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Applications of Imaging Technology in Radiation Research

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Abstract

Imaging research and advances in systems engineering have enabled the transition of medical imaging from a means for accomplishing traditional anatomic visualization (i.e., orthopedic planar film X ray) to a means for noninvasively assessing a variety of functional measures. Perfusion imaging is one of the major highlights in functional imaging. In this work, various methods for measuring perfusion using widely-available commercial imaging modalities and contrast agents, specifically X ray and MR (magnetic resonance), will be described. The first section reviews general methods used for perfusion imaging, and the second section provides modality-specific information, focusing on the contrast mechanisms used to calculate perfusion-related parameters. The goal of these descriptions is to illustrate how perfusion imaging can be applied to radiation biology research.

INTRODUCTION

Imaging research and recent advances in systems engineering have enabled the transition of medical imaging from a means for accomplishing traditional anatomic visualization (i.e., orthopedic planar film X ray) to a means for noninvasively assessing a variety of functional measures. One of the major highlights in functional imaging is perfusion imaging. Measuring perfusion is useful because it is one of the fundamental physiologic parameters that describe the flow of nutrient/drug delivery to and from organs/tissues at the capillary level. Thus, it can be used as an indicator for diagnosis, as well as a measure of therapeutic efficacy (1). Perfusion should be distinguished from bulk blood flow, which occurs in blood vessels. There has been an increasing interest in using imaging as a non or minimally-invasive way to measure perfusion. For example, computed tomography (CT) has been used for brain stroke management (2–4), and X ray digital subtraction angiography (DSA) has been used for monitoring embolotherapy end points (5). There are multiple MR-based techniques that can be used to assess perfusion and vascular permeability, and these techniques have been used, as discussed below, in a wide variety of applications, including stroke, monitoring of antiangiogenic/antivascular therapy, differential diagnosis of tumor progression versus treatment effect, including radiation necrosis, etc. In this work, various methods for measuring perfusion using different imaging modalities will be described. The first section reviews general methods used for perfusion imaging, and the second section provides modality-specific focus [along with specific technique names (i.e., dynamic

contrast enhanced MRI, DCE-MRI)] on the contrast mechanism used to calculate perfusion. The goal of these descriptions is to illustrate how perfusion imaging can be applied to radiation biology research.

PERFUSION MEASUREMENT METHODS

Imaging-based approaches to perfusion measurements require sequential time point (i.e., dynamic) image acquisitions. Perfusion measures are based on the rate, amplitude, and duration of contrast agent wash-in, parenchyma filling, and contrast agent wash-out in a region of interest (ROI). Specifically, a number of methods exist that measure characteristics of how the image pixel intensity changes over time [signal intensity curve (SIC)] as the contrast agent enters, distributes, and washes out of the ROI. Typically, a tracer/contrast agent input, in the shape of a square impulse function at a proximal vessel location, will become a delayed and dispersed curve at a distal vessel location. For analysis of the data, mathematically-straightforward semi-empirical methods, and mathematically-complex model-based approaches have been proposed.

Perfusion Measurement Methods: Mathematically Straightforward Approaches

The mathematically straightforward model provides independent approaches that are effective in the direct measurement of SIC characteristics.

Figure 1 shows a representative SIC. The letters represent direct measurements of the curve characteristic: (A) maximum enhancement (maximum amplitude of SIC), (B) arrival time (time from administration of contrast agent to time of contrast agent detection in an ROI of interest), (C) mean transit time (MTT, time to reach center of gravity of SIC, sometimes expressed as the time it takes to reach the average SIC value), (D) wash-in rate (upward slope of pixel signal intensity change), (E) wash-out rate (downward slope of pixel signal intensity change), (F) brevity of enhancement (time between middle of wash-in and wash-out rate), and (G) blood volume (BV, area under SIC). In addition, combinations/ratios of the above direct measurements can be performed and often are compared between two ROIs, i.e., an input function ROI and the perfusion area of interest ROI. The input function is typically an arterial vessel AIF (arterial input function) proximal to the perfusion area of interest and serves as a reference for comparison and/or mitigation of downstream perfusion effects because of contrast agent delivery. For example, Mullani *et al.* defines perfusion as the peak enhancement of the perfusion ROI divided by the area under the SIC of an ROI in the aorta (6). Other formulations take the ratio of peak tissue ROI enhancement to the peak AIF enhancement (2), or a ratio of the area under the tissue and AIF SICs (7).

