

Please note that this is a work in progress and send corrections and additions (including abstract) as BibTeX files to: David Busch, drbusch@sdf.org.

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- Children’s Hospital of Philadelphia <http://www.chop.edu/doctors/licht-daniel-j#.VsSpC3UrKkA>
- Daegu Gyeongbuk Institute
- ICFO- The Institute of Photonic Sciences https://www.icfo.eu/research/group_details.php?id=29
- Martinos Center, Center for Biomedical Imaging, MGH <https://www.nmr.mgh.harvard.edu/lab/optics>
- New York Medical College <http://fisherworks.net/>
- University of Kentucky <http://bioptics.engineering.uky.edu/>
- University of Geneva <https://www.unige.ch/medecine/radio/en/groupes-de-recherche/234binzoni/>
- University of Konstanz
- University of Modena <http://www.dii.unimore.it/optolab/index.php>
- University of Pennsylvania <http://www.physics.upenn.edu/yodhlab/>
- University of Picardie Jules Verne <https://www.u-picardie.fr/labo/GRAMFC/index.php?lang=en>
- University of Rochester <https://www.urmc.rochester.edu/labs/Choe-Lab/>
- University of Texas Arlington <https://mentis.uta.edu/explore/profile/fenghua-tian> <https://mentis.uta.edu/explore/profile/hanli-liu>
- University of Texas Southwestern <https://www.utswanesthesia.org/david-r-busch/>
- Western University <http://www.lawsonimaging.ca/imaging/node/1644/full>
- Wright State University <http://www.optical-bioimaging.org/contact.html>
- Meiji University

- Commercialization

- Hemophotonics hemophotonics.com/
- ISS iss.com/biomedical/instruments/metaox.html
- RMD rmdinc.com/blood-flow-and-oxygenation/

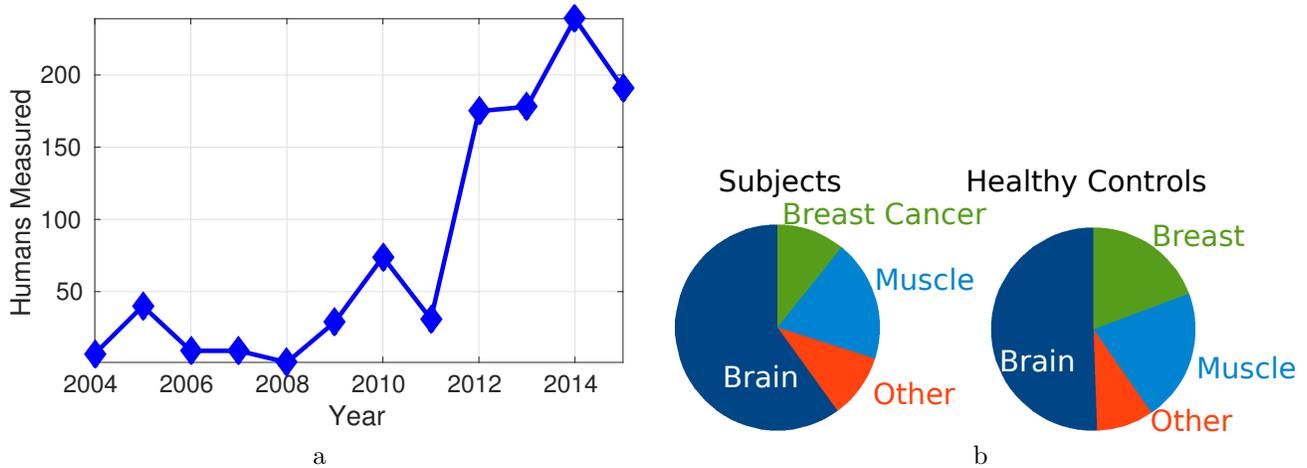


Figure 1: Summary of human subjects measured with DCS, 2004-2014 (a) by year and (b) by organ.

Citations to sort []

References

- [1] T. Durduran, R. Choe, W. B. Baker, and A. G. Yodh. Diffuse optics for tissue monitoring and tomography. *Reports on Progress in Physics*, 73(7):076701, June 2010.
- ANNOTATION: review
ABSTRACT: This review describes the diffusion model for light transport in tissues and the medical applications of diffuse light. Diffuse optics is particularly useful for measurement of tissue hemodynamics, wherein quantitative assessment of oxy- and deoxy-hemoglobin concentrations and blood flow are desired. The theoretical basis for near-infrared or diffuse optical spectroscopy is developed, and the basic elements of diffuse optical tomography are outlined. We also discuss diffuse correlation spectroscopy, a technique whereby temporal correlation functions of diffusing light are transported through tissue and are used to measure blood flow. Essential instrumentation is described, and representative brain and breast functional imaging and monitoring results illustrate the workings of these new tissue diagnostics.
- [2] R. Choe and T. Durduran. Diffuse optical monitoring of the neoadjuvant breast cancer therapy. *IEEE J. Sel. Topics in Quantum Electron.*, 18(99):1367–1386, 2012.
- ANNOTATION: review
ABSTRACT: Recent advances in the use of diffuse optical techniques for monitoring the hemodynamic, metabolic and physiological signatures of the neoadjuvant breast cancer therapy effectiveness is critically reviewed. An extensive discussion of the state-of-the-art diffuse optical mammography is presented alongside a discussion of the current approaches to breast cancer therapies. Overall, the diffuse optics field is growing rapidly with a great deal of promise to fill an important niche in the current approaches to monitor, predict and personalize neoadjuvant breast cancer therapies
- [3] G. Yu. Diffuse correlation spectroscopy (dcs): A diagnostic tool for assessing tissue blood flow in vascular-related diseases and therapies. *Current Medical Imaging Reviews*, 8(3):194–210, 2012.
- ANNOTATION: review
ABSTRACT: The development and clinical application of a novel near-infrared diffuse correlation spectroscopy (DCS) have been reviewed in this paper. DCS measures speckle fluctuations of near-infrared diffuse light in tissue, which are sensitive to the motions of red blood cells. DCS offers several new features which make it appealing for blood flow measurement such as noninvasiveness, high temporal resolution (up to 100 Hz), portability, and relatively large penetration depth (up to 1.5 centimeters). DCS technology can be utilized for bedside monitoring of tissue blood flow as exemplified by applications involving tumors, brains, and skeletal muscles. In these investigations, DCS measurements show promise for quantification of tissue hemodynamic status, for diagnosis of vascular-related diseases (e.g., cancers, stroke, peripheral arterial disease), and for continuous monitoring and evaluation of therapeutic effects (e.g., chemotherapy, radiation therapy, photodynamic therapy, arterial revascularization).
- [4] G. Yu. Near-infrared diffuse correlation spectroscopy in cancer diagnosis and therapy monitoring. *Journal of biomedical optics*, 17(1):0109011–19, 2012.
- ANNOTATION: review
ABSTRACT: A novel near-infrared (NIR) diffuse correlation spectroscopy (DCS) for tumor blood flow measurement is introduced in this review paper. DCS measures speckle fluctuations of NIR diffuse light in tissue, which are sensitive to the motions of red blood cells. DCS offers several attractive new features for tumor blood flow measurement such as noninvasiveness, portability, high temporal resolution, and relatively large penetration depth. DCS technology has been utilized for continuous measurement of tumor blood flow before, during, and after cancer therapies. In those pilot investigations, DCS hemodynamic measurements add important new variables into the mix for differentiation of benign from malignant tumors and for prediction of treatment outcomes. It is envisaged that with more clinical applications in large patient populations, DCS might emerge as an important method of choice for bedside management of cancer therapy, and it will certainly provide important new information about cancer physiology that may be of use in diagnosis.
- [5] D. R. Busch, R. Choe, T. Durduran, and A. G. Yodh. Towards non-invasive characterization of breast cancer and cancer metabolism with diffuse optics. *PET Clinics*, 8(3):345–365, 2013.
- ANNOTATION: DCS, review
ABSTRACT: Diffuse optical spectroscopies provide noninvasive, nonionizing, serial measurements of tissue blood flow, oxygenation, and concentration. These physiologic parameters provide a window into tissue metabolism without necessitating the use of ionizing radiation or transport to imaging suites. Current clinical investigations of diffuse optical mammography include applications of diffuse optical tomography and monitoring to neoadjuvant chemotherapy, contrast agent discovery, computer-aided detection, and measurement of breast oxygen metabolism. Diffuse optical measurements hold significant promise for commercialization and clinical integration.
- [6] Turgut Durduran and Arjun G Yodh. Diffuse correlation spectroscopy for non-invasive, micro-vascular cerebral blood flow measurement. *NeuroImage*, 85:51–63, 2014.
- ANNOTATION: review
ABSTRACT: Diffuse correlation spectroscopy (DCS) uses the temporal fluctuations of near-infrared (NIR) light to measure cerebral blood flow (CBF) non-invasively. Here, we provide a brief history of DCS applications in the brain with an emphasis on the underlying physical ideas, common instrumentation and validation. Then we

describe recent clinical research that employs DCS-measured CBF as a biomarker of patient well-being, and as an indicator of hemodynamic and metabolic responses to functional stimuli.

