorable outcome of all the radiological predictors they looked at after thrombolytic therapy. Not only did this one study demonstrate this physiologic phenomenon, but there are also 8 other stroke studies [37-44] performed prior to that study that showed exactly the same results: patient outcome depends on collateral circulation.

It is important to remember that, regardless of what the patient collateral circulation is, it is meaningless unless you actually have tissue that can be salvaged in order to affect the ultimate outcome by performing a thrombectomy. In a study from Miteff et al. [45], the investigators looked at 92 patients with acute ischemic stroke symptoms presented in less than 6 hours; they considered all radiological parameters that were available to predict infarction, including NCCT, CT perfusion, CTA, collaterals by CTA, etc. When considering the volume of infarction and estimated tissue at risk, they concluded that *"perfusion CT mismatch is a prerequisite for a favorable clinical response",* and that all patients below a mismatch ratio of 3 had an unfavorable outcome, regardless of their collateral and reperfusion status at the time of completion.

So, we understand that collateral status is important, and that identifying areas of penumbra is important. It is important to remember that there are multiple ways of determining collateral circulation – by CT or MRI perfusion imaging or angiography or conventional angiography – but not all of these studies give the same information. This brings us to the current practice trend using dynamic multiphase CT angiography to understand collateral circulation.

Let's look at dynamic multiphase CTA versus CT perfusion for understanding collateral flow.

Dynamic multiphase CTA is based upon performing a CT angiogram; then, multiple successive scans are performed through the brain parenchyma in order to find the progress of the contrast within the distal vasculature including retrograde flow. Normally, two or more acquisitions are performed and there is a grading system that looks at opacification of con-

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trast in the vessels. The collateral status can be divided into separate, broad, individual categories: either a good collateral status when the contrast has an opacification nearly back to the level of occlusion; a more intermediate status when there is only partial circulation; or a poor collateral status when little contrast appears on the delayed acquisition.

Multiple papers have been recently published, showing that this dynamic multiphase collateral circulation correlates with the degree of infarction. In a paper from Cheng-Ching et al. [46], they concluded that *"the presence of poor collateral status on admission may be associated with large strokes"*. They found that a greater than 50% CTA collateral status had a negative correlation with a large infarct. That should not be surprising since we have known for many years that collateral circulation correlates with ultimate infarct size. But just simply demonstrating the presence of a correlation does not necessarily mean that it is a useful parameter for making clinical decision during stroke treatment. There are many parameters that correlate with the infarct, and even in that cited paper, the authors state that other parameters correlate with the infarct including hyperlipidemia, coronary artery disease, CT/CTA ASPECTS score. Furthermore in this paper, when we look at the data of the individual patients, it is interesting to see that the collateral circulation status does not necessarily correlate closely with the ultimate infarct. For example, some patients with absent collaterals who presented at varying times from the onset of symptoms could have anywhere from almost no infarct up to areas of very large, life threatening infarcts. So, the multiphase dynamic collateral status certainly does generally correlate with infarct, but it does not give useful information about outcome on an individual patient basis.

A study from Vagal et al. [47] supported the use of CT angiographic collateral status for the management of stroke patients. They looked at the multiphase CTA results, determined a patient collateral status and correlated that with the ultimate result. What they concluded is that *"the CTA collaterals correlated moderately well with CTP measured core with an inverse relation. The strength of our study is that we have demonstrated association between CTA collateral status and CTP parameters in a randomized trial setting"*.

They added: *"this is clinically relevant as CTA collateral assessment may be an alternative for CTP, potentially obviating the need for an additional CTP study"*. But again, just a simple association is not powerful enough to give us the detailed and accurate information that we need. If we look more closely at this study, we can see that yes, there is a moderate correlation between collaterals and core volume and between collaterals and mismatch, but there was insufficient evidence to conclude about an association and correlation between collaterals and tissue at risk. Most importantly, the data is so weak that the ischemic core volume does not demonstrate a significant difference between the status grades.

In conclusion, multiphase CTA collateral assessment has not been demonstrated to provide accurate information regarding the size or location of either infarct or penumbra in ischemic stroke in an individualized patient manner; precisely the situation in which you want individualized care. Perfusion imaging (CT or MR) however provides accurate, individualized and reliable information regarding infarct and penumbra on a voxel by voxel basis.

Take home message

In summary, perfusion imaging for acute ischemic stroke:

1. Provides accurate determination of both irreversibly infarcted tissue and penumbra on a per voxel basis and allows for individualized treatment decisions including endovascular therapy.
2. Is superior to CTA collateral status for determining size and location of infarct and penumbra for patients with occlusive ischemic stroke.
3. Technique counts: we need to use correct indices for infarct and penumbra, scan a large enough territory to be accurate, use more accurate algorithms (Bayesian, oSVD), use local AIF as opposed to global, and use automated CT perfusion with computer generated thresholds.
4. Perfusion imaging, with or without diffusion imaging depending on radiographic resources, should be performed as part of the evaluation of every acute ischemic stroke patient, especially when considering thrombolytic therapy.

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Teleradiology

Nicolas Girouin, MD
Radiologist in Norimagerie group, Lyon, France;
Associate and co-founder of IMADIS.

"Standardization guarantees an optimal care to the patient"

Nicolas Girouin, graduated from University Claude Bernard (Lyon 1, France), is a radiologist specialized in emergency imaging, genito-urinary imaging and peripheral vascular imaging. He is co-founder and CEO of the IMADIS company of teleradiology located in Lyon.

IMADIS is a French company composed of radiologists, dedicated to the telemedicine management of radiological emergencies. The radiologists work as a team, day and night, in two different clinical centers specially designed and equipped for this activity. With a territorial coverage of 3 million inhabitants, IMADIS is the radiological structure number one in France for the management of radiological emergencies.

Olea Imagein: Could you please introduce yourself and IMADIS company to our readers?

Nicolas Girouin: I am a radiologist specialized in emergency, urinary and vascular imaging. Associate and co-founder of the IMADIS company, I also practice as a liberal radiologist in several clinics based in Lyon, France (Norimagerie group).

IMADIS is specialized in the management of emergency in the teleradiology field.

O.I: In your opinion, what are the advantages of teleradiology in the stroke emergency context?

N.G: The main advantage of the teleradiology concept we practice at IMADIS is the great availability of the radiologists team specialized in emergency care. The organization based on on-call and on-duty radiologists allows a constant attendance and reactivity 24/7, whatever the number of radiologists physically present at IMADIS. In the stroke context, this system highly contributes reducing the time that elapses between the patient's arrival and the treatment decision, and hence reducing his/her handicap.

O.I: What are the constraints and limitations of teleradiology?

N.G: The main constraint is first of all linked to the necessary changes to make in the medical organization regarding patient management. With teleradiology, the care delivered to the patient is

not modified, however the physical absence of the radiologist implies a higher formalization and traceability related to the patient's condition and management.

A teleradiological care always begins with an examination requirement written by the patient's doctor, detailing the patient's situation and questioning the radiologist about several medical aspects. Based on these information, the radiologist prescribes the most adapted imaging protocol, which is then carried out by an MR tech or radiographer. The medical images are finally interpreted by the radiologist, and the results are sent to the patient's doctor. Specific and efficient tools are necessary to handle these different steps and exchanges: information systems specialized in telemedicine, broadband lines, secure transfer tools, etc. The French Law with the telemedicine decree, the CNIL (French Commission on Information Technology and Liberties) and now the GDPR (General Data Protection Regulation) on regulate these multiple transmissions in order to

> "The main advantage of teleradiology [...] is the great availability of the radiologists team specialized in emergency care."

ensure their safety. The technical dimension is also a potential limiting factor. We need very high speed Internet connections to transfer data in a minimum of time, especially in an emergency context; furthermore, these connections need to handle ever-growing sizes of images series, due to the improvement and refinement of both scanners and imaging protocols.
Finally, all exams are not feasible with telemedicine, especially interventional radiology: it is not possible today for a remote clinician to perform a thrombectomy. But who knows!

O.I: How important is a unified acquisition protocol in the teleradiology context?

N.G: In our opinion, unifying the acquisition protocols is fundamental, for three reasons.

First, a unified imaging protocol allows to standardize as far as possible the quality of the images acquired on scanners from different vendors. We receive today images provided by all constructors present in France; even if each of them has its own "visual signature", a similar quality would ease their work to switch from one patient to another.

Secondly, it provides a standardization of the patient care management and allows the follow-up of evolutions regarding recommendations and practices. Today, we need to regularly – on an annual basis – update our protocols, since we, at IMADIS, consider that they have an « expiration date ». For example, our protocol for exploring suspicions of acute stroke is one of those that has the most evolved in the last 10 years.

Third and last, unified acquisition protocols allow the radiologist to know exactly how many images are expected. In summary, standardization guarantees an optimal care to the patient.

O.I: How does an automated post-processing solution help you in your clinical practice?

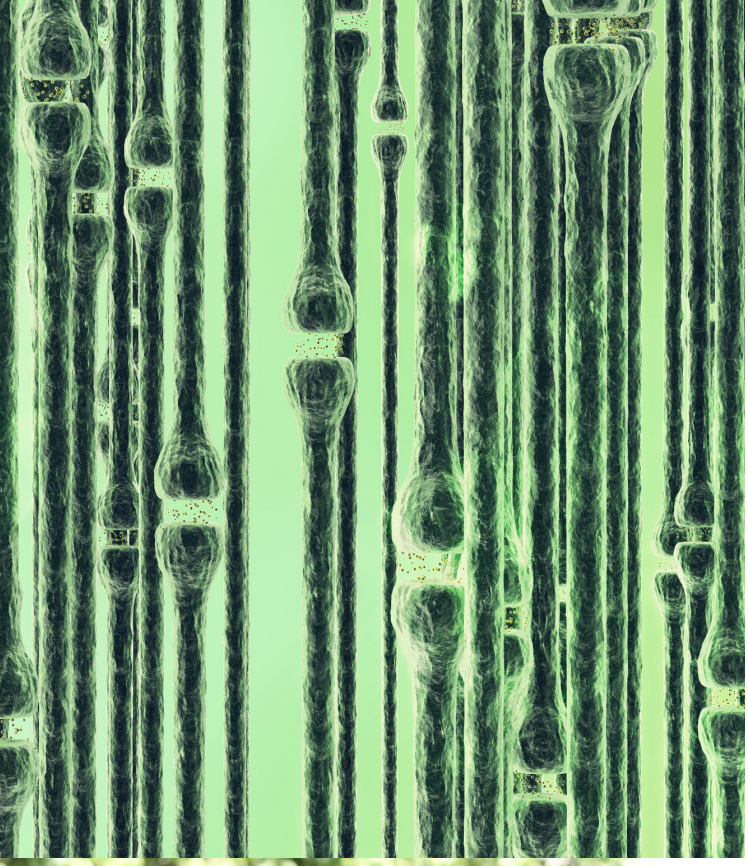
N.G: Thanks to Olea Sphere®, we could start performing cerebral perfusion at IMADIS!
The robustness and the simplicity of the automated post-processing allow each caring actor to focus on the essentials: the patient. By removing the potential concerns regarding post-processing, the radiographers find themselves in familiar territory, which consists in adapting a protocol to patient specificities. Without the need for a complex training as it is usual for a new tool, the radiologist can focus on the exam's interpretation.