An advantage of these direct-model independent SIC characteristic measures is that the computations are simple. A challenge in using these methods is calibrating relative signal intensity measurements to absolute metrics, such as if inter-patient comparisons are being made or curve properties are being related to a physiologic phenomenon; intra-patient perfusion measurements pre- and post-therapy offers a comparison of relative change due to therapy. Major limitations to the direct measurement method include the subject's cardiovascular status (e.g., cardiac output), contrast agent injection characteristics (the specific agent used, site of injection, injection rate, etc.), and image acquisition problems (i.e., motion artifacts, noise), which can mask the actual perfusion characteristics being evaluated. Furthermore, such model-independent direct measures often result in the units of measurement being represented as arbitrary values (8). The impact of motion artifacts can be mitigated using fast-image acquisition, cardio-ventilatory image synchronization (pro- or retrospective), and post-processing (e.g., motion compensation, gamma variate fitting to smooth noisy SICs, etc.) (3, 9); the mathematically complex approaches attempt to mitigate these effects. These approaches use elements of the direct SIC measurements described

above to estimate perfusion, and two popular methods are discussed later in this article: Patlak analysis and deconvolution. A number of methods exist that are based on these popular methods, and specific details are provided in the imaging modality sections below.

Perfusion Measurement Methods: More Mathematically-Complex Model-Based Approaches

Patlak analysis is a graphical analysis method based on a compartment model that uses linear regression to identify the influx constant and the distribution volume of the tracer between arterial plasma and tissue (10, 11). If t is time, R is the amount of contrast agent in the tissue ROI, c is the concentration of contrast agent in the blood plasma/arterial ROI, K is the influx constant (rate constant by which the contrast agent moves from the intravascular space to the extravascular, extracellular space), and V_0 is the tissue distribution volume, then:

$$R(t) = K \int c(t) dt + V_0 c(t),$$

which can be rearranged to yield

$$\frac{R(t)}{c(t)} = K \frac{\int c(t) dt}{c(t)} + V_0$$

The unknown constants, K (mL tissue/(mL plasma min)) and V_0 can be solved by linear regression by plotting:

$$\frac{R(t)}{c(t)} (\text{y-axis}) \text{ vs } \frac{\int c(t) dt}{c(t)} (\text{x-axis})$$

The slope is the permeability constant (K) and the y-intercept is the relative blood-to-tissue distribution volume (V_0). This method assumes that contrast-agent behavior can be approximated by a two-compartment pharmacokinetic model, where the blood plasma compartment is in equilibrium with the blood supply and there is only unidirectional tracer flow into the tissue compartment. Therefore, this technique is relevant during the early phase of the contrast agent extravasation from the vascular space into the extracellular/extravascular space. A number of refinements have been made to Patlak analysis to account for reversible movement of contrast from tissue to blood plasma, tracer binding, and other parameters, making the measurement more accurate and reflective of what is happening on a physiologic level (10, 12).

Deconvolution is another model-based method to calculate perfusion parameters from dynamic SIC data. Here, effects of the vasculature on the contrast concentration curve are removed through deconvolution, which leaves the perfusion information. This is mathematically expressed as:

$$C_{v01}(t) = C_a(t) \otimes h(t) = F_t \int_0^t C_a(\tau) R(t - \tau) d\tau$$

where C_{V01} is the tracer concentration within a ROI, t is time, $\otimes$ denotes convolution, h is the transport function (the probability density function of transit-time characteristic of flow and vascular structure), F_t is the flow (blood flow, BF), C_a is the arterial input function concentration, and R is the residue function (the fraction of injected tracer still present in the vasculature at time t and is a function of the local tissue vasculature). The goal is to solve for F_t . However, this equation does not have a straightforward solution because R is, “an unknown function dependent on local vascular structure” (8). A number of deconvolution methods exist to solve this inverse problem including: (1) assuming a specific shape for R (typically a decreasing exponential), (2) inverse Fourier transform, and (3) solution with an algebraic reformulation using singular-value decomposition (SVD).