- [7] Erin M Buckley, Ashwin B Parthasarathy, P Ellen Grant, Arjun G Yodh, and Maria Angela Franceschini. Diffuse correlation spectroscopy for measurement of cerebral blood flow: future prospects. *Neurophotomics*, 1(1):011009, July 2014.

ANNOTATION: review

ABSTRACT: Diffuse correlation spectroscopy (DCS) is an emerging optical modality used to measure cortical cerebral blood flow. This outlook presents a brief overview of the technology, summarizing the advantages and limitations of the method, and describing its recent applications to animal, adult, and infant cohorts. At last, the paper highlights future applications where DCS may play a pivotal role individualizing patient management and enhancing our understanding of neurovascular coupling, activation, and brain development.

- [8] Flora Wong. Cerebral blood flow measurements in the neonatal brain. *Prenatal and Postnatal Determinants of Development*, pages 69–87, 2016.

ANNOTATION: review

ABSTRACT: Cerebrovascular lesions and hypoxic-ischaemic brain injury are important causes of acquired neonatal brain injury in term and preterm newborn infants, which lead to significant morbidity and long-term mortality. Improved understanding of the cerebral hemodynamics and metabolism in the immature brain, and blood flow responses to physiological and external stimuli would aid understanding of the pathogenesis of neonatal brain injury. There has been increasing research interest and clinical demand to study the neonatal brain, with the exploration of the bedside and real-time measurement of cerebral hemodynamics in guiding therapy and predicting outcome. The major techniques which allow the assessment of cerebral blood flow (CBF) with relative ease at the bedside in the neonatal intensive care unit include near-infrared spectroscopy (NIRS), and transcranial Doppler ultrasonography. Diffuse optical correlation spectroscopy (DCS) is a new technique for which portable devices are currently being developed to continuously monitor relative changes in microvascular CBF at the bedside. DCS can potentially be combined with NIRS to provide continuous simultaneous measurement of changes in CBF and oxygenation, and enables the quantification of cerebral metabolic rate of oxygen. Functional studies have also been utilized with NIRS and magnetic resonance imaging to elucidate the connections between localized cortical activity and cerebral hemodynamic responses during early human development. To utilize and translate cerebral hemodynamic measurements in clinical management, future research should aim to establish clinically relevant parameters and references range for cerebral perfusion and oxygenation for the neonatal population.

- [9] Sergio Fantini, Angelo Sassaroli, Kristen T. Tgavalekos, and Joshua Kornbluth. Cerebral blood flow and autoregulation: current measurement techniques and prospects for noninvasive optical methods. *Neurophotomics*, 3(3):031411, 2016.

ANNOTATION: dcs, review

ABSTRACT: Abstract. Cerebral blood flow (CBF) and cerebral autoregulation (CA) are critically important to maintain proper brain perfusion and supply the brain with the necessary oxygen and energy substrates. Adequate brain perfusion is required to support normal brain function, to achieve successful aging, and to navigate acute and chronic medical conditions. We review the general principles of CBF measurements and the current techniques to measure CBF based on direct intravascular measurements, nuclear medicine, X-ray imaging, magnetic resonance imaging, ultrasound techniques, thermal diffusion, and optical methods. We also review techniques for arterial blood pressure measurements as well as theoretical and experimental methods for the assessment of CA, including recent approaches based on optical techniques. The assessment of cerebral perfusion in the clinical practice is also presented. The comprehensive description of principles, methods, and clinical requirements of CBF and CA measurements highlights the potentially important role that noninvasive optical methods can play in the assessment of neurovascular health. In fact, optical techniques have the ability to provide a noninvasive, quantitative, and continuous monitor of CBF and autoregulation.

- [10] Erin M Buckley, Dalton Hance, Thomas Pawlowski, Jennifer Lynch, Felice B Wilson, Rickson C Mesquita, Turgut Durduran, Laura K Diaz, Mary E Putt, Daniel J Licht, Mark A Fogel, and Arjun G Yodh. Validation of diffuse correlation spectroscopic measurement of cerebral blood flow using phase-encoded velocity mapping magnetic resonance imaging. *J. Biomed. Opt.*, 17(3):037007, Mar 2012.

ANNOTATION: hypercapnia

ABSTRACT: Diffuse correlation spectroscopy (DCS) is a novel optical technique that appears to be an excellent tool for assessing cerebral blood flow in a continuous and non-invasive manner at the bedside. We present new clinical validation of the DCS methodology by demonstrating strong agreement between DCS indices of relative cerebral blood flow and indices based on phase-encoded velocity mapping magnetic resonance imaging (VENC MRI) of relative blood flow in the jugular veins and superior vena cava. Data were acquired from 46 children with single ventricle cardiac lesions during a hypercapnia intervention. Significant increases in cerebral blood flow, measured both by DCS and by VENC MRI, as well as significant increases in oxyhemoglobin concentration, and total hemoglobin concentration, were observed during hypercapnia. Comparison of blood flow changes measured by VENC MRI in the jugular veins and by DCS revealed a strong linear relationship, $R=0.88$, $p<0.001$, slope=0.910.07. Similar correlations were observed between DCS and VENC MRI in the superior vena cava, $R=0.77$, slope=0.990.12, $p<0.001$. The relationship between VENC MRI in the aorta and DCS, a negative control, was weakly correlated, $R=0.46$, slope=1.770.45, $p<0.001$.

- [11] Varsha Jain, Erin M Buckley, Daniel J Licht, Jennifer M Lynch, Peter J Schwab, Maryam Y Naim, Natasha A Lavin, Susan C Nicolson, Lisa M Montenegro, Arjun G Yodh, et al. Cerebral oxygen metabolism in neonates with congenital heart disease quantified by mri and optics. *Journal of Cerebral Blood Flow & Metabolism*, 34(3):380–388, 2014.

ANNOTATION: Validation of absolute CBF, N=32 CHD neonates, also assessment of baseline parameters and response to hypercapnia

ABSTRACT: Neonatal congenital heart disease (CHD) is associated with altered cerebral hemodynamics and increased risk of brain injury. Two novel noninvasive techniques, magnetic resonance imaging (MRI) and diffuse optical and correlation spectroscopies (diffuse optical spectroscopy (DOS), diffuse correlation spectroscopy (DCS)), were employed to quantify cerebral blood flow (CBF) and oxygen metabolism (CMRO2) of 32 anesthetized CHD neonates at rest and during hypercapnia. Cerebral venous oxygen saturation (SvO2) and CBF were measured simultaneously with MRI in the superior sagittal sinus, yielding global oxygen extraction fraction (OEF) and global CMRO2 in physiologic units. In addition, microvascular tissue oxygenation (StO2) and indices of microvascular CBF (BFI) and CMRO2 (CMRO2i) in the frontal cortex were determined by DOS/DCS. Median resting-state MRI-measured OEF, CBF, and CMRO2 were 0.38, 9.7 mL/minute per 100 g and 0.52 mL O2/minute per 100 g, respectively. These CBF and CMRO2 values are lower than literature reports for healthy term neonates (which are sparse and quantified using different methods) and resemble values reported for premature infants. Comparison of MRI measurements of global SvO2, CBF, and CMRO2 with corresponding local DOS/DCS measurements demonstrated strong linear correlations (R^2 0.69, 0.67, 0.67; $P < 0.001$), permitting calibration of DOS/DCS indices. The results suggest that MRI and optics offer new tools to evaluate cerebral hemodynamics and metabolism in CHD neonates.

- [12] S. A. Carp, G. P. Dai, D. A. Boas, M. A. Franceschini, and Y. R. Kim. Validation of diffuse correlation spectroscopy measurements of rodent cerebral blood flow with simultaneous arterial spin labeling MRI; towards MRI-optical continuous cerebral metabolic monitoring. *Biomedical Optics Express*, 1(2):553–565, Sep 2010.

ANNOTATION: hypercapnia

ABSTRACT: Cerebral blood flow (CBF) during stepped hypercapnia was measured simultaneously in the rat brain using near-infrared diffuse correlation spectroscopy (DCS) and arterial spin labeling MRI (ASL). DCS and ASL CBF values agree very well, with high correlation ($R=0.86$, $p < 10^{-9}$), even when physiological instability perturbed the vascular response. A partial volume effect was evident in the smaller magnitude of the optical CBF response compared to the MRI values (averaged over the cortical area), primarily due to the inclusion of white matter in the optically sampled volume. The 8.2 and 11.7 mm mid-separation channels of the multi-distance optical probe had the lowest partial volume impact, reflecting 75 % of the MR signal change. Using a multiplicative correction factor, the ASL CBF could be predicted with no more than 10% relative error, affording an opportunity for real-time relative cerebral metabolism monitoring in conjunction with MR measurement of cerebral blood volume using super paramagnetic contrast agents.

