Perfusion Session:

What is perfusion, and how do we measure it?

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Highlights

* *Perfusion is the critical aspect of blood flow to an organ and reflects the delivery of oxygen and nutrients to tissue at the capillary level.*
* *Numerous imaging techniques are used to measure blood flow, or cerebral blood flow in the case of the brain, each with its pro's & con's.*
* *Perfusion imaging is likely to play a more important role in medical imaging because of its ability to provide additional information not captured by structural imaging alone and therefore is likely to be used to guide therapy and interventions.*

Target audience:

Individuals interested in understanding more about blood flow, hemodynamics, vascular physiology and how MRI can be used to estimate perfusion

What is perfusion?

Every minute ~1000 mL of blood feeds heart (250 mL of blood) and brain tissues (750 mL of blood) with the primary purpose of providing oxygenated blood and nutrients (Mitchell & Blomqvist, 1971, Pubmed ID). Perfusion happens in each of the body's organs and is a quantitative measure of physiology that can be ascertained through various techniques. The units for perfusion have been preserved consistently in the literature over time and are: mL of blood per 100g of tissue per min, or mL/100g/min. In this lecture we will discuss what these units represent and how these units came to be. As is the case with any empirical measurement, we must know what we are measuring before we conduct our experiment. This may seem trivial, but it is now possible to collect perfusion images in absolute units and in a "*push-button*" format with MRI (***Figure 2***, Alsop et al., MRM 2014, Pubmed ID), so it is important to know how these estimates are made and understand the assumptions & limitations.

Figure 1 shows conceptually what perfusion is *in relation* to blood flow. "Blood flow" and "perfusion" are terms that are often used interchangeably, but it is important to note that perfusion reflects a specific aspect of blood flow & vascular physiology. Namely, perfusion is the delivery of nutrients, such as oxygen dissolved in blood, to a volume of tissue in an organ via the capillaries. For this to happen there needs to be an exchange between vascular and tissue spaces. In the case of oxygen perfusing tissue, the oxygen exchange corresponds to diffusion down the concentration gradient, from blood vessel to tissue, a process that is governed by the partial pressure of oxygen. Therefore, delivery of oxygen is a quintessential "service" that allows the tissue to maintain its metabolic rate. Hence perfusion supports the metabolic rate of oxygen consumption and these two physiological measures are related to one another by the tissue's oxygen extraction fraction. Failure to supply sufficient oxygen leads to ischemia, with the most explicit examples of ischemia being myocardial infarction in the heart or ischemic stroke in the brain. Perfusion also facilitates the clearance of waste products and dissipates heat, which are other key aspects for maintaining tissue health / homeostasis.

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In a healthy individual, blood enters an organ via an artery at close to 100% oxygen saturation and blood leaves the organ via a vein with an oxygenation level that is down to ~65% in the case of the brain. A perfusion image can therefore provide quite pertinent information. The image itself will have signal intensities that vary by tissue type and whose intensity corresponds to absolute perfusion in units of mL/100g/min. ***Figure 2*** illustrates that the perfusion image is not "flat" because there is typically a well delineated spatial pattern (in this case grey vs white matter differences in perfusion level). Next, perfusion levels in an organ are not static, instead they can change over short and long time scales. For example, caffeine is a vasodilator in the body and a vasoconstrictor in the brain (Mulderink TA et al., NeuroIm 2002, Pubmed ID), which will lead to increased perfusion in peripheral organs and decreased perfusion in the brain. Neurodegenerative diseases like Alzheimer's disease, atherosclerosis and cerebrovascular diseases like stroke are characterized to varying extents as hypoperfusion syndromes.

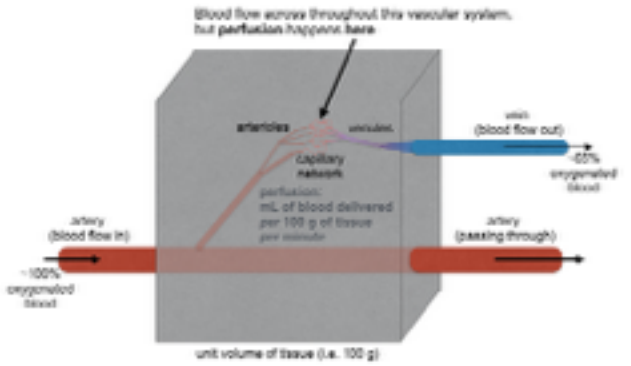

Figure 1: A conceptual diagram showing how blood flow represents the movement of blood throughout the entire vascular network (i.e. arteries, capillaries, veins, etc), whereas perfusion occurs at the tissue level within a capillary network.