The advantage of assuming R 's value is that it makes the mathematical processing straightforward. However, the level of accuracy is directly dependent on an accurate model. The *a priori* information about the vasculature is often not known, which makes this technique error-prone. Direct inverse Fourier transform takes advantage of the convolution theorem that states convolution in the Fourier domain is multiplication. Thus, R and F can be solved by taking the inverse Fourier transform of $C_{V01}(t)/C_a(t)$ at every time point. Note here that the residue and flow functions are solved together. The drawback is that this approach is very sensitive to noise, the impact of which can be mitigated using frequency domain filters (13). The convolution equation above (note that the residue and flow functions are solved together), assuming equally spaced sampling (t), can be reformulated into an algebraic reformulation that is a discretized representation:

$$C_{v01}(t) = \int_0^t C_a(\tau)R(t-\tau)d\tau \approx \Delta t \sum_{i=0}^j C_a(t_i)R(t_j - t_i)$$

This can then be represented in matrix form:

$$\Delta t \begin{pmatrix} C_a(t_1) & 0 & \cdots & 0 \\ C_a(t_2) & C_a(t_1) & \cdots & 0 \\ \vdots & \vdots & \cdots & \vdots \\ C_a(t_N) & C_a(t_{N-1}) & \cdots & C_a(t_1) \end{pmatrix} \cdot \begin{pmatrix} R(t_1) \\ R(t_2) \\ \vdots \\ R(t_N) \end{pmatrix} = \begin{pmatrix} C_{v01}(t_1) \\ C_{v01}(t_2) \\ \vdots \\ C_{v01}(t_N) \end{pmatrix}$$

or in shorthand vector notation, $A \cdot \vec{b} = \vec{c}$, where A and $\vec{c}$ are measured and $\vec{b}$ is to be solved. SVD is used to obtain A^{-1} and the diagonal matrix. The main benefit of using SVD is the elimination of noise (oscillating or meaningless in a biomedical context) by setting values in the SVD diagonal matrix below a threshold (e.g., 10–20%) to zero. By doing so, the solution for $\vec{b}$ is the best possible in a least squared sense for the vector norm of $A \cdot \vec{b} = \vec{c}$. The relative flow is taken as the maximum value in $\vec{b}$. A drawback of this method is that it is computationally intensive as compared to the previous, and more direct, measurement methods. Further expanding on the SVD approach, Calamante *et al.* showed that contrast-agent bolus-delay effects can be corrected by realigning the distal and input function SICs to a common signal maximum (7–9). Lin *et al.* calibrated the relative flow measurements (taking into consideration that the residue and flow functions are solved together) to absolute flow measurements for the aorta in the rodent (14).

Perfusion Measurement Methods: Summary

The approaches described above calculate certain parameters of perfusion; an overarching framework is the central volume principle, which states: *Blood volume (BV) = Blood flow (BF) × Mean transit time (MTT)*.

Thus, measurement of two of these parameters (sometimes using a combination of mathematically straightforward and complex equations) can calculate the third (15). Often, the organ ROI is appended to BV and BF as a prefix. For example, cerebral blood volume is CBV and pulmonary blood flow is PBF. Furthermore, the BV and BF are often measured in relative (usually in reference to another vessel, *e.g.*, the aorta), rather than in absolute, units. Though not always shown, an “r” prefix is used to indicate that the reported measures are relative. For example, relative cerebral blood volume is rCBV.

The mathematical method selected largely depends on computational efficiency, the need for absolute/calibrated measurements, and the selection of a perfusion model (contrast-agent and tissue-dependent) that best represents actual physiology. In certain cases, for example, Patlak and deconvolution techniques show similar results (16). The sections below describe the specific applications of perfusion in popular imaging modalities. Some perfusion measurement methods are preferred in one modality over another, in part due to the physical mechanisms of image acquisition and contrast-agent-signal intensity characteristics.

IMAGING MODALITIES

Computed Tomography (CT) Perfusion

CT perfusion imaging is a commonly utilized approach because of its reproducibility, linear relationship between signal intensity change and contrast agent concentration, ability to capture volumetric information with sufficient field of view (FOV), and ability to obtain image acquisitions rapidly enough to provide accurate SICs. Iodinated X ray contrast agents that are intravenously delivered using a power injector are the indicator tracers used for calculating blood flow and perfusion. CT perfusion is able to provide absolute perfusion measurements, typically as mL/min of blood per mL of tissue, because the change in X ray attenuation (CT number or Hounsfield Unit) is directly proportional to the concentration of X ray contrast agent.