As mentioned before, Olea Sphere® furthermore allows the standardization of cerebral perfusion post-processing coming from different scanners and vendors: computing and visualization of the parametric maps are similar whatever the model of machine the images are acquired on.

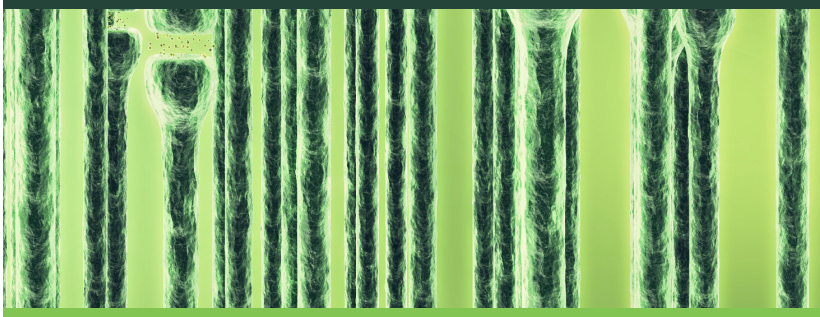
> "The robustness and the simplicity of the automated post-processing allow each caring actor to focus on the essentials: the patient."

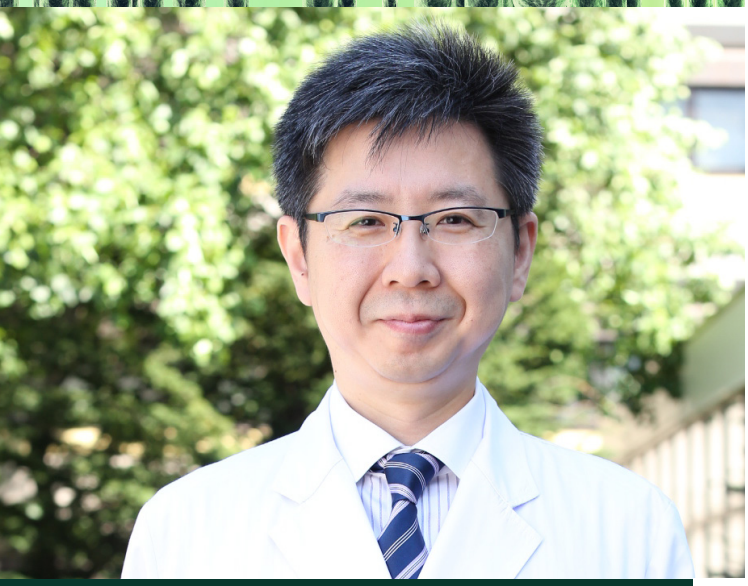
Therefore, Olea Sphere® fostered our growth; we could enlarge our team of radiologists and extend our collaborations with other hospitals without being hindered by the learning process of a new imaging technique.

Olea Sphere® helps us remain relevant with the critically short amount of time allocated for acute stroke management. Today at IMADIS, for a patient with suspected acute stroke, the radiologist is on the phone with the clinician only 10 minutes after the reception of the first CT-scan images without injection.



Importance of accuracy





"Bayesian-based deconvolution is the best method to accurately quantify CBF"

Kohsuke Kudo, MD, PhD
Clinical Professor,
Department of Diagnostic and Interventional Radiology,
Hokkaido University Hospital,
Sapporo, Japan.

Kohsuke Kudo studied medicine at Hokkaido University School of Medicine from 1989 to 1995. After graduation, he entered the Department of Radiology in the same institution, and completed a doctoral degree in Hokkaido University Graduate School of Medicine in 2003. In 2006, he was a visiting assistant professor in Wayne State University for a year. In 2008, he was appointed assistant professor at Iwate Medical University, and associate professor in the Department of Diagnostic Radiology at Hokkaido University Hospital in 2013. Since 2016, he holds the current position of clinical Professor.

Kohsuke Kudo is a member of several academic societies: Japan Radiological Society (JRS), Radiological Society of North America (RSNA), Japanese Society of Neuroradiology (JSN), Japanese Society of Magnetic Resonance in Medicine (JSMRM), International Society of Magnetic Resonance in Medicine (ISMRM), Japanese Society of Cerebral Blood Flow and Metabolism (JSCBFM). He received awards from the same organizations. He is the author of about 160 peer-reviewed publications. His major interest is stroke and dementia imaging, and new methods development.

Olea Imagein: Could you present to our readers the evolution of acute ischemic stroke patient management?

Kohsuke Kudo: In 1996, intravenous (IV) administration of alteplase (recombinant tissue plasminogen activator, rtPA) was approved by the FDA in the US. From then, alteplase started to be used worldwide and better recovery was observed in stroke patients. However, many of them were still excluded from the treatment since the time window of IV rtPA was only 3 hours. A few years later, this time window was extended to 4.5 hours, and more patients could benefit from this reperfusion strategy. Lately, mechanical thrombectomy using stent retriever was placed in the limelight and used up to 24 hours after symptom onset.

O.I: How did perfusion imaging change stroke management?

K.K: Numerous studies were conducted to investigate how perfusion imaging could be used as an inclusion criteria for IV rtPA or other agents. Some of them showed better outcome (for example DIAS and DEFUSE), while others did not (for example EPITHET and DIAS-2).

Regarding mechanical thrombectomy performed less than 6 hours after stroke onset, many clinical trials (REVASCAT, SWIFT PRIME, EXTEND-IA, ESCAPE) demonstrated better patient outcome using perfusion imaging. Moreover, recent results of the DAWN and DEFUSE-3 trials showed that thrombectomy had a high efficacy even beyond the 6-hour time window. Therefore, perfusion imaging is now recommended for patient selection more than 6 hours after suspected onset of symptoms in the latest issue of AHA/ASA guidelines.
We are now treating patients more safely, without severe adverse effects, using perfusion imaging for stroke management.

O.I: What was the situation after deconvolution models were introduced?

K.K: Deconvolution is important as Tmax (time to maximum of the residue function) is the current clinical standard of perfusion imaging criteria. Tmax is not a physiological parameter, it becomes available only after the deconvolution process.

In the concept of diffusion/perfusion mismatch, a variety of parameters was introduced such as time-to-peak (TTP), mean transit time (MTT), etc. However, Tmax survived as it is easy to use once deconvolution is conducted. The current standard of perfusion abnormality is Tmax > 6s. In addition, Tmax is also an index of severe ischemia (Tmax > 8s, 10s, etc.).

O.I: Very early on, you and your colleagues developed original deconvolution methods. In addition, you tested and validated the Bayesian-based deconvolution method. As an expert in perfusion post-processing, in what way do these improvements bring consistency and accuracy in the computation?

K.K: As I mentioned before, Tmax is the current standard though not a physiological parameter. However, cerebral blood flow (CBF) is physiologically and pathologically more important since it represents the blood flow per unit volume of the brain. Tmax is meaningless while CBF determines the energy production in neurons and glial cells. Therefore, assessing an accurate measurement of CBF should be more important.

So far, many researchers used Tmax because of its simplicity; however, in the future, I believe that the quantification of CBF will become more important. Based on our comparison using digital phantom, which simulates various conditions of ischemic tissue, Bayesian-based deconvolution is the best method to accurately quantify CBF; indeed, most of other deconvolution methods (including Singular Value Decomposition, SVD) produced evaluation errors regarding this parameter.

In the early stage of Bayesian-based deconvolution, the time of analysis was too long to be used in clinical practice. But now, thanks to the development of Olea Medical® and the improvement of computational power, the calculation time becomes short enough to be used in acute stroke management.

Advice for post-processing

"A fruitful collaboration between radiologists and neurologists"

Matthieu Rutgers, MD
Neurologist, Head of the ESO certified Stroke Unit at Europe Hospitals, Brussels, Belgium; Former Vice-President of Belgium Stroke Council.

Matthieu Rutgers studied medicine at the Catholic University of Louvain in Brussels, Belgium from 1995 to 2002. He performed his fellowship in Neurology in the same institution and then successively in the Stroke Center of Lille CHRU University Hospital in France, and in the Stroke Center of Lausanne University Hospital in Switzerland. Since 2008, he is the Head of the Stroke Unit at Europe Hospitals, Brussels, Belgium, which is one of the very first European Stroke Organization (ESO) certified Stroke Unit in Europe. In 2014, he was appointed President of the Scientific Board of the Belgium Stroke Council, and Vice-President of Belgium Stroke Council in 2016.

Olea Imagein: Could you please share with our readers your feeling about the future of stroke imaging?

Matthieu Rutgers: Imaging is a significant part of stroke management in the broad sense – and first of all, obviously, to distinguish ischemic from hemorrhagic stroke. Regarding ischemic stroke, multimodal imaging – including both angiography and perfusion, allows the radiologists to provide multiple information that will help us, as neurologists, in making better therapeutic decision.

O.I: What does Olea Sphere® bring you in your daily clinical practice?

M.R: We have been using Olea Sphere® software for many years now at Europe Hospitals in Brussels, in its fully-automatized mode. In our institution, there is a Stroke Unit, but we have to refer patients to a Stroke Center for a potential thrombectomy. Olea Sphere® software, allowing the assessment of core, penumbra and mismatch, helps us a lot in defining the good candidates for thrombectomy on time – "time is brain".