- [13] G. Yu, T. F. Floyd, T. Durduran, C. Zhou, J. Wang, J. A. Detre, and A. G. Yodh. Validation of diffuse correlation spectroscopy for muscle blood flow with concurrent arterial spin labeled perfusion MRI. *Opt. Exp.*, 15:1064–1075, 2007.

ANNOTATION: N=7

ABSTRACT: Calf blood flow was measured simultaneously in healthy human subjects ($n = 7$) during cuff inflation and deflation using near-infrared diffuse correlation spectroscopy (DCS) and arterial spin labeled perfusion MRI (ASL-MRI). The DCS and ASL-MRI data exhibited highly correlated absolute and relative dynamic flow responses in each individual ($p < 0.001$). Peak flow variations during hyperemia were also significantly correlated, though more for relative ($p = 0.003$) than absolute ($p = 0.016$) flow. Repeated measurement variation was less than 8% for both modalities. The results provide much needed quantitative blood flow validation of the diffuse optical correlation method in humans.

- [14] Ryan Rosenberry, Chandan Ganesh, Fenghua Tian, and Michael D. Nelson. Measurement of skeletal muscle blood flow with near-infrared diffuse correlation spectroscopy. *The FASEB Journal*, 31(1 Supplement):840.17, 2017.

ANNOTATION: N=10, healthy adult, muscle

ABSTRACT: Direct continuous noninvasive measurement of local muscle blood flow in humans remains limited. Conventional measurements of limb blood flow, such as Doppler ultrasound or venous occlusion plethysmography, measure changes in bulk conduit flow and do not provide regional information. Near-infrared diffuse correlation spectroscopy (DCS) is an emerging technique for non-invasive measurement of local muscle blood flow at the microvascular level. In order to better understand the strengths and limitations of this novel approach, we performed a validation study by comparing muscle blood flow changes measured by DCS and Doppler ultrasound during exercise. Ten subjects were recruited for this study (age: 27.3 yrs; female/male: 1/9; BMI: 27.03.6 kg/m²). The DCS probe was affixed to the forearm over the belly of the flexor digitorum profundus. Brachial artery blood velocity and diameter were measured with Doppler ultrasound, integrated, and reported as brachial artery blood flow. After a brief period of rest, each participant performed rhythmic handgrip exercise at 20% and 50% of their maximum voluntary contraction (MVC). As expected, brachial artery blood flow increased significantly from baseline by 312±56% at 20% MVC, and 613±90% at 50% MVC. Blood flow index (BFI), the primary output from DCS, shared a similar change from baseline, increasing 112±18% and 262±35%, respectively. To more appropriately compare these two approaches, the data were normalized to each persons individual maximum for each respective technique. Remarkably, the increase in skeletal muscle blood flow was strikingly similar between the two techniques, when reported in normalized units (20%: 0.42±0.03 vs. 0.45±0.03; 50%: 0.69±0.04 vs. 0.79±0.02, DCS vs. BA flow, respectively). The change in skeletal muscle blood flow by DCS and Doppler ultrasound were also strongly correlated ($r^2=0.77$,

$p < 0.001$). Taken together, these data show that DCS and Doppler ultrasound quantify the same temporal dynamics of skeletal muscle blood flow during exercise. While these results are indeed encouraging, more work is needed to fully validate this approach for measuring local microvascular blood flow in humans. Support or Funding Information This work was supported by an Interdisciplinary Research Program grant from the University of Texas at Arlington.

- [15] Mikie Nakabayashi and Yumie Ono. Detection of blood flow speed in shallow and deep tissues using diffuse correlation spectroscopy. *Advanced Biomedical Engineering*, 6:53–58, 2017.

ANNOTATION: N=14, adult muscle, cuff ischemia and skin temperature change.

ABSTRACT: Diffuse correlation spectroscopy (DCS) is an emerging optical technique for noninvasive measurement of hemodynamics of living tissues. Using emitter and detector optical probes attached to the body surface, DCS estimates the mean speed of blood flow in the tissue, through which the emitted near-infrared light propagates (blood flow index: BFI). The advantage of DCS is that the mean blood flow in deeper tissues such as muscle layers can be measured noninvasively. To investigate the sensitivity of DCS in detecting the physiological changes of blood flow in deep and shallow tissues, we measured the blood flow speed in 14 healthy participants during a reactive hyperemia test and skin temperature changes. In the reactive hyperemia test, blood flow returned to the steady state faster in deep tissues than in shallow tissues, and temperature-dependent reallocation of local blood flow in shallow and deep tissues was clearly observed. These results demonstrate that DCS can measure the differences in physiological blood flow dynamics in deep and shallow tissues, suggesting the potential use of DCS to noninvasively quantify changes at microcirculation level in both shallow and deep tissue layers.

- [16] Yuya Murakami, Yumie Ono, and Masashi Ichinose. Blood flow measurement of human skeletal muscle during various exercise intensities using diffuse correlation spectroscopy (dcs). In *Proc. of SPIE Vol.*, volume 10059, pages 100591Z–1, 2017.

ANNOTATION: N=7, adult, muscle, exercise intensity

ABSTRACT: We studied blood flow dynamics of active skeletal muscle using diffuse correlation spectroscopy (DCS), an emerging optical modality that is suitable for noninvasive quantification of microcirculation level in deep tissue. Seven healthy subjects conducted 0.5 Hz dynamic handgrip exercise for 3 minutes at intensities of 10, 20, 30, and 50 maximal voluntary contraction (MVC). DCS could detect the time-dependent increase of the blood flow response of the forearm muscle for continuous exercises, and the increase ratios of the mean blood flow through the exercise periods showed good correlation with the exercise intensities. We also compared blood flow responses detected from DCS with two different photon sampling rates and found that an appropriate photon sampling rates should be selected to follow the wide-ranged increase in the muscle blood flow with dynamic exercise. Our results demonstrate the possibility for utilizing DCS in a field of sports medicine to noninvasively evaluate the dynamics of blood flow in the active muscles.

- [17] Chandan-Ganesh Bangalore-Yogananda, Ryan Rosenberry, Sagar Soni, Hanli Liu, Michael D. Nelson, and Fenghua Tian. Concurrent measurement of skeletal muscle blood flow during exercise with diffuse correlation spectroscopy and doppler ultrasound. *Biomed. Opt. Express*, 9(1):131–141, Jan 2018.

ANNOTATION: DCS, muscle, N=9

ABSTRACT: Noninvasive, direct measurement of local muscle blood flow in humans remains limited. Diffuse correlation spectroscopy (DCS) is an emerging technique to measure regional blood flow at the microvascular level. In order to better understand the strengths and limitations of this novel technique, we performed a validation study by comparing muscle blood flow changes measured with DCS and Doppler ultrasound during exercise. Nine subjects were measured (all males, 27.4 ± 2.9 years of age) for a rhythmic handgrip exercise at 20% and 50% of individual maximum voluntary contraction (MVC), followed by a post-exercise recovery. The results from DCS and Doppler ultrasound were highly correlated ($R = 0.99 \pm 0.02$). DCS was more reliable and less susceptible to motion artifact.

- [18] Turgut Durduran, Chao Zhou, Erin M Buckley, Meeri N Kim, Guoqiang Yu, Regine Choe, J. William Gaynor, Thomas L Spray, Suzanne M Durning, Stefanie E Mason, Lisa M Montenegro, Susan C Nicolson, Robert A Zimmerman, Mary E Putt, Jiongjiang Wang, Joel H Greenberg, John A Detre, Arjun G Yodh, and Daniel J Licht. Optical measurement of cerebral hemodynamics and oxygen metabolism in neonates with congenital heart defects. *J. Biomed. Opt.*, 15(3):037004, 2010.

ANNOTATION: N=12, neonate, ASL validation

ABSTRACT: We employ a hybrid diffuse correlation spectroscopy (DCS) and near-infrared spectroscopy (NIRS) monitor for neonates with congenital heart disease ($n=33$). The NIRS-DCS device measured changes during hypercapnia of oxyhemoglobin, deoxyhemoglobin, and total hemoglobin concentrations; cerebral blood flow ($rCBF(DCS)$); and oxygen metabolism ($rCMRO(2)$). Concurrent measurements with arterial spin-labeled magnetic resonance imaging ($rCBF(ASL-MRI)$, $n=12$) cross-validate $rCBF(DCS)$ against $rCBF(ASL-MRI)$, showing good agreement ($R=0.7$, $p=0.01$). The study demonstrates use of NIRS-DCS on a critically ill neonatal population, and the results indicate that the optical technology is a promising clinical method for monitoring this population.

- [19] Chao Zhou, Stephanie A. Eucker, Turgut Durduran, Guoqiang Yu, Jill Ralston, Stuart H. Friess, Rebecca N. Ichord, Susan S. Margulies, and Arjun G. Yodh. Diffuse optical monitoring of hemodynamic changes in piglet brain with closed head injury. *J. Biomed. Opt.*, 14(3):034015, 2009.