CT perfusion was first proposed by Leon Axel in 1980 and realized in practical clinical applications 10–20 years later, especially with the advent of multislice helical CT scanners (17–19) that allowed for multislice image acquisitions with sufficient temporal resolution (*i.e.*, <5 s). Prior to multislice CT, perfusion measurements could be made, but with limited anatomic coverage, which could result in partial volume effects (underestimation of perfusion) where only a portion of contrast bolus is within section thickness (19). A major clinical application of CT perfusion is in ischemic stroke management. In an ischemic (as opposed to hemorrhagic) stroke, a thrombus occludes an arterial vessel supplying blood to the brain. This type of stroke presents with two zones of injury: the core ischemic zone and the surrounding ischemic penumbra. In the core zone, there is severe ischemia (usually immediately surrounding the thrombus site), which often leads to cerebral cell death. Around the core zone is the ischemic penumbra where there is a rim of mildly-to-moderately ischemic tissue that may be salvageable if treatments, such as tissue plasminogen activator (tPA), can be quickly administered after diagnosis. Success of reperfusion and saving as much cerebral tissue as possible relies on rapid diagnosis and treatment (4).

Figure 2 reproduced from Wintermark *et al.* (4), shows defects of cerebral perfusion after a stroke using three popular imaging techniques: perfusion CT (PCT), MR diffusion-weighted imaging (DWI), and MR perfusion-weighted imaging (PWI). While the imaging mechanisms are quite different between PCT, DWI, and PWI, the indications for acute stroke treatment were shown to be similar across these three imaging techniques (4). Of interest here is that the infarct core (red) and the penumbra area (green) calculated from the PCT findings can be visualized as a color overlay. The infarct core and penumbral area were defined as areas where the MTT was increased >145% when compared to the healthy

cerebral tissue on the contralateral side, and $CBV < 2 \text{ mL}/100 \text{ g}$ for the infarct core or $CBV > 2 \text{ mL}/100 \text{ g}$ for the penumbral area. The detection of stroke and its extent can be imaged on CT angiography (CTA) and perfusion measured using CT perfusion (2).

Small animal CT perfusion can also be performed and Badea *et al.* showed how novel image acquisition strategies can mitigate rapid cardioventilatory motion artifacts present in rodents (20).

X Ray Fluoroscopy and Digital Subtraction Angiography (DSA)

C-arm-based X ray techniques, such as fluoroscopy and DSA, are the imaging modality of choice for interventional radiology, where rapid, real-time imaging plays a critical role in vascular and cardiac procedures. An iodinated contrast agent is usually injected (manually or using a power injector) through intravascular catheters to provide vascular image enhancement. In addition to obtaining anatomic blood vessel visualization, the rapid image acquisition [most commercially-available C-arm systems can operate upwards of 30 frames-per-second, though many use lower frame rates (i.e., 3 frames-per-second to lower X-ray dose)] allows for visualization and measurements of perfusion-related parameters, including contrast agent wash-in, parenchyma filling, and contrast agent wash-out (21).

The advantage of planar X-ray-based imaging is the high temporal resolution, intra-procedural availability, and lower costs compared to CT or MRI. However, as a 2D-imaging technique it is limited by superposition artifacts (i.e., overlapping vessels), and image quality can suffer substantially due to motion artifacts (e.g., ventilation motion). Nevertheless, work has been done to mitigate these impacts through efforts such as cardiac and ventilatory gated imaging (14) and using tomosynthesis to obtain more volumetric information while still retaining high temporal sampling (22).

Two-dimensional DSA perfusion can be used for stroke management. Brain imaging quality is minimally impacted by the effects of cardiac and ventilation motion and, in certain imaging orientations, blood vessel superposition can be minimized.

Figure 3 shows representative perfusion color maps (time-to-arrival, Metric-B in Fig. 1) that were calculated from anterior-posterior DSA before and after stroke treatment. Note how poorly perfused areas of the brain become reperfused as reflected by arrival-time information (compare red circles) after treatment. In addition, previously perfused areas show a decrease in arrival time after treatment (more red than blue in the color bar). Both features indicate perfusion restoration.

An area of emerging perfusion work is in embolotherapy, specifically for transcatheter arterial chemoembolization (TACE). This interventional radiology procedure delivers drug-loaded (doxorubicin) or radioactive (Y-90) microspheres to selectively treat liver lesions. To date, the end point of delivery is still operator-/subjective-based. Generally, too much microsphere delivery can lead to reflux into healthy organs, while too little delivery can lead to suboptimal results. This delivery is made more difficult by the fact that the microspheres, specifically drug-loaded beads and radiospheres, are radiolucent.