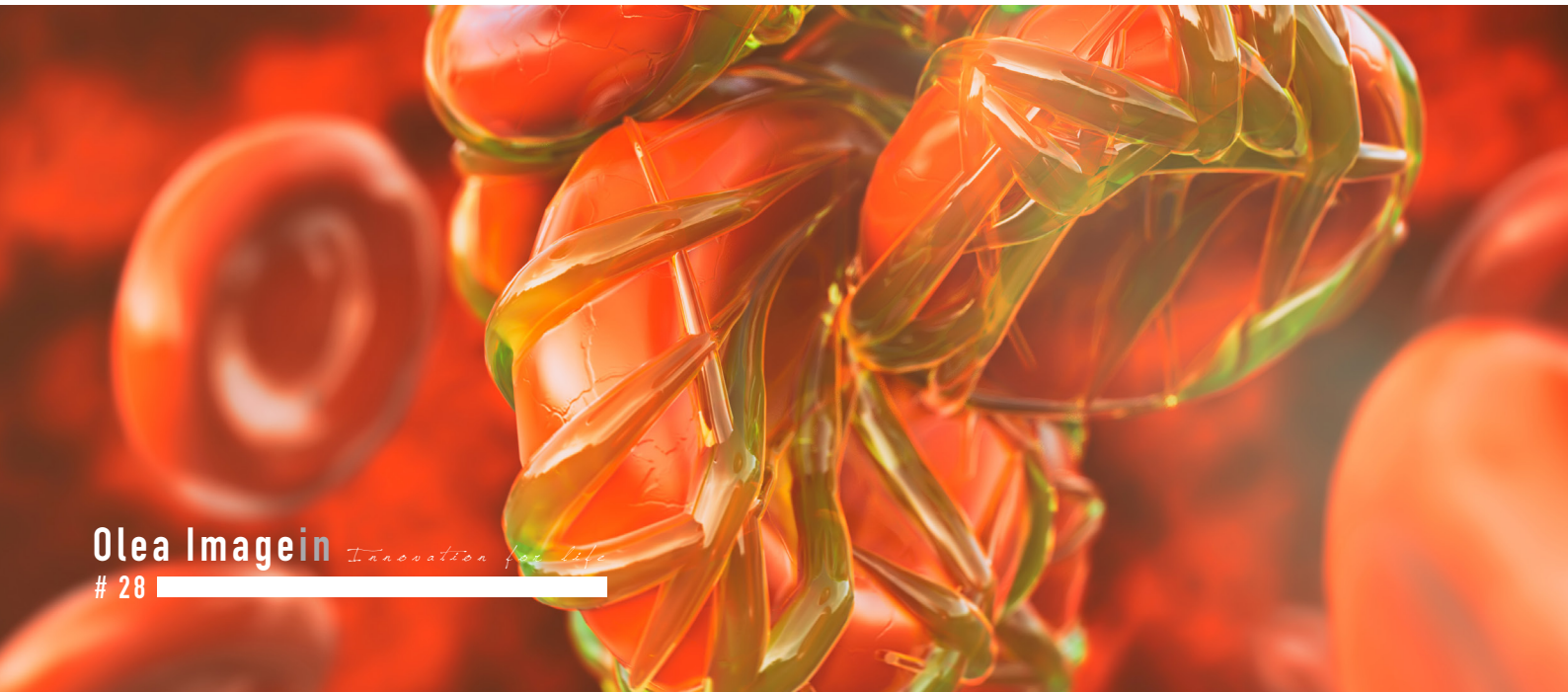
O.I: Would you like to provide advices regarding the use of post-processing software?

M.R: Post-processing software including automatized perfusion computation, like Olea Sphere®, are wonderful and innovative tools that provide tremendous amount of information to neurologists. However, in some ways, they do not replace the collaboration with radiologists – that is the experience I have gained. A fruitful collaboration between radiologists and neurologists, with the help of these automatized tools, allows to benefit more from them. That is a first important thing. Also, in the field, medically and scientifically speaking, we have seen with the recent publications of DAWN and DEFUSE 3 clinical trials that perfusion imaging provides a great deal of information in therapeutic decision for these patients who present with unknown or late (after 6 hours) stroke onset.

> "Olea Sphere® [...] helps us a lot in defining the good candidates for thrombectomy on time."

O.I: What is your opinion regarding the latest clinical trials you just mentioned?

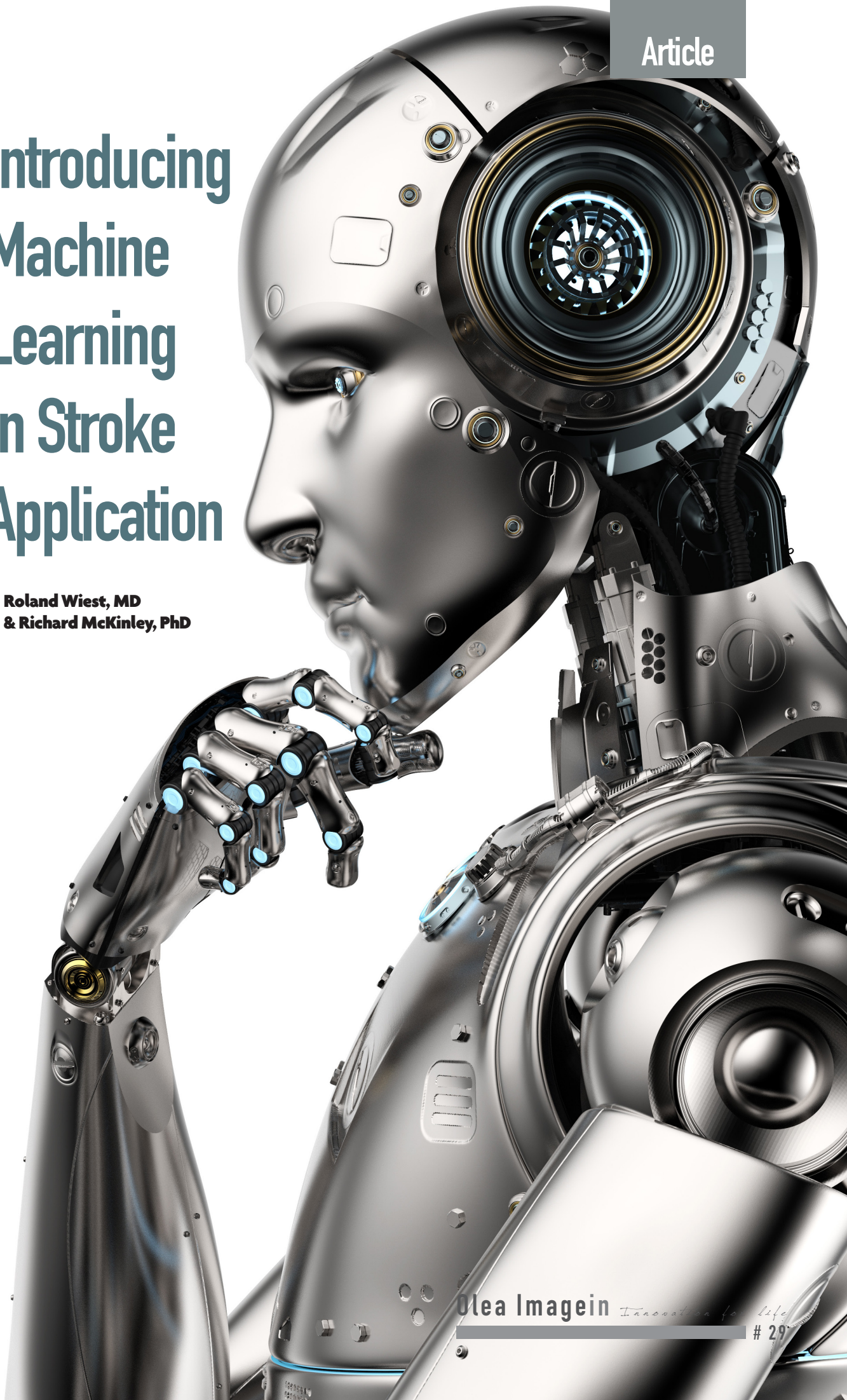
M.R: Recent clinical trials such as DAWN and DEFUSE 3 obviously change the game. The guidelines and recommendations are not published yet, even if the Americans in the AHA guidelines, at the beginning of the year, already indicated that they would take these studies into account and thus consider performing perfusion imaging. But it is something a little off-label that we already did beforehand, convinced that perfusion imaging and favorable mismatch were ultimately far more important decision criteria than time alone. The results of these studies confirm this point.



Article

Introducing Machine Learning in Stroke Application

Roland Wiest, MD
& Richard McKinley, PhD



Endovascular retrieval of intracranial clots with mechanical thrombectomy is now standard treatment for acute ischemic stroke patients presenting with a large vessel occlusion. According to new guidelines of the American Heart Association (AHA), patients presenting within six hours of symptom onset may be treated if they had a pre-stroke mRS of 0 or 1, and present with an ICA or M1 occlusion and an ASPECTS score greater than six. Beyond this 6-hour threshold, up to 24 hours, eligibility for mechanical thrombectomy is based on advanced imaging criteria: these criteria are derived from the DAWN [1] and DEFUSE 3 [2] trials, and require that patients show either a clinical imaging mismatch (DAWN) or a mismatch between the size of the ischemic core (the tissue already undergoing cytotoxic edema) and the ischemic penumbra (the tissue which is not already lost, but which is sufficiently hypoperfused to be at risk).

Since rescuing as much penumbral tissue as possible is the goal of endovascular therapy, accurate identification of the penumbra is the primary aim of advanced imaging in acute stroke. The standard definition of penumbra (as used, for example, in the DEFUSE 3 trial) is tissue with a Tmax greater than six seconds as derived from perfusion imaging. This definition creates several problems: first, different perfusion post-processing algorithms may differ in the values of calculated Tmax. Second, Tmax, as shown by Calamante et al. [3], is not on its own physiologically meaningful, but is rather a biomarker reflecting a combination of delay, dispersion, and, to a lesser degree, mean transit time. It is therefore not possible to directly apply clinically established Tmax thresholds to methodologies, such as Bayesian deconvolution, which directly estimate the pure arterial-tissue delay. Finally, the tissue identified by a threshold is typically an overestimate of the tissue-at-risk.

Researchers at the Support Center for Advanced Neuroimaging (SCAN), hosted by the Institute of Diagnostic and Interventional Neuroradiology at the University of Bern and Inselspital, have recently developed a prototype solution to solve the problem of identifying tissue-at-risk, by replacing thresholds on perfusion maps by machine-learning.

FASTER [4] (Fully Automated Stroke Tissue Estimation using Random forests) predicts, within the hypoperfused region, which areas will infarct even in the case of reperfusion, and what tissue is at risk when reperfusion is not established. Underlying FASTER are two machine-learning models, trained on cases from the Bernese Stroke database; one was trained on patients who had total recanalization (corresponding to a TICI grade of 3), and the other on patients who had a complete lack of recanalization (TICI grade of 0). The training and prediction are made using data from acute T2-weighted, T1-weighted post-contrast, diffusion-weighted MRI, and maps derived from perfusion MRI (TTP, Tmax, CBF and CBV). The system identifies tissue at risk by predicting the extent of the final infarction in the case of both a strong and a weak response to therapy: the difference between those two predictions can be then interpreted as the model's assessment of the potentially salvageable tissue.