ANNOTATION: 18 piglets, fluorescent microsphere validation

ABSTRACT: We used a nonimpact inertial rotational model of a closed head injury in neonatal piglets to simulate the conditions following traumatic brain injury in infants. Diffuse optical techniques, including diffuse reflectance spectroscopy and diffuse correlation spectroscopy DCS, were used to measure cerebral blood oxygenation and

blood flow continuously and noninvasively before injury and up to 6 h after the injury. The DCS measurements of relative cerebral blood flow were validated against the fluorescent microsphere method. A strong linear correlation was observed between the two techniques $R=0.89$, $p<0.00001$. Injury-induced cerebral hemodynamic changes were quantified, and significant changes were found in oxy- and deoxy-hemoglobin concentrations, total hemoglobin concentration, blood oxygen saturation, and cerebral blood flow after the injury. The diffuse optical measurements were robust and also correlated well with recordings of vital physiological parameters over the 6-h monitoring period, such as mean arterial blood pressure, arterial oxygen saturation, and heart rate. Finally, the diffuse optical techniques demonstrated sensitivity to dynamic physiological events, such as apnea, cardiac arrest, and hypertonic saline infusion. In total, the investigation corroborates potential of the optical methods for bedside monitoring of pediatric and adult human patients in the neurointensive care unit.

- [20] Meeri Kim, Turgut Durduran, Suzanne Frangos, Brian Edlow, Erin Buckley, Heather Moss, Chao Zhou, Guoqiang Yu, Regine Choe, Eileen Maloney-Wilensky, Ronald Wolf, M. Grady, Joel Greenberg, Joshua Levine, Arjun Yodh, John Detre, and W. Kofke. Noninvasive measurement of cerebral blood flow and blood oxygenation using near-infrared and diffuse correlation spectroscopies in critically brain-injured adults. *Neurocrit Care*, 12(2):173–180, April 2010.

ANNOTATION: N=7

ABSTRACT: Abstract Background This study assesses the utility of a hybrid optical instrument for noninvasive transcranial monitoring in the neurointensive care unit. The instrument is based on diffuse correlation spectroscopy (DCS) for measurement of cerebral blood flow (CBF), and near-infrared spectroscopy (NIRS) for measurement of oxy- and deoxy-hemoglobin concentration. DCS/NIRS measurements of CBF and oxygenation from frontal lobes are compared with concurrent xenon-enhanced computed tomography (XeCT) in patients during induced blood pressure changes and carbon dioxide arterial partial pressure variation. Methods Seven neurocritical care patients were included in the study. Relative CBF measured by DCS (rCBFDCS), and changes in oxy-hemoglobin (?HbO₂), deoxy-hemoglobin (?Hb), and total hemoglobin concentration (?THC), measured by NIRS, were continuously monitored throughout XeCT during a baseline scan and a scan after intervention. CBF from XeCT regions-of-interest (ROIs) under the optical probes were used to calculate relative XeCT CBF (rCBFXeCT) and were then compared to rCBFDCS. Spearman's rank coefficients were employed to test for associations between rCBFDCS and rCBFXeCT, as well as between rCBF from both modalities and NIRS parameters. Results rCBFDCS and rCBFXeCT showed good correlation ($r_s = 0.73$, $P = 0.010$) across the patient cohort. Moderate correlations between rCBFDCS and ?HbO₂?/THC were also observed. Both NIRS and DCS distinguished the effects of xenon inhalation on CBF, which varied among the patients. Conclusions DCS measurements of CBF and NIRS measurements of tissue blood oxygenation were successfully obtained in neurocritical care patients. The potential for DCS to provide continuous, noninvasive bedside monitoring for the purpose of CBF management and individualized care is demonstrated.

- [21] Zhe Li, Wesley B. Baker, Ashwin B. Parthasarathy, Tiffany S. Ko, Detian Wang, Steven Schenkel, Turgut Durduran, Gang Li, and Arjun G. Yodh. Calibration of diffuse correlation spectroscopy blood flow index with venous-occlusion diffuse optical spectroscopy in skeletal muscle. *Journal of Biomedical Optics*, 20(12):125005, 2015.

ANNOTATION: human, adult, N=10

ABSTRACT: We investigate and assess the utility of a simple scheme for continuous absolute blood flow monitoring based on diffuse correlation spectroscopy (DCS). The scheme calibrates DCS using venous-occlusion diffuse optical spectroscopy (VO-DOS) measurements of arm muscle tissue at a single time-point. A calibration coefficient (γ) for the arm is determined, permitting conversion of DCS blood flow indices to absolute blood flow units, and a study of healthy adults (N=10) is carried out to ascertain the variability of γ . The average DCS calibration coefficient for the right (i.e., dominant) arm was $\gamma=(1.24\pm 15)\times 10^8 \text{ mL } 100\text{mL}^{-1}\text{min}^{-1}/(\text{cm}^2/\text{s})$. However, variability can be significant and is apparent in our site-to-site and day-to-day repeated measurements. The peak hyperemic blood flow overshoot relative to baseline resting flow was also studied following arm-cuff ischemia; excellent agreement between VO-DOS and DCS was found ($R^2=0.95$, slope= 0.94 ± 0.07 , mean difference= -0.10 ± 0.45). Finally, we show that incorporation of subject-specific absolute optical properties significantly improves blood flow calibration accuracy.

- [22] Erin M. Buckley, Noah M Cook, Turgut Durduran, Meeri N Kim, Chao Zhou, Regine Choe, Guoqiang Yu, Susan Schultz, Chandra M Sehgal, Daniel J Licht, Peter H Arger, Mary E Putt, Hallam H Hurt, and Arjun G Yodh. Cerebral hemodynamics in preterm infants during positional intervention measured with diffuse correlation spectroscopy and transcranial doppler ultrasound. *Opt. Exp.*, 17(15):12571–12581, Jul 2009.

ANNOTATION: N=4, low birth weight premature infants, TCD validation

ABSTRACT: Four very low birth weight, very premature infants were monitored during a 12 degrees postural elevation using diffuse correlation spectroscopy (DCS) to measure microvascular cerebral blood flow (CBF) and transcranial Doppler ultrasound (TCD) to measure macrovascular blood flow velocity in the middle cerebral artery. DCS data correlated significantly with peak systolic, end diastolic, and mean velocities measured by TCD ($p(A) = 0.036, 0.036, 0.047$). Moreover, population averaged TCD and DCS data yielded no significant hemodynamic response to this postural change ($p<0.05$). We thus demonstrate feasibility of DCS in this population, we show correlation between absolute measures of blood flow from DCS and blood flow velocity from TCD, and we do not detect significant changes in CBF associated with a small postural change (12 degrees) in these patients.

- [23] Mina Nourhashemi, Mahdi Mahmoudzadeh, and Fabrice Wallois. Thermal impact of near-infrared laser in advanced noninvasive optical brain imaging. *Neurophotonics*, 3(1):015001, 2016.

ANNOTATION: computational

ABSTRACT: The propagation of laser light in human tissues is an important issue in functional optical imaging. We

modeled the thermal effect of different laser powers with various spot sizes and different head tissue characteristics on neonatal and adult quasirealistic head models. The photothermal effect of near-infrared laser (800nm) was investigated by numerical simulation using finite-element analysis. Our results demonstrate that the maximum temperature increase on the brain for laser irradiance between 0.127 (1mW) and 12.73W/cm² (100mW) at a 1mm spot size, ranged from 0.0025C to 0.26C and from 0.03C to 2.85C at depths of 15.9 and 4.9mm in the adult and neonatal brain, respectively. Due to the shorter distance of the head layers from the neonatal head surface, the maximum temperature increase was higher in the neonatal brain than in the adult brain. Our results also show that, at constant power, spot size changes had a lesser heating effect on deeper tissues. While the constraints for safe laser irradiation to the brain are dictated by skin safety, these results can be useful to optimize laser parameters for a variety of laser applications in the brain. Moreover, combining simulation and adequate in vitro experiments could help to develop more effective optical imaging to avoid possible tissue damage.

- [24] M. Diop, K. Verdecchia, T. Y. Lee, and K. St Lawrence. Calibration of diffuse correlation spectroscopy with a time-resolved near-infrared technique to yield absolute cerebral blood flow measurements. *Biomedical optics express*, 2(7):2068–2081, 2011.

ANNOTATION: piglet validation

ABSTRACT: A primary focus of neurointensive care is the prevention of secondary brain injury, mainly caused by ischemia. A noninvasive bedside technique for continuous monitoring of cerebral blood flow (CBF) could improve patient management by detecting ischemia before brain injury occurs. A promising technique for this purpose is diffuse correlation spectroscopy (DCS) since it can continuously monitor relative perfusion changes in deep tissue. In this study, DCS was combined with a time-resolved near-infrared technique (TR-NIR) that can directly measure CBF using indocyanine green as a flow tracer. With this combination, the TR-NIR technique can be used to convert DCS data into absolute CBF measurements. The agreement between the two techniques was assessed by concurrent measurements of CBF changes in piglets. A strong correlation between CBF changes measured by TR-NIR and changes in the scaled diffusion coefficient measured by DCS was observed ($R^2 = 0.93$) with a slope of 1.05 ± 0.06 and an intercept of 6.4 ± 4.3% (mean ± standard error).