Figure 4 shows an example of how perfusion measurements show the modification of blood flow due to embolization much better than DSA. The color map images of time-to-peak perfusion measurement vividly show the retardation in blood perfusion (more blue) after TACE. This perfusion measurement is special because it is calculated from DSA images; it brings added value because more information can be obtained from post-processing X ray scans that would take place as part of normal clinical practice. Also, no additional X ray

scan or dose is required. As a result of these findings, interest in developing a reproducible and quantifiable embolization end point based on perfusion is growing (5).

Magnetic Resonance Imaging (MRI)

An advantage of MR-based perfusion measurement is that there can be a number of image acquisition and analysis strategies arising from various contrast mechanisms that focus attention on specific aspects of perfusion; for example, dynamic susceptibility change MRI (DSC-MRI), which relies on rapid sampling (typically every 1.5 s) of a T2*-weighted SIC before, during, and following the first passage of a rapidly-injected bolus of contrast agent (most commonly a gadolinium chelate) to allow the computation of BV, MTT, and BF imaging biomarkers. Deconvolution methodologies, similar to those described above, are typically used to extract the BV and MTT data, and BF data are computed from BV and MTT using the central volume theorem. As with CT-perfusion applications, the deconvolution model, if the SIC is monitored for sufficient duration, allows for the estimation of the permeability surface area product (PS); perfusion parameters obtained from DSC-MRI applications are analogous to those obtained from CT perfusion applications. Disadvantages of DSC-MRI techniques relative to perfusion CT include inferior in-plane spatial resolution, more complicated data analysis due to the nonlinearity of the SIC compared to contrast agent concentration, and cost. Advantages include the absence of radiation dose and the ability to interrogate a larger volume of anatomy. Details of the DSC-MRI data analysis strategies are thoroughly described in chapter 4 of the text edited by Jackson *et al.* (23).

Dynamic contrast enhanced MRI (DCE-MRI) relies on rapid sampling (typically every 4–10 s) of a T1-weighted SIC from the vascular space and from the ROI before, during, and following contrast agent injection to allow the computation of vascular volume fraction (v_p), endothelial volume transfer constant (K^{trans}), contrast agent reflux rate (k_{ep}), and extravascular/extracellular volume fraction (v_e). Commonly applied analysis strategies in DCE-MRI applications are based on a two-compartment pharmacokinetic model (24). Differences in the details of the analysis strategies are most commonly: (1) whether or not the vascular volume fraction is included, i.e.:

$$C_{ROI}(t) = K^{trans} C_p(t) \otimes e^{-k_{ep}t} + v_p C_p(t) \quad (3 - \text{parameter generalized kinetic model})$$

versus

$$C_{ROI}(t) = K^{trans} C_p(t) \otimes e^{-k_{ep}t} \quad (2 - \text{parameter kinetic model})$$

and (2) whether the plasma compartment contrast agent concentration, $C_p(t)$, is measured (patient-derived arterial input function) or is assumed based on prior reported data (population-derived arterial input function). The remaining parameter of interest, v_e , can be obtained as K^{trans}/k_{ep} . Again, it should be noted that conversion of SIC data to contrast agent concentration data requires a nonlinear transformation based on the native tissue (pre-contrast agent administration), T_1 relaxation values and the specific pulse sequence used, and the acquisition parameters used for that pulse sequence. As a result of the complexities of these conversions, some investigators perform the DCE-MRI pharmacokinetic analysis using the measured SIC data directly without conversion to contrast agent concentration. Details of these models and data analysis strategies are described in chapter 6 of the text edited by Jackson *et al.* (23).

A common problem for both CT- and MR-based perfusion-imaging techniques using commonly administered contrast agents relates to the size/molecular weight of the agent itself. Most commonly-administered contrast agents have molecular weights in the ~500–700 Dalton range and, as such, extravasate with relatively high rates for all tissues outside the blood-brain barrier. In DCE-MRI applications, for example, this results in the K^{trans} parameter reflecting both the delivery of the agent (flow), as well as the permeability (extraction) in lesions associated with high leakage of the contrast agent (24). If the flow is not the limiting factor, then K^{trans} is a direct measure of the permeability-surface-area product. If flow is limiting, however, then K^{trans} is most generally a measure of the extraction-flow product. Both DCE-MRI and DCE-CT would benefit from the availability of approved contrast agents with higher molecular weight.