When applied to an independent test set of cases from the Bernese Stroke register, FASTER provided a better delineation of tissue-at-risk than thresholding on perfusion and diffusion maps, even after those thresholded maps had been hand-corrected. In particular, when identifying the hypoperfused tissue at risk of infarction, manual delineation based on thresholding Tmax maps achieved a sensitivity of 0.87, a specificity of 0.998 and a precision of 0.13, while the prediction arising from FASTER had a sensitivity of 0.79, a specificity of 0.998 and a precision of 0.33.

The increased precision of FASTER can be further seen in its increased ability to predict the volume of final infarctions. In test cases which had a poor response to therapy (TICI 1-2a), the mean difference in volume between the manually-segmented perfusion lesion and the final lesion was 121 ml (±55ml), while the mean difference in volume between the automatically defined tissue-at-risk and the final lesion was 30 ml (±26ml).

In a follow-up study, the team investigated the relationship between imaging features and three months clinical assessments. To support clinically implementable prediction model building with information from feature

analysis, the correlation of lesion loads (as defined by co-registration to a standard template space and superimposition of a cytoarchitectonic atlas) and clinical outcome (as measured by 3 months NIHSS score) were investigated. The analysis was made for chronic lesion loads, and for lesion loads as predicted by FASTER. This knowledge can be used to extract a selection of important features to make reliable predictions on neurological scores. We have identified a significant correlation between lesion load mapping before therapy and NIHSS › mRS after 3 months for several WM tracts (e.g. corticospinal tract) and GM eloquent areas (e.g. primary somatosensory cortex). The results support superiority for the clinical utilization of the automatically predicted volumes from FASTER over the simpler DWI and PWI lesion delineations. We are currently extending the model to applications of CT perfusion imaging and by integration of a model-free, convolutional neural network (CNN) based architecture to predict perfusion maps without SVD.

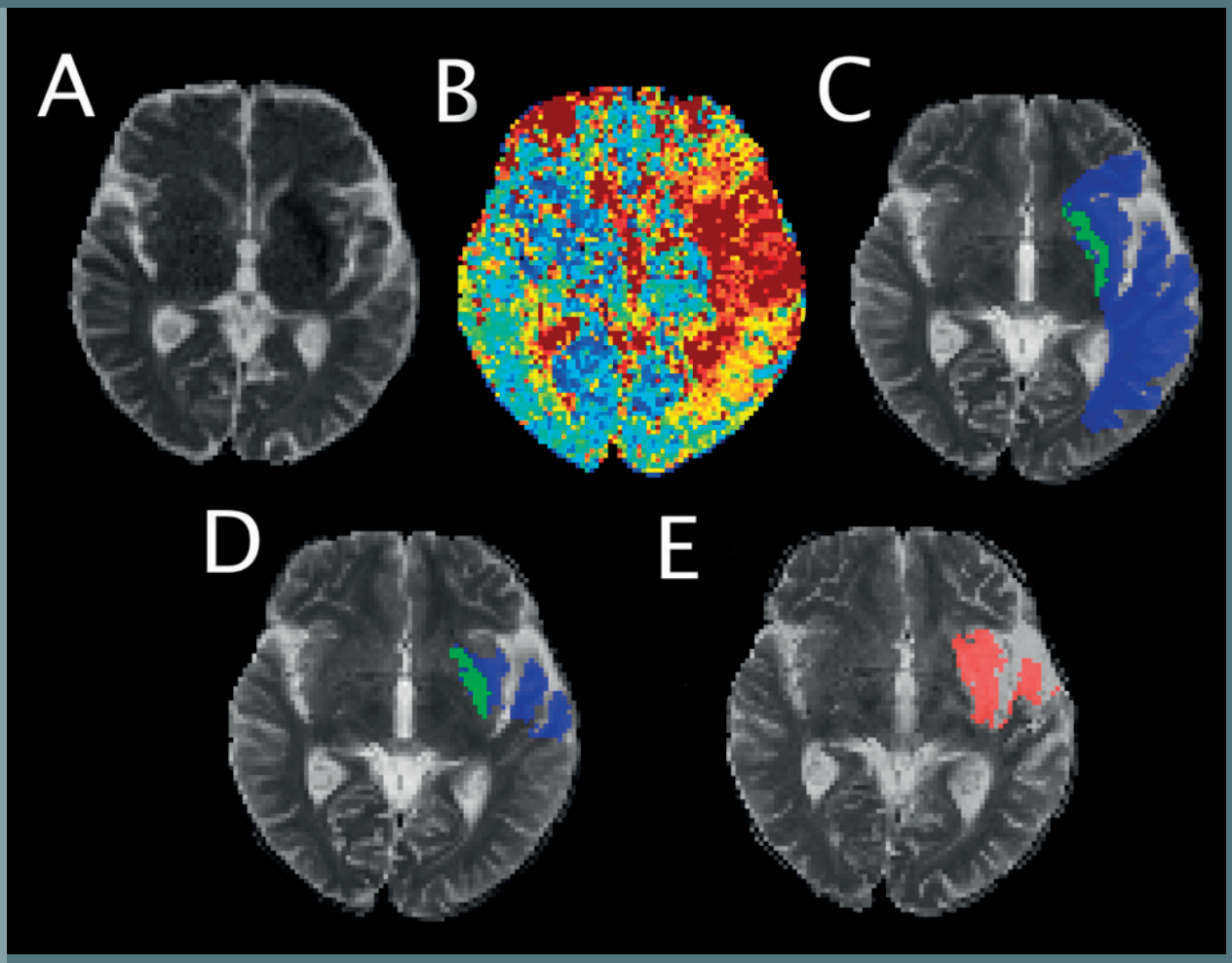


Figure 1: Imaging of an acute stroke case, showing ADC from DWI imaging (A), Tmax from perfusion imaging (B), and the threshold-based ischemic core (green) and penumbra (blue) (C). The output of FASTER (D) shows a similar infarct core (green) but a smaller region at risk (blue). The 90-day T2 follow-up (E) shows that tissue damage was restricted to the region predicted by FASTER, despite perfusion restoration to the territory at risk (TICI 1).

Roland Wiest, MD
Professor of Advanced Neuroimaging at the University of Bern, Switzerland; Director of the Support Center for Advanced Neuroimaging (SCAN); Vice Chair at the University Institute of Diagnostic and Interventional Neuroradiology.

Prof. Roland Wiest currently holds the position of Professor of advanced neuroimaging at the University of Bern, Switzerland, heading the Support Center for Advanced Neuroimaging (SCAN), and of the Deputy Chair at the Institute of Diagnostic and Interventional Neuroradiology. He received training in Neurology/Neurophysiology and Radiology/Neuroradiology in Munich and Augsburg, Germany and Bern, Switzerland. His main focus of research is the development, implementation and validation of automated image analysis tools into clinical practice.

Richard McKinley, PhD
Researcher scientist at the Support Center for Advanced Neuroimaging (SCAN) in Bern, Switzerland.

Dr Richard McKinley studied Pure and Applied Mathematics at the University of Cambridge and holds a PhD in computer science from the University of Bath. At the Support Centre for Advanced Neuroimaging in Bern, he develops machine learning techniques with applications to neuroimaging. His research focuses on image segmentation techniques for identifying lesions and neuroanatomical structures, and on the prediction of tissue damage and patient outcome in stroke.

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Article

Deep Learning Artificial Intelligence For Stroke and Hemorrhage Evaluation

Peter Chang, MD

Olea Imagein *Innovation for life*
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Acute stroke is a leading cause of long-term disability, with over 800,000 patients affected every year in the United States alone and over 15 million patients worldwide. In a patient with suspected stroke, the first most important question that must be answered in therapeutic decision-making is determining the presence of hemorrhage (e.g. bleed) in the brain using CT imaging. In the absence of a bleed, life-saving blood-thinning medications can be administered to reopen the obstructed vessel that is depriving brain tissue of the critical oxygen it needs to survive. However, if blood has already leaked from the brain vessels, administration of that same, otherwise life-saving medication will result in worsening hemorrhage and possibly death.

Currently, there are several key challenges to rapid and accurate detection of a brain bleed in the setting of stroke. First, given the increased workload of radiologist physicians and growing exam complexity (e.g. more images per exam), overall time to exam interpretation and report generation has gradually risen with a delay of up to several hours now commonly seen in the after-hours ER setting. Second, subtle areas of small volume blood can be misinterpreted by humans, particularly non-imaging experts (e.g. neurologists, ER physicians) who oftentimes may be reviewing images by themselves to expedite care. Because of this, new technology targeting hemorrhage detection of CT exams represents a promising opportunity to improve patient outcomes.

Deep learning artificial intelligence (AI) is an emerging form of machine learning that has gained tremendous popularity over the past five to six years. The technique is distinguished from earlier forms of AI by its ability to extract and learn important features from data without any direct human input during the training process. Deep learning convolutional neural networks (CNNs) now represent the top-performing approach in various computer vision benchmarks, with new state-of-the-art techniques now surpassing human performance on various tasks. Given this, there has been massive potential associated with the application of CNNs to medical imaging problems.

However, despite the early promise and hype, no tool based on deep learning AI is currently being used to interpret images in clinical practice. In part, one of the key limitations thus far has been the lack of algorithm customization for medical datasets. In fact, most implementations currently reuse generic architectures described by Google or Facebook trained on everyday objects (e.g. cats, dogs); by contrast, images for medical diagnosis exhibit many key differences (e.g. 3D volumes, high resolution, etc.) that remain unaccounted for using most current approaches. In addition, deep learning is a data-intensive technique often requiring millions of example images for algorithm training. Curating such a dataset is extraordinarily challenging in medicine, often requiring extensive time and human resources, and is thus rarely found in current healthcare AI projects.

Recognizing these common limitations, our group at the Center for AI in Diagnostic Medicine (CAIDM) spanning the UC Irvine Healthcare System has focused on creating the necessary tools and infrastructure to support large-scale deep learning projects. To properly engage the problem of hemorrhage detection on CT, we first curated a large database of over 10,000 patients with suspected stroke yielding over half a million head CT images. Next, I personally explored many different underlying AI designs to identify a strategy that best approximated the interpretation process of a human radiologist. The final approach that I established involved a two-step AI that first glanced at a given image to identify potential areas of abnormality and then individually attended to each suspicious region before making a final diagnosis (Figure 1). Using my experience as a radiologist, I also designed the AI to account for 3D contextual information from images in adjacent regions of the brain.