- [25] Katelyn Gurley, Yu Shang, and Guoqiang Yu. Noninvasive optical quantification of absolute blood flow, blood oxygenation, and oxygen consumption rate in exercising skeletal muscle. *Journal of Biomedical Optics*, 17(7):0750101, July 2012.

ANNOTATION: N=9, healthy adults

ABSTRACT: This study investigates a method using novel hybrid diffuse optical spectroscopies [near-infrared spectroscopy (NIRS) and diffuse correlation spectroscopy (DCS)] to obtain continuous, noninvasive measurement of absolute blood flow (BF), blood oxygenation, and oxygen consumption rate (VO₂/VO₂) in exercising skeletal muscle. Healthy subjects (n=9) performed a handgrip exercise to increase BF and VO₂/VO₂ in forearm flexor muscles, while a hybrid optical probe on the skin surface directly monitored oxy-, deoxy-, and total hemoglobin concentrations ([HbO₂/HbO₂], [Hb], and THC), tissue oxygen saturation (StO₂/StO₂), relative BF (rBF/rBF), and relative oxygen consumption rate (rVO₂/rVO₂). The rBF/rBF and rVO₂/rVO₂ signals were calibrated with absolute baseline BF and VO₂/VO₂ obtained through venous and arterial occlusions, respectively. Known problems with muscle-fiber motion artifacts in optical measurements during exercise were mitigated using a novel gating algorithm that determined muscle contraction status based on control signals from a dynamometer. Results were consistent with previous findings in the literature. This study supports the application of NIRS/DCS technology to quantitatively evaluate hemodynamic and metabolic parameters in exercising skeletal muscle and holds promise for improving diagnosis and treatment evaluation for patients suffering from diseases affecting skeletal muscle and advancing fundamental understanding of muscle and exercise physiology.

- [26] Gregor Dietsche, Markus Ninck, Christian Ortoft, Jun Li, Franck Jaillon, and Thomas Gisler. Fiber-based multispeckle detection for time-resolved diffusing-wave spectroscopy: characterization and application to blood flow detection in deep tissue. *Applied optics*, 46(35):8506–8514, 2007.

ANNOTATION: healthy, wrist

ABSTRACT: We present a technique for the measurement of temporal field autocorrelation functions of multiply scattered light with subsecond acquisition time. The setup is based on the parallel detection and autocorrelation of intensity fluctuations from statistically equivalent but independent speckles using a fiber bundle, an array of avalanche photodiodes, and a multichannel autocorrelator with variable integration times between 6.5 and 104 ms. Averaging the autocorrelation functions from the different speckles reduces the integration time in diffusing-wave spectroscopy experiments drastically, thus allowing us to resolve nonstationary scatterer dynamics with single-trial measurements. We present applications of the technique to the measurement of arterial and venous blood flow in deep tissue. We find strong deviations both of the shape and characteristic decay time of autocorrelation functions recorded at different phases of the pulsation cycle from time-averaged autocorrelation functions.

- [27] Yu Shang, Youquan Zhao, Ran Cheng, Lixin Dong, Daniel Irwin, and Guoqiang Yu. Portable optical tissue flow oximeter based on diffuse correlation spectroscopy. *Opt. Lett.*, 34(22):3556–3558, Nov 2009.

ANNOTATION: N=2, Calf muscle

ABSTRACT: A portable diffuse correlation spectroscopy (DCS) flowmeter has been extended to measure both tissue blood flow and oxygenation (namely, DCS flow oximeter). For validation purposes, calf muscle blood oxygenation during cuff inflation and deflation was measured concurrently using the DCS flow oximeter and a commercial tissue oximeter. The oxygenation traces from the two measurements exhibited similar dynamic responses, and data were highly correlated ($r_{\text{mean}} > 0.9$, $p < 10^{-5}$, $n=10$). The portable, inexpensive, and easy-to-use DCS flow oximeter holds promise for bedside monitoring of tissue blood flow and oxygenation in clinics.

- [28] Yu Shang, TB Symons, Turgut Durduran, and Guoqiang Yodh, Arjun G and Yu. Effects of muscle fiber motion on diffuse correlation spectroscopy blood flow measurements during exercise. *Biomedical optics express*, 1(2):500–511, 2010.
- ANNOTATION: N=1, healthy adult muscle
 ABSTRACT: The influence of muscle fiber motion during exercise on diffuse correlation spectroscopy (DCS) measurements of skeletal muscle blood flow is explored. Isotonic (with muscle fiber motion) and isometric (without muscle fiber motion) plantar flexion exercises were performed at 30% of maximal force on a dynamometer, and muscle blood flow was continuously monitored on the medial gastrocnemius (calf) muscle of a healthy volunteer using DCS. During exercise, dynamometer recordings including footplate position, footplate angular velocity, and plantar flexion torque were obtained. Muscle fiber motions introduced artifacts into the DCS signals, causing an overestimation of blood flow changes. We show how proper co-registration of dynamometer recordings and DCS measurements enables separation of the true blood flow responses during exercise from those affected by the motion artifacts.
- [29] Markus Ninck, Markus Untenberger, and Thomas Gisler. Diffusing-wave spectroscopy with dynamic contrast variation: disentangling the effects of blood flow and extravascular tissue shearing on signals from deep tissue. *Biomedical optics express*, 1(5):1502–1513, 2010.
- ANNOTATION: ex vivo kidney
 ABSTRACT: We investigate the effects of blood flow and extravascular tissue shearing on diffusing-wave spectroscopy (DWS) signals from deep tissue, using an ex vivo porcine kidney model perfused artificially at controlled arterial pressure and flow. Temporal autocorrelation functions $g(1)(t)$ of the multiply scattered light field show a decay which is described by diffusion for constant flow, with a diffusion coefficient scaling linearly with volume flow rate. Replacing blood by a non-scattering fluid reveals a flow-independent background dynamics of the extravascular tissue. For a sinusoidally driven perfusion, field autocorrelation functions $g(1)(t)$ depend on the phase t within the pulsation cycle and are approximately described by diffusion. The effective diffusion coefficient $D_{\text{eff}}(t)$ is modulated at the driving frequency in the presence of blood, showing coupling with flow rate; in the absence of blood, $D_{\text{eff}}(t)$ is modulated at twice the driving frequency, indicating shearing of extravascular tissue as the origin of the DWS signal. For both constant and pulsatile flow the contribution of extravascular tissue shearing to the DWS signal is small.
- [30] Daniel Irwin, Lixin Dong, Yu Shang, Ran Cheng, Mahesh Kudrimoti, Scott D Stevens, and Guoqiang Yu. Influences of tissue absorption and scattering on diffuse correlation spectroscopy blood flow measurements. *Biomedical optics express*, 2(7):1969–1985, 2011.
- [31] Yu Lin, Lian He, Yu Shang, and Guoqiang Yu. Noncontact diffuse correlation spectroscopy for noninvasive deep tissue blood flow measurement. *Journal of Biomedical Optics*, 17(1):010502–1–010502–3, 2012.
- ANNOTATION: N=9, muscle
 ABSTRACT: Abstract. A noncontact diffuse correlation spectroscopy (DCS) probe has been developed using two separated optical paths for the source and detector. This unique design avoids the interference between the source and detector and allows large source-detector separations for deep tissue blood flow measurements. The noncontact probe has been calibrated against a contact probe in a tissue-like phantom solution and human muscle tissues; flow changes concurrently measured by the two probes are highly correlated in both phantom ($R^2=0.89$) and real-tissue ($R^2=0.77$, $n=9$) tests. The noncontact DCS holds promise for measuring blood flow in vulnerable (e.g., pressure ulcer) and soft (e.g., breast) tissues without distorting tissue hemodynamic properties.
- [32] Jing Dong, Renzhe Bi, Jun Hui Ho, Patricia S P Thong, Khee-Chee Soo, and Kijoon Lee. Diffuse correlation spectroscopy with a fast Fourier transform-based software autocorrelator. *Journal of Biomedical Optics*, 17(9):0970041, Sep 2012.
- [33] R. C. Mesquita, X. Lu, D. L. Minkoff, P. M. Vora, C. Favilla, M. Chandra, S. S. Schenkel, David R. Busch, J. H. Greenberg, J. A. Detre, and A. G. Yodh. Influence of probe pressure on the diffuse correlation spectroscopy blood flow signal: extra-cerebral contributions. *Biomedical Optics Express*, 4:978–994, 2013.
- ANNOTATION: N=8, healthy adults
 ABSTRACT: A pilot study explores relative contributions of extra-cerebral (scalp/skull) versus brain (cerebral) tissues to the blood flow index determined by diffuse correlation spectroscopy (DCS). Microvascular DCS flow measurements were made on the head during baseline and breathholding/hyperventilation tasks, both with and without pressure. Baseline (resting) data enabled estimation of extra-cerebral flow signals and their pressure dependencies. A simple two-component model was used to derive baseline and activated cerebral blood flow (CBF) signals, and the DCS flow indices were also cross-correlated with concurrent Transcranial Doppler Ultrasound (TCD) blood velocity measurements. The study suggests new pressure-dependent experimental paradigms for elucidation of blood flow contributions from extra-cerebral and cerebral tissues.
- [34] Ting Li, Yu Lin, Yu Shang, Lian He, Chong Huang, Margaret Szabunio, and Guoqiang Yu. Simultaneous measurement of deep tissue blood flow and oxygenation using noncontact diffuse correlation spectroscopy flow-oximeter. *Sci Rep*, 3:1358, 2013.
- ANNOTATION: N=10, forearm muscle
 ABSTRACT: We report a novel noncontact diffuse correlation spectroscopy flow-oximeter for simultaneous quantification of relative changes in tissue blood flow (rBF) and oxygenation ([oxygenation]). The noncontact probe was compared against a contact probe in tissue-like phantoms and forearm muscles ($n = 10$), and the dynamic trends in both rBF and [oxygenation] were found to be highly correlated. However, the magnitudes of [oxygenation]