Unlike each of these techniques, which require the administration of an exogenous contrast agent, arterial spin labeling MRI (ASL-MRI) uses labeled arterial blood water, which is an endogenous contrast agent, to allow for the computation of BF-imaging biomarkers. While a variety of specific implementations of ASL-MRI have been proposed and are in use in research centers and, more recently, available on commercial MR systems, the basic principle is that the magnetization in the blood is inverted prior to entering the imaging volume, and this tagging causes the magnetization from the blood entering the imaging volume to differ from that of the tissues within the imaging volume. Two sets of images are obtained: one without tagging (control) and one with tagging. The image sets are subtracted, which results in perfusion-weighted images. To convert these perfusion-weighted images to quantitative blood flow images requires additional information, including the T1 relaxation rate for the tissues of interest (R_{1T}) and arterial blood (R_{1A}), as well as the magnetization-labeling-efficiency of the blood (α), the blood-brain partition coefficient (λ), and labeled blood transit time (δ) (the BF) can be calculated from the following equation:

$$\frac{M_T^{control} - M_T^{label}}{M_T^{control}} \cong \frac{BF2\alpha}{\lambda R_{1T}} e^{-R_{1A}\delta}$$

The required parameters are either measured directly (e.g., patient-specific R_{1T} measurements), or estimated from prior experiments or literature values (e.g., literature values of λ). Details of the various implementations of ASL-MRI are provided in the references (25–28).

The obvious advantage of ASL-MRI lies in the absence of any need for exogenous contrast agent. The disadvantages relative to contrast-agent-enhanced techniques, however, are less sensitivity (requiring multiple signal averages with the concomitant longer scan time), and challenges obtaining multiple acquisition sections with comparable measurement accuracy. However, with recent increased scrutiny on gadolinium contrast agents due to the purported association of such contrast agents with nephrogenic systemic fibrosis (NSF) in a small number of patients with severe renal insufficiency, and the ability to obtain repeated BF measures in a single imaging session, commercial implementations of ASL-MRI are now available and applications are expanding, particularly on 3.0T systems where the added signal-to-noise ratio is advantageous, in these applications.

Selecting the appropriate MR-based perfusion strategies (described above) for use in a given application depends on the specific quantitative imaging biomarker(s) of interest, and the capabilities of the available MR instrumentation. Examples of DSC-MRI, DCE-MRI, and ASL-MRI are given below.

MRI, like CT, can also be used for stroke management because it produces similar diagnostic results (29). The advantages of MRI over CT are that a larger volume of interest can be investigated, there is no ionizing radiation, and susceptibility-weighted MRI techniques can also detect microbleeds. The drawbacks are that MRI is more time-consuming and more expensive, which makes it less available than CT in emergency departments, and less often used for monitoring in an acute stroke setting (4). In Fig. 2, functional imaging biomarker data from DW-MRI and DSC-MRI acquisition show cerebral blood perfusion defects. The DW-MRI images show enhancement in the stroke area due to restrictions in diffusion. The DSC-MRI relative MTT images show protracted cerebral transit time (red), indicating abnormal blood flow. The level of regional agreement as visualized in DW-MRI and DSC-MRI can be used to estimate a time-course estimate of infarct progression and functional impairment (30). MR-based perfusion studies in a small animal model have been carried out using novel MR pulse sequences that can meet the high spatial and temporal resolution demands observed in these small animals (31).

There are numerous examples of DCE- and DSC-MRI applications in the assessment of targeted therapies, particularly with anti-angiogenic/anti-vascular agents and radiation therapy (32–40). In anti-angiogenic/anti-vascular therapy applications, profound decreases in DCE-MRI K^{trans} measures (35–65%), for example, are frequently reported, often as early as 24–48 h following initial dose (41–46). As a result, DCE-MRI imaging biomarker measures have been increasingly used as secondary/exploratory end points in Phase I/II clinical trials of novel anti-angiogenic/ anti-vascular agents. In radiation oncology applications, both DCE-MRI and DSC-MRI applications have demonstrated that areas of tumors that exhibit poor perfusion measures at baseline (e.g., low values of BV , BF , v_p , and/or K^{trans}), or demonstrate no or minimal increase during radiation therapy, are typically associated with poor outcomes (e.g., local failure) (32–40). Finally, while ASL applications currently are fewer in number than contrast-enhanced applications, reported studies include those addressing the management of cerebrovascular disease, central nervous system neoplasms, and epilepsy (47–49). As ASL capabilities have recently been made available on high-field MR scanners from all major vendors, it is anticipated that these applications will increase in number rather quickly. Figure 5 illustrates applications of DCE- and DSC-MRI in the case of a patient with glioblastoma multiforme, and Fig. 6 illustrates ASL-MRI.