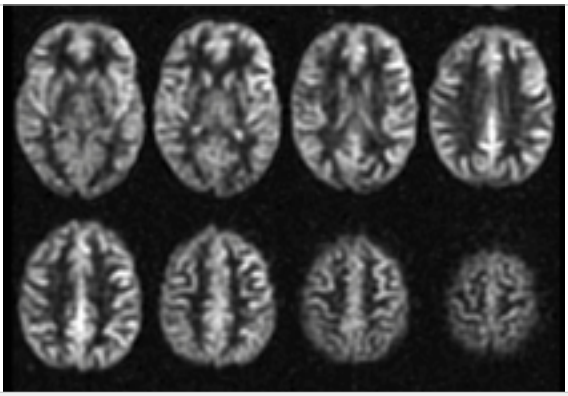

Figure 2: Representative perfusion axial images of the human brain achieved using arterial spin labeling (ASL). The relative signal intensity corresponds to the perfusion level (adapted from Alsop et al., 2014, Pubmed ID).

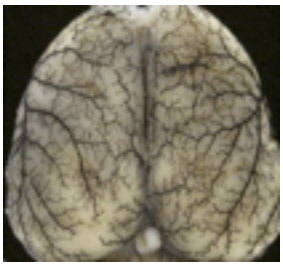

Figure 3. Arteries, arterioles and small vessels that are dark in this image while non-vascular tissue is bright. This microsphere perfusion example is from a rat brain (adapted from Busch HJ, et al., JCBFM 2011, Pubmed ID).

What makes a technique ideally suited to measure perfusion is an important question, and there are good reviews on this topic (Wintermark M, 2005, Stroke, Pubmed ID), (Donahue MJ, 2012, Stroke, Pubmed ID). It is interesting to note, however, that Posner in 1972 described that the ideal cerebral blood flow technique should be: 1. non-invasive, 2. instantaneous and repeatable, 3. provide regional and total flow, and 4. capable of measuring flow and metabolism (this last characteristic remains an on-going challenge!) (Posner JB, Stroke 1972, Pubmed ID). And for the most part this list remains topical in the current perfusion imaging literature.

In this lecture we will discuss the different blood flow techniques that are capable producing a perfusion estimates. While injection of ***microspheres perfusion*** is considered a gold-standard technique for blood flow / volume, it is invasive and is typically only ever used for animal perfusion studies.

Nuclear Medicine and ***computed tomography*** offer multiple approaches for perfusion imaging. In the case of ***positron emission tomography***, the radioisotope ^{15}O can be delivered as a gas or injected intravenously as $H_2{}^{15}O$. ***Single photon emission tomography*** can also be used to measure perfusion through the use of various contrast agents (that are mostly derived from ^{99m}Tc, the most common medical radioisotope).

Lastly, there are several ways that MRI can be used to measure hemodynamics, including blood volume (the "VASO" technique), total blood flow & intra-arterial velocity (phase contrast angiography) and even blood oxygenation approaches, however, there are really only two MRI techniques that are used to make whole organ perfusion images. The first technique, ***dynamic susceptibility contrast*** (**DSC**), relies on the first passage of an injected Gadolinium-based contrast agent (for review see Ostergaard L., JMRI 2005, Pubmed ID). The second technique, ***arterial spin labeling*** (***ASL***), relies on an "out of volume" preparation to magnetically labeling blood water prior to its detection in the volume of interest. ASL therefore does not rely on an exogeneous contrast agent. At this point there are many comparison studies that contrast ASL and DSC in different clinical populations, and represents the necessary due diligence on the part of the MRI perfusion community (Weber MA, Invest Radiol 2003, Pubmed ID), (Nael K, et al., Stroke 2013, Pubmed ID).

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