measured by the two probes were significantly different. Monte Carlo simulations and phantom experiments revealed that the arm curvature resulted in a significant underestimation (-20%) for the noncontact measurements in ρ [oxygenation], but not in rBF. Other factors that may cause the residual discrepancies between the contact and noncontact measurements were discussed, and further comparisons with other established technologies are needed to identify/quantify these factors. Our research paves the way for noncontact and simultaneous monitoring of blood flow and oxygenation in soft and vulnerable tissues without distorting tissue hemodynamics.

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ANNOTATION: Theoretical development, validation in pig

ABSTRACT: We develop and validate a Modified Beer-Lambert law for blood flow based on diffuse correlation spectroscopy (DCS) measurements. The new formulation enables blood flow monitoring from temporal intensity autocorrelation function data taken at single or multiple delay-times. Consequentially, the speed of the optical blood flow measurement can be substantially increased. The scheme facilitates blood flow monitoring of highly scattering tissues in geometries wherein light propagation is diffusive or non-diffusive, and it is particularly well-suited for utilization with pressure measurement paradigms that employ differential flow signals to reduce contributions of superficial tissues.

- [36] Juliette Selb, David A. Boas, Suk-Tak Chan, Karleyton C. Evans, Erin M. Buckley, and Stefan A. Carp. Sensitivity of near-infrared spectroscopy and diffuse correlation spectroscopy to brain hemodynamics: simulations and experimental findings during hypercapnia. *Neurophotonics*, 1(1):015005, 2014.

ANNOTATION: hypercapnia

ABSTRACT: Abstract. Near-infrared spectroscopy (NIRS) and diffuse correlation spectroscopy (DCS) are two diffuse optical technologies for brain imaging that are sensitive to changes in hemoglobin concentrations and blood flow, respectively. Measurements for both modalities are acquired on the scalp, and therefore hemodynamic processes in the extracerebral vasculature confound the interpretation of cortical hemodynamic signals. The sensitivity of NIRS to the brain versus the extracerebral tissue and the contrast-to-noise ratio (CNR) of NIRS to cerebral hemodynamic responses have been well characterized, but the same has not been evaluated for DCS. This is important to assess in order to understand their relative capabilities in measuring cerebral physiological changes. We present Monte Carlo simulations on a head model that demonstrate that the relative brain-to-scalp sensitivity is about three times higher for DCS (0.3 at 3cm) than for NIRS (0.1 at 3cm). However, because DCS has higher levels of noise due to photon-counting detection, the CNR is similar for both modalities in response to a physiologically realistic simulation of brain activation. Even so, we also observed higher CNR of the hemodynamic response during graded hypercapnia in adult subjects with DCS than with NIRS.

- [37] Wesley B. Baker, Ashwin B. Parthasarathy, Tiffany Ko, David R. Busch, K. Abramson, Rickson C. Mesquita, T. Durduran, Joel H. Greenberg, D. Kung, and Arjun G. Yodh. Probe pressure modulation algorithm reduces extra-cerebral contamination in optical measurements of cerebral hemodynamics. *Neurophotonics*, 2(3):035004–035004, 2015.

ANNOTATION: Theoretical development, N=2 functional activation

ABSTRACT: We introduce and validate a pressure measurement paradigm that reduces extracerebral contamination from superficial tissues in optical monitoring of cerebral blood flow with diffuse correlation spectroscopy (DCS). The scheme determines subject-specific contributions of extracerebral and cerebral tissues to the DCS signal by utilizing probe pressure modulation to induce variations in extracerebral blood flow. For analysis, the head is modeled as a two-layer medium and is probed with long and short source-detector separations. Then a combination of pressure modulation and a modified Beer-Lambert law for flow enables experimenters to linearly relate differential DCS signals to cerebral and extracerebral blood flow variation without a priori anatomical information. We demonstrate the algorithm's ability to isolate cerebral blood flow during a finger-tapping task and during graded scalp ischemia in healthy adults. Finally, we adapt the pressure modulation algorithm to ameliorate extracerebral contamination in monitoring of cerebral blood oxygenation and blood volume by near-infrared spectroscopy.

- [38] Parisa Farzam and Turgut Durduran. Multidistance diffuse correlation spectroscopy for simultaneous estimation of blood flow index and optical properties. *Journal of biomedical optics*, 20(5):055001–055001, 2015.

ANNOTATION: phantom, mouse validation

ABSTRACT: Traditionally, diffuse correlation spectroscopy (DCS) measures microvascular blood flow by fitting a physical model to the measurement of the intensity autocorrelation function from a single source-detector pair. This analysis relies on the accurate knowledge of the optical properties, absorption, and reduced scattering coefficients of the medium. Therefore, DCS is often deployed together with diffuse optical spectroscopy. We present an algorithm that employs multidistance DCS (MD-DCS) for simultaneous measurement of blood flow index, as well as an estimate of the optical properties of the tissue. The algorithm has been validated through noise-free and noise-added simulated data and phantom measurements. A longitudinal in vivo measurement of a mouse tumor is also shown. MD-DCS is introduced as a stand-alone system for small source-detector separations (<2cm) for noninvasive measurement of microvascular blood flow.

- [39] Matthew Tivnan, Rajan Gurjar, David E Wolf, and Karthik Vishwanath. High frequency sampling of ttl pulses on a raspberry pi for diffuse correlation spectroscopy applications. *Sensors*, 15(8):19709–19722, 2015.

ANNOTATION: RMD,

ABSTRACT: Diffuse Correlation Spectroscopy (DCS) is a well-established optical technique that has been used

for non-invasive measurement of blood flow in tissues. Instrumentation for DCS includes a correlation device that computes the temporal intensity autocorrelation of a coherent laser source after it has undergone diffuse scattering through a turbid medium. Typically, the signal acquisition and its autocorrelation are performed by a correlation board. These boards have dedicated hardware to acquire and compute intensity autocorrelations of rapidly varying input signal and usually are quite expensive. Here we show that a Raspberry Pi minicomputer can acquire and store a rapidly varying time-signal with high fidelity. We show that this signal collected by a Raspberry Pi device can be processed numerically to yield intensity autocorrelations well suited for DCS applications. DCS measurements made using the Raspberry Pi device were compared to those acquired using a commercial hardware autocorrelation board to investigate the stability, performance, and accuracy of the data acquired in controlled experiments. This paper represents a first step toward lowering the instrumentation cost of a DCS system and may offer the potential to make DCS become more widely used in biomedical applications.

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- [45] Stefan A. Carp, Parisa Farzam, Norin Redes, Dennis M. Hueber, and Maria Angela Franceschini. Combined multi-distance frequency domain and diffuse correlation spectroscopy system with simultaneous data acquisition and real-time analysis. *Biomed. Opt. Express*, 8(9):3993–4006, Sep 2017.
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ANNOTATION:

ABSTRACT:

- [47] Tanja Dragojević, Joseph L Hollmann, Davide Tamborini, Davide Portaluppi, Mauro Buttafava, Joseph P Culver, Federica Villa, and Turgut Durduran. Compact, multi-exposure speckle contrast optical spectroscopy (scos) device for measuring deep tissue blood flow. *Biomedical Optics Express*, 9(1):322–334, 2018.

ANNOTATION: DCS, SCOS, Adult, N=2

ABSTRACT: Speckle contrast optical spectroscopy (SCOS) measures absolute blood flow in deep tissue, by taking advantage of multi-distance (previously reported in the literature) or multiexposure (reported here) approach. This method promises to use inexpensive detectors to obtain good signal-to-noise ratio, but it has not yet been implemented in a suitable manner for a mass production. Here we present a new, compact, low power consumption, 32 by 2 single photon avalanche diode (SPAD) array that has no readout noise, low dead time and has high sensitivity in low light conditions, such as in vivo measurements. To demonstrate the capability to measure blood flow in deep tissue, healthy volunteers were measured, showing no significant differences from the diffuse correlation spectroscopy. In the future, this array can be miniaturized to a low-cost, robust, battery operated wireless device paving the way for measuring blood flow in a wide-range of applications from sport injury recovery and training to, on-field concussion detection to wearables.