Currently, such quantitative imaging biomarkers are considered to be secondary or exploratory end points in clinical trials or in clinical applications. To move such measures from secondary/ exploratory end points to primary end points will require the completion of additional efforts necessary to qualify such imaging biomarkers (50). This is true not only for MR-based imaging biomarkers, but for all imaging biomarkers. As such, several organizations, including the Radiological Society of North America, through its Quantitative Imaging Biomarker Alliance (<http://qibawiki.rsna.org>) are actively working with equipment vendors, users, etc., to promulgate methodologies that will, “Improve the value and practicality of quantitative biomarkers by reducing variability across devices, patients and time.”, and to work with the Food and Drug Administration, for example, to qualify such quantitative imaging biomarkers.

CONCLUSION

There is a wide variety of noninvasive image-based perfusion measurement methods. The selection of which method to use largely depends on the imaging modality and computational/data analysis resources available, the need to minimize radiation dose, and/or the desire for absolute or relative measures. As functional imaging systems achieve faster acquisition rates, higher spatial resolution, and particularly if novel contrast agents (e.g., higher molecular weight and/or targeted) become available, current and novel perfusion

measurement methods will become more accurate, shift from relative to absolute measures, and potentially be used as standard of care in more clinical settings.

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FIG. 1. Representative signal intensity curve (SIC) showing mathematically straightforward perfusion measurements: (A) maximum enhancement, (B) arrival time, (C) mean transit time, (D) wash-in rate, (E) wash-out rate, (F) brevity of enhancement, (G) blood volume (area under SIC).

FIG. 2.

Defects of cerebral perfusion after stroke as visualized using three popular imaging techniques: perfusion CT (PCT), MR diffusion-weighted imaging (DWI), and MR perfusion-weighted imaging (PWI). In the same areas, CT and MR angiography (bottom row) anatomical imaging also show cerebral blood vessel filling defects. PCT shows areas of infarct core (red) and penumbral area (green). DWI images show enhancement in the stroke area due to blood stasis. PWI colormap shows relative MTT where red represents a protracted cerebral transit time, indicating abnormal blood flow. Permissions granted for reproduction from M. Wintermark, *et al.* (4).

FIG. 3.

Representative perfusion color maps calculated from 2D anterior-posterior DSA X ray (2D Perfusion, Philips Healthcare, Best, The Netherlands) before and after carotid artery stenting (treatment area shown by arrow). In this case, the perfusion metric used is time-of-contrast agent arrival. Note how areas of the brain become repurified and show arrival time information (compare red circles) after treatment. In addition, previously perfused areas show a decrease in contrast arrival time after treatment (more red than blue in the color bar). Both of these features indicate perfusion restoration.

FIG. 4.

Patient with innumerable neuroendocrine lesions. Note how the image enhancement as seen on DSA appears similar before and after TACE therapy. However, 2D perfusion analysis (2D Perfusion, Philips Healthcare, Best, The Netherlands) of time-to-peak enhancement show dramatic retardation in blood flow (more blue), especially over the lesions, due to the embolization. (Images courtesy of Jean-François Geschwind, and Nikhil Bhagat, at Johns Hopkins Hospital, Baltimore, MD.)

FIG. 5.

Example images from a patient with glioblastoma multiforme: (Panel A) T2-weighted image, (panel B) T2-FLAIR (fluid attenuated inversion recovery) image, (panel C) T1-weighted image post contrast agent injection, (panel D) a single frame from a DCE-MRI acquisition, (panel E) the SIC from a lesion ROI (short arrow) and the vascular input ROI (long arrow), (panel F) a computed K^{trans} map, (panel G) a single frame from a DSC-MRI acquisition, (panel H) the SIC from a lesion ROI (short arrow) and the vascular input ROI (long arrow), (panel I) a computed rCBV map.

FIG. 6.

ASL image creation: Control and labeled images are obtained and a difference image (control – label) is created. As the signal, difference is relatively small, multiple signal averages are obtained and result in a perfusion-weighted image. To convert the perfusion-weighted image to a quantitative rCBF map, additional data is required, including a calculated T1 map, as well as measured or assumed values for α (labeling efficiency); λ (blood-brain partition constant); and δ (labeled blood transit time).