The final AI model trained on our large retrospective cohort yielded an algorithm that was over 98% accurate in identification of hemorrhage. Importantly, this was a significant improvement over previous efforts utilizing smaller datasets, weaker annotations and generic AI algorithms. Furthermore, the algorithm remained accurate even on small microhemorrhages less than 0.1 ml in volume, the types of bleed that a human could realistically fail to identify.

To further validate this approach, beginning February 2018 we have implemented a live inference pipeline to use the trained AI to automatically screen every head CT obtained in the emergency room at our hospital.
Our preliminary data shows that thus far, the algorithm is extremely robust and accurate. We are currently awaiting FDA investigational device exemption (IDE) to integrate the results of the proposed computer-aided detection (CADe) device into daily clinical practice. Two primary use-cases have been proposed. First, such a tool can be used to screen head CT exams and reorder

the radiology worklist such that exams with suspicious findings can be prioritized for human interpretation first. Second, given the promising accuracy in detection of subtle hemorrhage, the algorithm can be used as a second-reader to alert a radiologist of possible abnormalities prior to signing a report.

Looking beyond the first step of the stroke therapeutic pathway, we envision that AI can be used to improve the entire downstream triage process. This includes identification and characterization of large-vessel occlusion (e.g. blood vessel clot), aneurysm, collateral vascularization and core infarct evolution on perfusion imaging.

Many of these techniques have only recently been described and we, as part of the medical imaging community, are just beginning to understand the types of therapeutic decisions that can be informed by these types of data. Nonetheless, in just the past several years, dramatic changes to stroke treatment guidelines have already been implemented based on improved characterization of these many complex variables. Currently, none of this assessment is being augmented by AI tools, and given the strength of deep learning algorithms to extract meaning from complex datasets, stroke triage and evaluation represent a promising frontier for this powerful new technology.

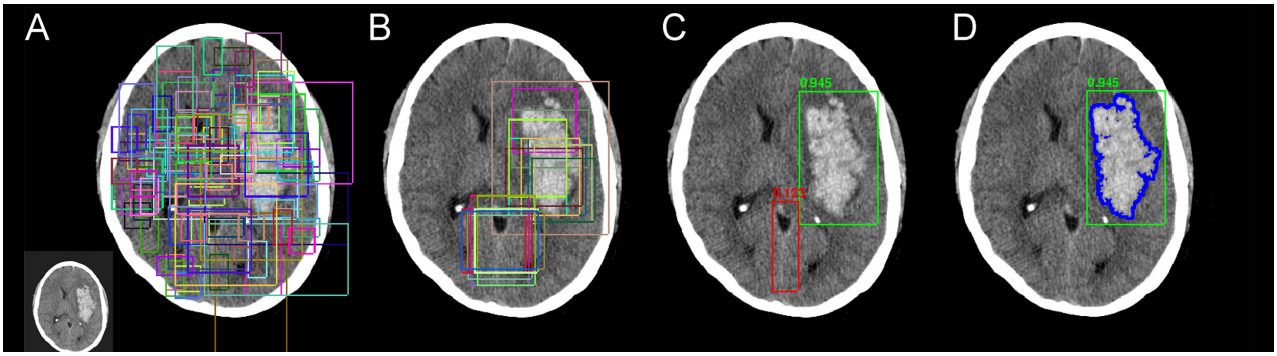


Figure 1: Two-step AI process for hemorrhage detection on CT that first glanced at a given image (A) to identify potential areas of abnormality (B) and then individually attended to each suspicious region (C) before making a final diagnosis (D).

> “... given the strength of deep learning algorithms to extract meaning from complex datasets, stroke triage and evaluation represent a promising frontier for this powerful new technology.”

Peter Chang, MD
Director of the Center for Artificial Intelligence in Diagnostic Medicine (CAIDM), UC Irvine Healthcare, Orange, CA, USA - CEO, Avicenna.ai

e-STROKE SUITE

Michalis Papadakis, PhD
CEO and co-founder of Brainomix

Michalis Papadakis is co-founder and CEO of Brainomix. He holds a PhD in neurosciences from UCL School of Pharmacy and was the Scientific Director of the preclinical stroke lab at the University of Oxford. He has been an invited speaker at international stroke conferences and has 20 publications in the field of cerebral ischemia and translational stroke research studies.

"... provide medical professionals with the solutions they need to make confident decisions resulting in better treatment outcomes"

Olea Imagein: Could you please introduce yourself and Brainomix company to our readers?

Michalis Papadakis: I am the CEO and one of the co-founders of Brainomix. The Brainomix story started a few years ago when I was the Scientific Director of the preclinical stroke lab at the University of Oxford doing research on stroke biomarkers. Together with the head of my group, Prof. Alastair Buchan, who is a Professor of Stroke Medicine, we realized that automating stroke imaging using artificial intelligence (AI) would address a key barrier preventing many patients from receiving life-saving stroke treatment: the lack of readily available expertise to interpret brain CT scans, which is a key parameter directing treatment decisions. Prof. Buchan, who is a world authority on stroke, had invented the ASPECTS method, which is a clinically-validated imaging biomarker for stroke, but back then it was not used in routine clinical practice.

We were fortunate that our timing coincided with the advent of powerful AI methods that allowed us to automate ASPECTS and the assessment of CT scans. At the same time, endovascular thrombectomy was introduced as a powerful stroke treatment and ASPECTS was recommended in international guidelines for patient selection. We started Brainomix with a handful of founders and received valuable support from both the University of Oxford as well as Innovate UK (the UK's innovation agency) which helped us raise our first non-dilutive funding, allowing us to develop and clinically validate e-ASPECTS.

I often look back on those years and it is hard, even for me, to believe how much we have achieved in so little time. What started with an idea, evolved into a spin-off from the University of Oxford and now we are an international company with presence across most of the major markets in the world, employing a team of people including medical professionals, PhDs, software developers and other business professionals. Compared to when we started, we are now larger, better equipped, with more solutions to offer and a large volume of installations around the world directly impacting stroke treatment decisions. Our solutions are trusted by some of the world's authorities in the field and some of the best university hospitals. This trust is what drives our vision forward. A vision which is described in our motto. We are here to provide medical professionals with the solutions they need to make confident decisions resulting in better treatment outcomes.

O.I: Brainomix and Olea Medical® recently entered into a partnership to launch the e-STROKE SUITE. Could you tell us more about this solution?

M.P: After developing e-ASPECTS we developed e-CTA, which is a powerful solution to drive assessment of CT angiography (CTA) scans of stroke patients. We soon realized that advanced imaging with CT and MR perfusion was becoming a prerequisite for stroke treatment, especially following the results of the DAWN and DEFUSE-3 trials for stroke patients admitted to hospitals more than 6 hours from symptom onset.

We identified that to complete our offering, we had to partner with the best CT and MR perfusion post-processing software currently available which was provided by Olea Medical® with Olea Sphere® software. That's how our partnership with Olea Medical® and the completion of the e-STROKE SUITE was born.

2018 is a milestone year for us as we introduced the e-STROKE SUITE together with Olea Medical®. The e-STROKE SUITE is the most comprehensive software solution for doctors treating patients suffering from ischemic stroke. Our solution offers:

- e-ASPECTS, which helps doctors assess the ASPECTS score and volume of ischemia on non-contrast CT images;
- e-CTA, which standardizes the assessment of collaterals on CTA scans and helps to assess the site of occlusion;
- Olea Sphere®, which automatically computes core, penumbra and mismatch ratio using CT perfusion or MR diffusion and perfusion images.

We launched this solution in May 2018 during ESOC in Gothenburg, Sweden and the response we received was phenomenal. We had large hospitals approaching us as well as smaller ones, which often look for a hub and spoke network. With the e-STROKE SUITE, we can address the increasing clinical need of stroke imaging at this network level.

We are now delivering on the promise we made. We are offering a solution that will help physicians treating stroke to become more confident about their decision making, so that the right patient gets the right treatment as soon as possible. We will continue to do so and stand by the side of the physicians wherever they are, whatever they need.

Simon Nagel, MD
Neurologist at Heidelberg University Hospital, Germany

Simon Nagel is a board certified neurologist with a subspecialisation in neurointensive care medicine. He received his training in Heidelberg under Prof. Werner Hacke and was a post-doc for Prof. Alastair Buchan in Oxford between 2007 and 2009. Since 2012, he is a consultant at the Department of Neurology of Heidelberg University Hospital, and since 2016, he holds an extracurricular Professorship at the University of Heidelberg. His clinical interests are in stroke, neurointensive care medicine and neurological emergency disorders. His research focus is in diagnosis and treatment of acute ischemic stroke, cerebral sinus thrombosis and experimental cerebral ischemia models and neuroprotection.

Olea Imagein: What does e-STROKE SUITE bring to clinical practice?

Simon Nagel: The e-STROKE SUITE so far offers the most comprehensive automated imaging post-processing solution for patients with acute ischemic stroke syndromes. The e-STROKE SUITE offers the possibility to automatically assess a non-contrast-enhanced CT for signs of acute ischemia, it allows automated assessment of collateral supply on a CTA and is able to quantify the ischemic core and penumbra on a CTP. It is therefore fully equipped to analyze all clinically available CT imaging modalities, depending on what the local imaging standard is comprised of.

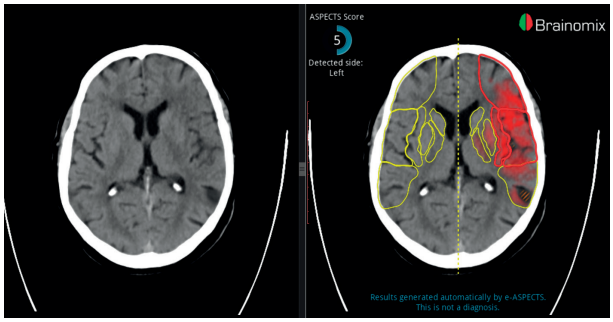
O.I: What are the main advantages of this solution?

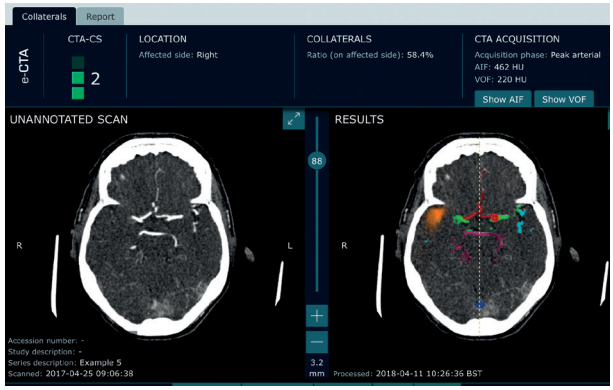
S.N: The main advantage is the complete assessment of all CT imaging modalities on one platform. The clinical user does not need to check different applications for each imaging modality. Physicians can review the processed images and results either directly within the local PACS system, on their mobile device or on a Web based interface. Results are available within minutes to ensure no time delay in clinical decision making.