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- [53] Tiziano Binzoni, Bruno Sanguinetti, Dimitri Van de Ville, Hugo Zbinden, and Fabrizio Martelli. Probability density function of the electric field in diffuse correlation spectroscopy of human bone in vivo. *Applied Optics*, 55(4):757–762, 2016.
- [54] Wesley Boehs Baker. *Optical Cerebral Blood Flow Monitoring of Mice to Men*. PhD thesis, University of Pennsylvania, 2015.
- [55] Igor Blanco. *Diffuse optical monitoring of cerebral hemodynamics in experimental and clinical neurology*. PhD thesis, ICFO—The Institute of Photonic Sciences, 2015.
 ANNOTATION: ICFO, Human Sleep Apnea and Stroke
 ABSTRACT:
- [56] David A. Boas. *Diffuse Photon Probes of Structural and Dynamical Properties of Turbid Media: Theory and Biomedical Applications*. PhD thesis, University of Pennsylvania, Philadelphia, PA USA, 1996.
- [57] Erin M. Buckley. *Cerebral Hemodynamics in High-Risk Neonates Probed by Diffuse Optical Spectroscopies*. PhD thesis, University of Pennsylvania, 2011.
- [58] David R. Busch. *Computer-Aided, Multi-Modal, and Compression Diffuse Optical Studies of Breast Tissue*. PhD thesis, University of Pennsylvania, 2011.
 ANNOTATION: DCS applied in sham mammographic application, follow on paper Busch Academic Radiology, 2014
 ABSTRACT: Diffuse Optical Tomography and Spectroscopy permit measurement of important physiological parameters non-invasively through 10 cm of tissue. I have applied these techniques in measurements of human breast and breast cancer. My thesis integrates three loosely connected themes in this context: multi-modal breast cancer imaging, automated data analysis of breast cancer images, and microvascular hemodynamics of breast under compression. As per the first theme, I describe construction, testing, and the initial clinical usage of two generations of imaging systems for simultaneous diffuse optical and magnetic resonance imaging. The second project develops a statistical analysis of optical breast data from many spatial locations in a population of cancers to derive a novel optical signature of malignancy; I then apply this data-derived signature for localization of cancer in additional subjects. Finally, I construct and deploy diffuse optical instrumentation to measure blood content and blood flow during breast compression; besides optics, this research has implications for any method employing breast compression, e.g., mammography.
- [59] David Diaz. *Tissue Damage Characterization Using Non-invasive Optical Modalities*. DREXEL UNIVERSITY, 2016.
 ANNOTATION: DCS
 ABSTRACT: The ability to determine the degree of cutaneous and subcutaneous tissue damage is essential for proper wound assessment and a significant factor for determining patient treatment and morbidity. Accurate characterization of tissue damage is critical for a number of medical applications including surgical removal of nonviable tissue, severity assessment of subcutaneous ulcers, and depth assessment of visually open wounds. The main objective of this research was to develop a non-invasive method for identifying the extent of tissue damage underneath intact skin that is not apparent upon visual examination. This work investigated the relationship between tissue optical properties, blood flow, and tissue viability by testing the hypotheses that (a) changes in tissue oxygenation and/or microcirculatory blood flow measurable by Diffuse Near Infrared Spectroscopy (DNIRS) and Diffuse Correlation Spectroscopy (DCS) differ between healthy and damaged tissue and (b) the magnitude of those changes differs for different degrees of tissue damage. This was accomplished by developing and validating a procedure for measuring microcirculatory blood flow and tissue oxygenation dynamics at multiple depths (up to 1 centimeter) using non-invasive DCS and DNIRS technologies. Due to the lack of pressure ulcer animal models that are compatible with our optical systems, a proof of concept was conducted in a porcine burn model prior to conducting clinical trials in order to assess the efficacy of the system in-vivo. A reduction in total hemoglobin was

observed for superficial (5%) and deep burns (35%) along with a statistically significant difference between the optical properties of superficial and deep burns ($p < 0.05$). Burn depth and viable vessel density were estimated via histological samples. 42% of vessels in the dermal layer were viable for superficial burns, compared to 25% for deep burns. The differences detected in optical properties and hemoglobin content by optical measurements correlated with the extent of tissue injury observed in histological stains. After proof of concept in animals, a human study was conducted and optical data was collected from 20 healthy subjects and 8 patients at risk of developing pressure ulcers. Blood flow index (BFI) values from the sacral region of patients were compared with those of healthy volunteers. Prior to loading measurements, baseline BFI values were measured in subjects in lateral position. These values were systematically higher for patients who developed open ulcers than for the other research subjects. While under the loading position, patients who developed a pressure ulcer had a decrease in BFI from baseline values an order of magnitude larger than healthy subjects ($p < 0.01$) and patients whose redness dissipated ($p < 0.01$). The hyperemic response, when pressure was released as the patient was moved back to a lateral position, showed a decreasing trend from one session to the next for patients who developed open ulcers. Overall, this work presents a novel non-invasive method of pressure ulcer assessment and provides an improvement over current assessment methods. The obtained results suggest the system may potentially predict whether non-blanchable redness will develop into an advanced pressure ulcer within four weeks from initial observation.

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- [64] Jennifer M. Lynch. *Investigations of Cerebral Hemodynamics In Infants With Critical Congenital Heart Disease Using Diffuse Optics*. PhD thesis, University of Pennsylvania, 2014.
- [65] Ulas Sunar. *Monitoring Tumor Therapeutic Response with Diffuse Optical Spectroscopies*. PhD thesis, University of Pennsylvania, 2006.
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- [68] P Ellen Grant, Nadege Roche-Labarbe, Andrea Surova, George Themelis, Juliette Selb, Elizabeth K Warren, Kalpathy S Krishnamoorthy, David A Boas, and Maria Angela Franceschini. Increased cerebral blood volume and oxygen consumption in neonatal brain injury. *Journal of Cerebral Blood Flow & Metabolism*, 29(10):1704–1713, 2009.

ANNOTATION: ECMO 43 subjects, 7 wavelength FD-DOS, 4 regions on head. Subject separated into brain injury, unstable (inc. ECMO), stable, or healthy. Brain injury is not detected by StO₂, but by a combination of rCMRO₂ and CBV.

ABSTRACT: With the increasing interest in treatments for neonatal brain injury, bedside methods for detecting and assessing injury status and evolution are needed. We aimed to determine whether cerebral tissue oxygenation (StO₂), cerebral blood volume (CBV), and estimates of relative cerebral oxygen consumption (rCMRO₂) determined by bedside frequency-domain near-infrared spectroscopy (FD-NIRS) have the potential to distinguish neonates with brain injury from those with non-brain issues and healthy controls. We recruited 43 neonates <15 days old and ≥ 33 weeks gestational age (GA): 14 with imaging evidence of brain injury, 29 without suspicion of brain injury (4 unstable, 6 stable, and 19 healthy). A multivariate analysis of variance with Newman-Keuls post hoc comparisons confirmed group similarity for GA and age at measurement. StO₂ was significantly higher in brain injured compared with unstable neonates, but not statistically different from stable or healthy neonates. Brain-injured neonates were distinguished from all others by significant increases in CBV and rCMRO₂. In conclusion, although NIRS measures of StO₂ alone may be insensitive to evolving brain injury, increased CBV and rCMRO₂ seem to be useful for detecting neonatal brain injury and suggest increased neuronal activity and metabolism occurs acutely in evolving brain injury. Keywords: NIRS (near infrared spectroscopy), hypoxic ischemic injury, stroke, neonate, CBV (cerebral blood volume), CMRO₂ (cerebral metabolic rate of oxygen consumption)

- [69] Donna A. Goff, Erin M. Buckley, Turgut Durduran, Jiongjong Wang, and Daniel J. Licht. Noninvasive cerebral perfusion imaging in high-risk neonates. *Seminars in Perinatology*, 34(1):46 – 56, 2010.

ANNOTATION: Imaging the Developing Brain

ABSTRACT: advances in medical and surgical care of the high-risk neonate have led to increased survival. A significant number of these neonates suffer from neurodevelopmental delays and failure in school. The focus of clinical research has shifted to understanding events contributing to neurological morbidity in these patients. Assessing changes in cerebral oxygenation and regulation of cerebral blood flow (CBF) is important in evaluating the status of the central nervous system. Traditional CBF imaging methods fail for both ethical and logistical reasons. Optical near infrared spectroscopy (NIRS) is increasingly being used for bedside monitoring of cerebral oxygenation and blood volume in both very low birth weight infants and neonates with congenital heart disease. Although trends in CBF may be inferred from changes in cerebral oxygenation and/or blood volume, NIRS does not allow a direct measure of CBF in these populations. Two relatively new modalities, arterial spin-labeled perfusion magnetic resonance imaging and optical diffuse correlation spectroscopy, provide direct, noninvasive measures of cerebral perfusion suitable for the high-risk neonates. Herein we discuss the instrumentation, applications, and limitations of these noninvasive imaging techniques for measuring and/or monitoring CBF.