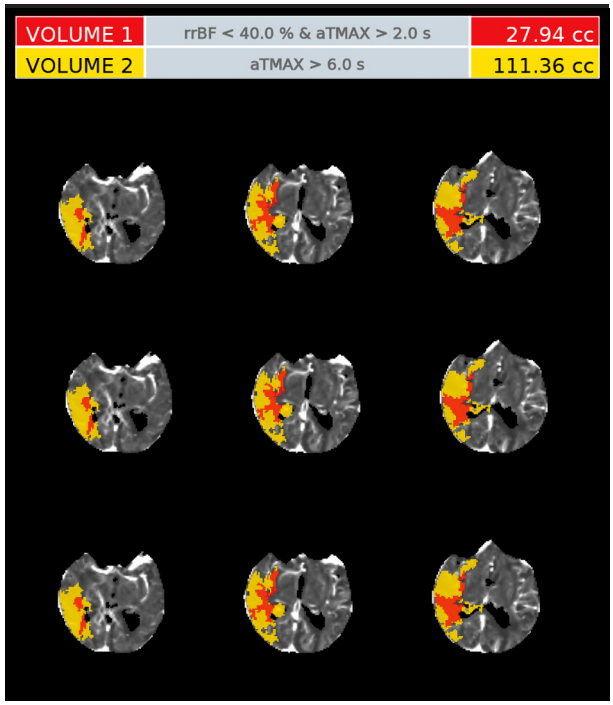
O.I: Did your daily routine change with the new stroke guidelines?

S.N: The updated American Heart Association (AHA) guidelines from early 2018 do not recommend CTP imaging in candidates for mechanical thrombectomy within 6 hours from onset, but only in patients that are last seen well between 6 to 24 hours, by adherence to the DAWN and DEFUSE 3 eligibility criteria. The European Stroke Organization (ESO) does also support mechanical thrombectomy in patients fulfilling the DAWN and DEFUSE 3 criteria. The German guidelines have not been updated yet, but our local standard operating procedure (SOP) for late thrombectomy also recommends CTP; this does not mean that an additional subgroup of patients cannot benefit as well from late thrombectomy. The control groups (i.e. best medical management) in both DAWN and DEFUSE 3 had a very poor outcome.

Within our Heidelberg Recanalization Registry, we found that patients presenting within 6 to 24 hours after last seen well may also be successfully selected by plain CT (ASPECTS ≥ 6) together with CTA for thrombectomy. These patients did similarly well as compared to the recent randomized controlled trials. More recently, we also started performing MRI in "Wake-Up" patients – i.e. presenting within 4 hours after waking up with their stroke symptoms (WAKE UP Trial criteria for thrombolysis). In general, in all patients in whom we consider to offer an acute recanalization therapy (thrombolysis or thrombectomy), we perform vessel imaging by either CTA or MRA.







Figures: e-ASPECTS, e-CTA and Olea Sphere® results

Advances in the management of wake-up patients

Salvador Pedraza, MD, PhD

Introduction

Stroke is the primary cause of disability in our society. Approximately 75% of stroke patients will survive, but half of them will be unable to live independently.
The stroke treatment is based on intravenous injection with recombinant tissue plasminogen activator (rtPA, alteplase); in the last years, the utility of mechanical thrombectomy has also been demonstrated.

Imaging protocol

New techniques with greater sensitivity in the diagnosis of acute stroke have been developed. Magnetic resonance imaging (MRI) is the most useful modality in this context [1,2], but computed tomography (CT) imaging remains a very good alternative to MRI.
The MRI of acute stroke must be multimodal with a combination of different sequences, such as T2*-weighted gradient-echo images (GE), Fluid-attenuated inversion recovery (FLAIR), Diffusion-weighted imaging (DWI), Perfusion-weighted imaging (PWI) and Magnetic resonance angiography (MRA).

Treatment

The accepted inclusion criteria to intravenous treatment with rtPA is a time window from symptom onset lower than 4.5 hours and the absence of hemorrhage [3].
However, in an important proportion of patients (14-27%), the time of symptom onset is not known, mainly because the stroke occurs during sleep time and the symptoms appear on wake-up. In this scenario strictly, it was not possible to treat wake-up patients with rtPA and there was a need to determine a method to treat them [4-6].

New imaging strategy to wake-up patients

Recently, the results of the Wake-up trial have been published in the New England Journal of Medicine [7] that provide an imaging strategy to treat these patients with an unknown time of stroke symptom onset. This study including 503 patients has been funded by the European Commission within the 7th Framework Programme.
The new proposed inclusion criteria consists in the presence of a DWI-FLAIR mismatch (Figure 1) with a hyperintense signal alteration on DWI but a normal signal on FLAIR, within the ischemic lesion; other ischemic lesions with a hyperintense signal on both DWI and FLAIR should be excluded. The use of this new imaging inclusion criteria combined with rtPA treatment was demonstrated as safe and providing an improved functional outcome to the patient compared with placebo.
In addition, the investigators of the Wake-up trial also showed that the interpretation of this imaging criteria was homogeneous [8], and this fact supports the reproducibility of the proposed imaging strategy in the treatment of acute stroke patients with wake-up and unknown symptoms onset.

Conclusions

The Wake-up trial demonstrated the utility and safety of the DWI-FLAIR mismatch as an efficient imaging criterion to treat patients with acute stroke and unknown time of symptom onset.

Declaration of interest

S. Pedraza has been member of the central reading board of the Wake-up trial.

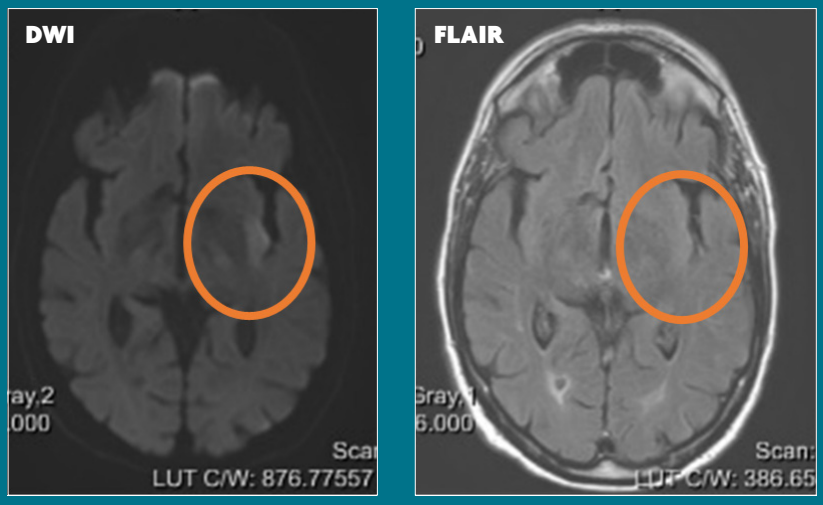


Figure 1: Left insular infarct (MCA territory). Mismatch DWI-FLAIR because DWI shows a high signal lesion and FLAIR a normal signal in the same area.

Salvador Pedraza, MD, PhD

Director of Radiology and Nuclear Medicine at Hospital Dr Josep Trueta and Hospital Santa Caterina, Girona, Spain; Director of Institute of Diagnostic Imaging (IDI), Girona, Spain; Member of Scientific Advisory Board at QUIBIM SL.

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Collateral circulation

David S Liebeskind, MD
Professor of Neurology at UCLA, Los Angeles, CA, USA;
Director of the Neurovascular Imaging Research Core.

"The better the collateral circulation, the better the reperfusion"

David S Liebeskind is Professor of Neurology at the University of California, Los Angeles (UCLA), where he is Director of Outpatient Stroke and Neurovascular Programs.

He is Director of the Neurovascular Imaging Research Core, leading global efforts to advance data science and precision medicine of stroke imaging for prevention, acute therapies and recovery after stroke.

He is Director of the UCLA Cerebral Blood Flow Laboratory, Associate Director of the UCLA Stroke Center and Director of the UCLA Vascular Neurology Residency Program, training the next generation of vascular neurologists and stroke experts.

He trained in Chemical Engineering at Columbia University and completed his MD at New York University School of Medicine. His postgraduate medical training included internship at Beth Israel Hospital, Boston and neurology residency at UCLA. After his residency, he completed a fellowship in stroke and cerebrovascular disease at UCLA and subsequently joined the faculty in the Departments of Neurology and Radiology at the University of Pennsylvania. He has advanced education, research and clinical care of stroke at UCLA since 2004.

His principal research interests include novel neuroimaging approaches to elucidate fundamental pathophysiology of cerebrovascular disease in humans, with a particular focus on the collateral circulation. His work on collateral perfusion in acute ischemic stroke draws on advances in noninvasive, multimodal CT and MRI and detailed analyses of digital subtraction angiography.

Olea Imagein: Your clinical research focuses on acute ischemic stroke imaging with a special involvement in cerebral collateral circulation. Could you please explain what this concept refers to, and the reasons of this interest?

David Liebeskind: Cerebral collateral circulation is an area of particular interest for us, as it is the main mechanism by which blood is supplied to the brain when an occlusion affects one of the arteries that normally provides flow. In the case of ischemic stroke, when principal arteries are blocked, the only source of blood flow remains via the collaterals.
It is therefore a critical fact that can salvage the artery territory.

O.I: What is the impact of collateral circulation on penumbral tissue in stroke events?

D.L: Collateral circulation has been identified as a singular blood flow factor in determining the outcome of acute ischemic stroke, for both untreated and treated patients with revascularization therapy. When revascularization is attempted, patients with better collateral circulation show lower degree of ischemia or infarction on brain imaging; they have less neurological deficits or lower stroke severity scores and better outcomes, overall.
This compensatory circulation is a plus for revascularization, since the patients with stronger and more robust collaterals recover better. They have superior

long-term outcomes, at 3 months but even earlier. When we look at images of the brain, we can see a much more prominent and dramatic response in terms of saving brain. We know that the better the collateral circulation, the better the recanalization; the likelihood of saving the vessels, as well as the degree of reperfusion and the extent to which we are able to restore blood flow downstream, is increased.

O.I: How can we accurately assess this collateral status?

D.L: There are many different ways for assessing collateral circulation. The reference standard has always been conventional angiography, which is obviously an invasive approach but still remains the mainstay of therapy with endovascular treatment in the brain.
Ideally, we want to identify the patients with better collaterals – and to know the degree of collateral circulation for prognostication – as early as possible, before performing angiography or even planning to do some. Ultimately, non-invasive imaging becomes very important in terms of understanding this degree of collateral circulation.

Many techniques can address and assess the strength of collaterals. Some of them directly measure the amount of visualization of anastomose connections between the arterial territories in the brain. Other methods evaluate the functional significance of the

blood flow supplied by collaterals. For example, perfusion studies will show the degree of blood flow that is supplied via the collateral downstream, also known as "collateral perfusion"; that is different from – though related to – the degree of collaterals that may be seen, for instance, on a singular or multiphase CT angiogram, or on other neuro non-invasive MRI-based angiography imaging approaches.
All these techniques slightly differ from their perspectives in characterizing the collateral circulation; therefore, the correlations between them are somewhat variable. Since the correspondence between the derived collateral grades may not be as robust as we would like it to be, each method may thus be used to define a population and distinguish groups of patients inside. The hope is of course to get a single and consistent approach that can systematically discriminate individual patient status.

O.I: What do you expect from advanced knowledge on collateral status in the future of stroke management?

D.L: Knowledge of this status is the most intuitive way to predict if an individual has a collateral circulation strong enough to sustain a complete occlusion of an artery and diminish the ischemia during the stroke event. We know that restoring the blood flow is the ideal answer to stroke. Therefore, we tend to treat with the best method that might be opening the vessel and provide the brain with normal blood flow patterns. Other strategies, which have been tried for several years, may be used to enhance collateral circulation. I think there will be significant future advances in these approaches. These may include strategies to dilate the collaterals, or improve the perfusion and blood flow sustained by these collaterals. This is an area of extensive research which I believe will be fruitful in the coming years.

O.I: How will the new stroke guidelines impact your clinical practice?

D.L: The guidelines include a tremendous number of topics: early management of acute ischemic stroke patients, imaging, diagnostic evaluations, endovascular therapy, and even a recommendation that supports consideration of collateral status. These guidelines have also been marked by a series of events this year, as some parts have been retracted or temporarily deleted. Therefore, we don't know what their full state really is yet. However, what we do know is that imaging is important and that the guidelines make general suggestions for practice. They recommend imaging to be leveraged in order to identify candidates for therapies at later time points, in the delayed 24 hours window. They also recommend the collateral circulation approaches we have been talking about, in order to define optimal candidates for treatment.

"The hope is of course to get a single and consistent approach that can systematically discriminate individual patient status."

Tae-Hee Cho, MD, PhD
Neurologist at the University Hospital of Lyon.
Researcher affiliated to the CREATIS laboratory in Lyon, France.

MARVELOUS Project

"Synergy in both fundamental and clinical research for stroke and myocardial infarction"

Olea Imagein: Could you please introduce yourself to our readers?

Tae-Hee Cho: I have been working as a neurologist at the University Hospital of Lyon for the last 15 years, in the vascular neurology department of Prof. Norbert Nighoghossian team. Our department is specialized in the management of acute stroke, where my daily activity is above all that of a caregiver. Our service, where the care management starts in parallel with the radiology department, is composed of 35 beds dedicated to stroke patients. I am also a teacher and a researcher affiliated to the CREATIS laboratory in Lyon. My research focuses on cerebral imaging as a prognostic tool and assistance to treatment for stroke patients. In this context, our team got involved in the MARVELOUS project.

O.I: Could you please describe the MARVELOUS project?

T.H.C: The MARVELOUS project is conducted as part of the "investments for the future", whose funding is granted by a RHU (University Hospital Research) program. The project involves clinical departments – the neurovascular and cardiovascular departments, the latter directed by Prof. Michel Ovize – as well as several academic research teams and private partners, including Olea Medical®.

MARVELOUS aims at improving the way we analyze and apply magnetic resonance imaging in the care of the two diseases that are responsible for the bulk of global disability and mortality: cerebral and myocardial infarction.

The MARVELOUS project started from a simple observation: the same patients often suffer from both pathologies, either successively or concomitantly. These patients often share the same risk factors, and will subsequently benefit from similar prevention programs.

Although the organs are different, their acute pathophysiology share many similarities: a sudden interruption of blood flow leads to cellular damage, even faster at the cerebral than at the myocardial level. In both cases, the most efficient treatment to save brain and heart tissue is to reopen the occluded artery and restore blood flow at the microvascular level (i.e. reperfusion). The similarities do not stop here, since the techniques to restore blood supply as well as the means of prevention also show analogies.

Therefore, one can find and foster a synergy in both fundamental and clinical research for stroke and myocardial infarction. The neurology and cardiology teams

in our institution enjoyed a fruitful collaboration for many years, and the MARVELOUS project is the logical outcome of these exchanges.

The objectives of MARVELOUS are to improve the care given to the patients by exploring two distinct parts: experimental research conducted through animal and cell modeling, and a clinical part. As part of the neurological team, I will mainly talk about brain.

The aim of the clinical part is to develop an enhanced imaging tool for the diagnostic and prognostic assessment of patients. Imaging plays a different role in stroke and myocardial infarction management, since no treatment can be decided without prior imaging

in stroke patients, whereas the cardiologists can more easily confirm their diagnosis. Indeed, when a patient presents stroke symptoms – hemiplegia, speech disorders – the clinician cannot assess without imaging if the patient suffers from a bleeding (cerebral hematoma), or from a more common cerebral infarction. Imaging is therefore essential.

For both brain and heart, imaging will help us assess the prognosis and guide treatment – especially for stroke. Not all stroke patients can benefit from revascularization, because extensive brain damage may already have occurred by the time they reach the health care system. In other patients with less severe blood flow reductions, treatment may be of benefit even beyond 12 hours from symptoms onset. Imaging is crucial in selecting the patients who can still benefit from blood flow restoration.

In France – this is not true in other parts of the world – MRI is the most widely used imaging modality for stroke. The MARVELOUS project aims at providing a better and more quantitative analysis of the parameters derived from MRI, and help reach effective therapeutic decisions at the individual level.

O.I: Where did the idea of studying both ischemic brain and heart come from?

T.H.C: From the perspective of neurologists, we have a prominent and absolutely essential need for cerebral imaging. But, in order to know "why" stroke happened, we also need cardiac imaging. Indeed, a large part of the stroke patients have a clot which started from the heart; in order to confirm or reject this diagnosis, a set of imaging assessment must be performed during the days following the stroke event, since the prevention treatments will differ according to the cases. If ultrasound imaging is still widespread, myocardial MRI is an emerging technique already used in our department. However, we wish to go further by proposing a simultaneous heart-brain MR imaging to scan the brain, the heart and the arteries between them in a single session, in order to accelerate the investigations related to the stroke cause.

"The MARVELOUS project aims at providing a better and more quantitative analysis of the parameters derived from MRI."

I am not a cardiologist, but as far as the heart is concerned, the imaging need is not as pronounced before treatment as it is after the treatment. Indeed, the patient's prognosis depends on the final size and location of the infarct. Also, our cardiologist colleagues believe that they could improve and adapt their treatments depending on the heart of each person. Myocardial MR imaging is not widely used yet, this will be the heart part of the MARVELOUS project.

O.I: How are you involved in the study?

T.H.C: As mentioned, MARVELOUS develops both experimental and clinical projects. I work in both aspects, by coordinating the imaging projects and collecting the clinical data. Olea Medical® is at the center of those topics, at the pre-clinical and clinical levels. Since the end of 2016, we are including stroke patients treated in our institution in an observational cohort. Clinical, biological and MRI data are collected in order to fully document patients' acute status and subsequent evolution. Preclinical and clinical MRI exams are analyzed with the Olea Sphere® software. I also manage the flow of data between the clinical center, the researchers and Olea Medical®.

O.I: What are your expectations regarding the clinical impact of this project?

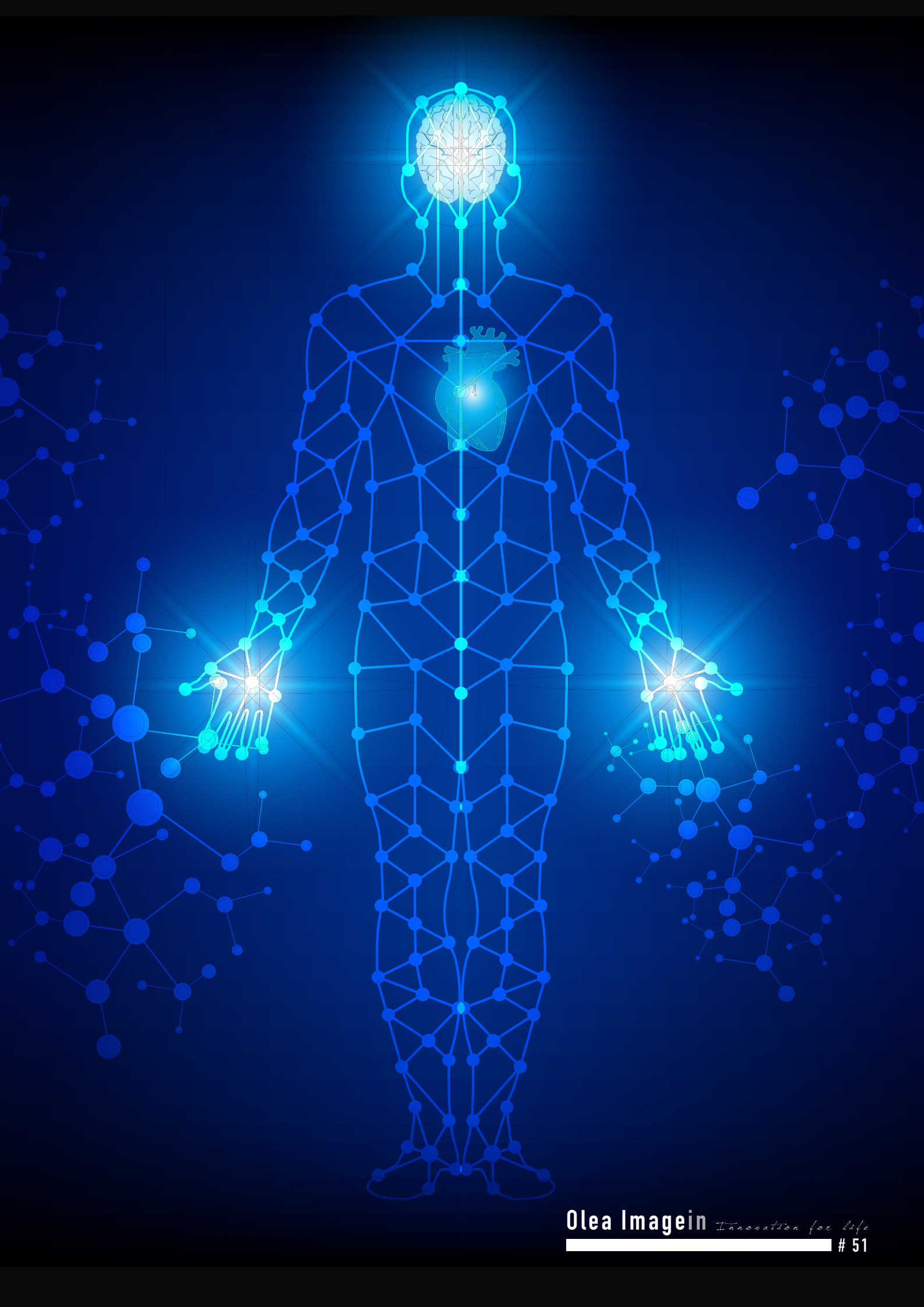
T.H.C: Our hope is to push the limits, to propose a more customized and meaningful approach. Until recently, clinical decision-making for cerebral infarction was based on rigid time limits. For example, the first positive trials that established the efficacy of mechanical thrombectomy in ischemic stroke only included patients in whom treatment could be carried out within the first six hours from symptoms onset. The majority of patients are still being admitted beyond this time window, or are without a definite onset time (the so-called wake-up strokes).

Two recent trials (DAWN and DEFUSE-3) showed significant progress in treating these patients, using neuroimaging criteria to select those most likely to benefit from reperfusion. Perfusion CT or MRI can identify patients who, although presenting late or with wake-up strokes, still have a significant amount of salvageable brain tissue. Still, these studies used 'one-size-fits-all', restrictive neuroimaging criteria in order to maximize the likelihood of a positive outcome.

In real-life clinical practice, deciding whether a given patient will benefit from treatment or not remains challenging. One of the central aim of the MARVELOUS project is thus to develop and validate a predictive tool allowing us to plot the final extent of the cerebral infarction from the baseline MRI data. We expect from MARVELOUS to get a precise idea of the brain state in a given individual, and evaluate the likely response to therapy in order to make the best personalized decision. Another application of such a predictive model would be to assess novel compounds or strategies in combination with reperfusion therapies by comparing observed and expected imaging outcomes in targeted phase II pilot studies.

In conclusion, the MARVELOUS project aims at developing useful tools for both the daily clinical practice and the evaluation of future treatments.

RHU MARVELOUS (ANR-16-RHUS-0009)



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Olea Imagein DIGEST: STROKE

Perfusion imaging is performed after the injection of intravenous contrast agent to non-invasively access the tissue and vascular hemodynamic characteristics. Cerebral perfusion mirrors the bloodstream conditions in the dense brain network. In case of artery occlusion, the pressure gradient drops, resulting in a decrease of blood flow or ischemia. Rapid cell death can then be observed in those vulnerable territories where a collateral protective circulation cannot be sufficiently recruited.

HEMODYNAMIC PARAMETERS

The assessment of CBF is of high prognostic significance to identify the extent and to target the right therapy of an ischemic stroke. Other parameters provide valuable information: the mean time the tracer remains within the voxel (MTT), the volume occupied by the tracer in the voxel (CBV), the time necessary to reach the maximum concentration after injection (TTP), and the delay between the injection in the artery and the tracer arrival in the voxel (Tmax/Delay).

All these parameters can be determined through the analysis of the tracer concentration curve c(t), expressed as the convolution product between the arterial input function (AIF) and the residue function, multiplied by CBF. In order to find solutions to this complex problem, deconvolution must be performed.

BAYESIAN DECONVOLUTION

Most deconvolution approaches use SVD algorithms. However, variability of CBF estimation, especially for CTP, were reported [1,2], and Tmax is always overestimated due to its dependency to MTT and to noise level [3,4]. SVD family of methods is known to strongly underestimate high parameters and overestimate low parameters [3-6]. This is why the Bayesian probability theory makes sense in this context, by evaluating the uncertainty of each parameter separately, canceling the potential inter-dependencies and adding robustness to the calculations. As a result, the pure value of arterial-tissue delay can be estimated regardless of MTT [4].

CORE AND PENUMBRA ASSESSMENT

The critically hypo-perfused ischemic core with irreversible damage is surrounded by the penumbra territory, where autoregulation is still preserved [7] but cell survival only permitted for a certain amount of time [8]. Since reperfusion risks can exceed favorable outcome in case of large core or lack of significant mismatch between core and penumbra [9], a robust estimate of their respective volumes is critical. In practice, core and penumbra volumes are calculated using thresholds.

MR DWI-PWI thresholds

DWI is fully established as a gold standard to assess the infarct core based on ADC thresholding ($< 0.6 \times 10^{-3}$ mm^2/s) [10-14]; and a consensus was reached in considering a longer Tmax (> 6s) as a proper predictor of the penumbra [10-12,15].

CTP thresholds

Although early research [7,16-17] focused on CBV, CBF was soon found to perform significantly better for core determination (relative CBF < 16% to 50%) [18-21]. rCBF < 30% or 40% – with respect to the healthy contralateral hemisphere, was hence accepted in most CTP clinical studies. However, the concept of double threshold was introduced to reduce the false-positive issue, and is nowadays widely applied: the core was restricted to regions with both low CBF and longer Tmax [22]. Using SVD, the combination of rCBF < 40% and Tmax > 2s was reported to provide the most accurate definition of the infarct core [23-27]. Using Bayesian, rCBF < 40% and Delay > 2s was found the most optimal [24-26,28-29].

The penumbra, characterized by longer Tmax (SVD)/ Delay (Bayesian) or delayed MTT, can be estimated from thresholds:

Tmax > 6s [22,24-27,30-32] or rMTT > 145% [7] using SVD;
Delay > 5s [28] or rMTT > 135% [24-26,29] using Bayesian.

Despite significant improvement over the years, the variability of CTP thresholds highlights the lack of tremendously important standardization. Bayesian algorithm has shown promising results; therefore, further clinical validations of thresholds with this method are ongoing.

COLLATERAL CIRCULATION

Besides prolonging the time that cells at risk can be saved, a good collateral blood supply can also be a predictor of reperfusion success [33]. Assuming that delays are more severe when collaterals are poor, most research focused on time-based hemodynamic maps such as Tmax or Delay [33].
In 2012, Boutelier et al. [4] observed that the Bayesian Delay was more consistent than the SVD Tmax for delineating arterial occlusion territory but also evaluating the collateral circulation. In 2013, Nicoli et al. [34] demonstrated that the combination of Delay (› 6s) and DWI lesion volume could assess for the degree of collateral flow and predict the rate of full recanalization after thrombectomy. Recently, Nael et al. [33] combined Delay with CBV to improve the prediction of the collateral status; a 94% diagnostic accuracy was obtained when compared to angiography. Robust, accurate, reproducible and physiologically meaningful, Delay map opens new research areas for clinicians to provide alternatives for collateral status assessment.

MR CONTRAST DOSE REDUCTION

The dose of contrast agent is of significant concern to patients, with the multiple contrast-enhanced sequences (angiography, perfusion) included in MR stroke protocols and the risk of contrast nephropathy [35]. However, contrast dose reduction is associated with higher noise and lower SNR, which is a major limiting factor. The Bayesian method, being less sensitive to low SNR conditions [4], can be used to reduce the contrast dose and accurately compute cerebral perfusion in low-dose protocols [36].

WHAT ABOUT VALIDATION?

Bayesian and SVD methods were compared with the expected true values using a digital phantom [37,38]. Sasaki et al. [37] concluded that "Bayesian estimation algorithm yielded CBF, CBV and MTT maps strongly correlated with the true values and MTT maps with better agreement than those produced by delay-insensitive SVD algorithms". Uwano et al. [38] stated that "Bayesian algorithm yielded accurate Delay and MTT values relative to the true values of the digital phantom".
Kudo et al. [39] investigated the performance of these methods in predicting the infarct volume in monkeys with MCA occlusion; the true final infarct volume was obtained after dissection of the brains. The authors concluded that "the Bayesian method was more reliable than oSVD deconvolution in estimating final infarct volume".
Titelbaum et al. [40] evaluated the quality of both Bayesian and oSVD methods in CTP stroke patients by comparing their results to consensual numerical references. They noted that "Bayesian CBF and MTT values were much closer to physiological values found in the literature" while "CBV values from both deconvolutions were very close".

The Bayesian method, nowadays used in clinical settings, is CE-marked and FDA-cleared within the Olea Sphere® software, which also includes SVD methods (i.e. sSVD, cSVD, oSVD).

GLOSSARY

CBF: cerebral blood flow
MTT: mean transit time
CBV: cerebral blood volume
TTP: time to peak
Tmax/Delay: time to maximum of the residue function
SVD: singular value decomposition (sSVD: standard; cSVD: block-circulant; oSVD: oscillation)
CTP: CT perfusion
DWI: diffusion-weighted imaging
PWI: perfusion-weighted imaging
ADC: apparent diffusion coefficient
SNR: signal to noise ratio
MCA: middle cerebral artery

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O	Y	I	G	J	X	L	O	M	X	F	S	O	T	Y
J	G	M	A	A	G	R	P	Z	P	T	S	X	E	C
K	O	H	X	C	N	Y	U	Y	R	E	K	F	L	I
D	L	J	S	C	E	S	E	O	C	K	U	I	E	S
V	O	R	E	U	D	P	K	Q	Q	H	N	N	R	L
Q	I	X	C	R	Y	E	A	T	N	T	L	O	A	A
U	D	B	R	A	P	X	W	O	E	N	A	I	D	R
J	A	W	A	C	Y	S	S	L	U	L	I	S	I	E
A	R	L	I	Y	E	F	L	E	R	V	C	U	O	T
T	O	H	L	A	R	I	E	C	O	D	I	F	L	A
K	R	J	Y	G	G	K	U	O	L	D	F	R	O	L
P	U	A	R	E	S	U	B	P	O	A	I	E	G	L
B	E	D	N	W	B	Z	J	Z	G	Z	T	P	Y	O
F	N	C	O	G	B	H	U	Z	Y	U	R	R	M	C
S	E	L	X	L	N	P	P	W	Q	Z	A	L	U	H

- STROKE
- NEURORADIOLOGY
- NEUROLOGY
- PERFUSION
- TELERADIOLOGY
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