- [70] Nadege Roche-Labarbe, Angela Fenoglio, Alpna Aggarwal, Mathieu Dehaes, Stefan A Carp, Maria Angela Franceschini, and Patricia Ellen Grant. Near-infrared spectroscopy assessment of cerebral oxygen metabolism in the developing premature brain. *Journal of Cerebral Blood Flow & Metabolism*, 32(3):481–488, 2011.

ANNOTATION: 56 neonates, longitudinal study, CMRO2 correlated to gestational age, saturation is less accurate than CMRO2 or BFI

ABSTRACT: Little is known about cerebral blood flow, cerebral blood volume (CBV), oxygenation, and oxygen consumption in the premature newborn brain. We combined quantitative frequency-domain near-infrared spectroscopy measures of cerebral hemoglobin oxygenation (SO(2)) and CBV with diffusion correlation spectroscopy measures of cerebral blood flow index (BF(ix)) to determine the relationship between these measures, gestational age at birth (GA), and chronological age. We followed 56 neonates of various GA once a week during their hospital stay. We provide absolute values of SO(2) and CBV, relative values of BF(ix), and relative cerebral metabolic rate of oxygen (rCMRO(2)) as a function of postmenstrual age (PMA) and chronological age for four GA groups. SO(2) correlates with chronological age ($r=-0.54$, P value ≤ 0.001) but not with PMA ($r=-0.07$), whereas BF(ix) and rCMRO(2) correlate better with PMA ($r=0.37$ and 0.43 , respectively, P value ≤ 0.001). Relative CMRO2 during the first month of life is lower when GA is lower. Blood flow index and rCMRO(2) are more accurate biomarkers of the brain development than SO(2) in the premature newborns.

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ANNOTATION: N=11, neonate

ABSTRACT: With the causes of perinatal brain injuries still unclear and the probable role of hemodynamic instability in their etiology, bedside monitoring of neonatal cerebral hemodynamics with standard values as a function of age are needed. In this study, we combined quantitative frequency domain near infrared spectroscopy (FD-NIRS) measures of cerebral tissue oxygenation (StO2) and cerebral blood volume (CBV) with diffusion correlation spectroscopy (DCS) measures of a cerebral blood flow index (CBFix) to test the validity of the CBV-CBF relationship in premature neonates and to estimate cerebral metabolic rate of oxygen (rCMRO2) with or without the CBFix measurement. We measured 11 premature neonates (28-34 weeks gestational age) without known neurological issues, once a week from one to six weeks of age. In nine patients, cerebral blood velocities from the middle cerebral artery were collected by transcranial Doppler (TCD) and compared with DCS values. Results show a steady decrease in StO2 during the first six weeks of life while CBV remains stable, and a steady increase in CBFix. rCMRO2 estimated from FD-NIRS remains constant but shows wide interindividual variability. rCMRO2 calculated from FD-NIRS and DCS combined increased by 40% during the first six weeks of life with reduced interindividual variability. TCD and DCS values are positively correlated. In conclusion, FD-NIRS combined with DCS offers a safe and quantitative bedside method to assess CBV, StO2, CBF, and rCMRO2 in the premature brain, facilitating individual follow-up and comparison among patients. A stable CBV-CBF relationship may not be valid for premature neonates.

- [72] Pei-Yi Lin, Nadège Roche-Labarbe, Mathieu Dehaes, Angela Fenoglio, P Ellen Grant, and Maria Angela Franceschini. Regional and hemispheric asymmetries of cerebral hemodynamic and oxygen metabolism in newborns. *Cerebral Cortex*, page bhs023, 2012.

ANNOTATION: FD+DCS, healthy newborns, regional variation

ABSTRACT: Understanding the evolution of regional and hemispheric asymmetries in the early stages of life is essential to the advancement of developmental neuroscience. By using 2 noninvasive optical methods, frequency-domain near-infrared spectroscopy and diffuse correlation spectroscopy, we measured cerebral hemoglobin oxygenation (SO(2)), blood volume (CBV), an index of cerebral blood flow (CBF(i)), and the metabolic rate of oxygen (CMRO(2i)) in the frontal, temporal, and parietal regions of 70 premature and term newborns. In concordance with results obtained using more invasive imaging modalities, we verified both hemodynamic (CBV, CBF(i), and SO(2)) and metabolic (CMRO(2i)) parameters were greater in the temporal and parietal regions than in the frontal region and that these differences increased with age. In addition, we found that most parameters were significantly greater in the right hemisphere than in the left. Finally, in comparing age-matched males and females, we found

that males had higher CBF(i) in most cortical regions, higher CMRO(2i) in the frontal region, and more prominent right-left CBF(i) asymmetry. These results reveal, for the first time, that we can detect regional and hemispheric asymmetries in newborns using noninvasive optical techniques. Such a bedside screening tool may facilitate early detection of abnormalities and delays in maturation of specific cortical areas.

- [73] Pei-Yi Lin, Nadege Roche-Labarbe, Mathieu Dehaes, Stefan Carp, Angela Fenoglio, Beniamino Barbieri, Katherine Hagan, P Ellen Grant, and Maria Angela Franceschini. Non-invasive optical measurement of cerebral metabolism and hemodynamics in infants. *JoVE (Journal of Visualized Experiments)*, 1(73):e4379–e4379, 2013.

ANNOTATION: DCS

ABSTRACT: Perinatal brain injury remains a significant cause of infant mortality and morbidity, but there is not yet an effective bedside tool that can accurately screen for brain injury, monitor injury evolution, or assess response to therapy. The energy used by neurons is derived largely from tissue oxidative metabolism, and neural hyperactivity and cell death are reflected by corresponding changes in cerebral oxygen metabolism (CMRO2). Thus, measures of CMRO2 are reflective of neuronal viability and provide critical diagnostic information, making CMRO2 an ideal target for bedside measurement of brain health. Brain-imaging techniques such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) yield measures of cerebral glucose and oxygen metabolism, but these techniques require the administration of radionucleotides, so they are used in only the most acute cases. Continuous-wave near-infrared spectroscopy (CWNIRS) provides non-invasive and non-ionizing radiation measures of hemoglobin oxygen saturation (SO2) as a surrogate for cerebral oxygen consumption. However, SO2 is less than ideal as a surrogate for cerebral oxygen metabolism as it is influenced by both oxygen delivery and consumption. Furthermore, measurements of SO2 are not sensitive enough to detect brain injury hours after the insult, because oxygen consumption and delivery reach equilibrium after acute transients. We investigated the possibility of using more sophisticated NIRS optical methods to quantify cerebral oxygen metabolism at the bedside in healthy and brain-injured newborns. More specifically, we combined the frequency-domain NIRS (FDNIRS) measure of SO2 with the diffuse correlation spectroscopy (DCS) measure of blood flow index (CBFi) to yield an index of CMRO2 (CMRO2i). With the combined FDNIRS/DCS system we are able to quantify cerebral metabolism and hemodynamics. This represents an improvement over CWNIRS for detecting brain health, brain development, and response to therapy in neonates. Moreover, this method adheres to all neonatal intensive care unit (NICU) policies on infection control and institutional policies on laser safety. Future work will seek to integrate the two instruments to reduce acquisition time at the bedside and to implement real-time feedback on data quality to reduce the rate of data rejection.

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- [78] Mathieu Dehaes, Henry H Cheng, Erin M Buckley, Pei-Yi Lin, Silvina Ferradal, Kathryn Williams, Rutvi Vyas, Katherine Hagan, Daniel Wigmore, Erica McDavitt, et al. Perioperative cerebral hemodynamics and oxygen metabolism in neonates with single-ventricle physiology. *Biomedical optics express*, 6(12):4749–4767, 2015.
- [79] Pei-Yi Lin, Katherine Hagan, Angela Fenoglio, P Ellen Grant, and Maria Angela Franceschini. Reduced cerebral blood flow and oxygen metabolism in extremely preterm neonates with low-grade germinal matrix-intraventricular hemorrhage. *Scientific reports*, 6, 2016.

ANNOTATION: DCS, neonates

ABSTRACT:

- [80] David R. Busch, Kelley Z. Kovatis, Madeline E. Winters, John J. Newland, Tiffany Ko, John J. Flibotte, Haresh Kirplani, and Daniel J. Licht. Optical measurement of blood flow in the extremely low birthweight neonate. In *Annual Meeting*, Milan, Italy, 2015. Engineering in Medicine and Biology Society, IEEE.

ANNOTATION: DCS, Extremely low birthweight neonates, N=7

ABSTRACT: Extremely low birth weight neonates (≤ 1000 g at birth) are vulnerable to hypo- and hyper-oxygenation. We demonstrate the use of a combined diffuse optical system to monitor hemodynamics throughout clinical care.

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- ANNOTATION: fDCS, N=9, healthy
 ABSTRACT: Activity of the human visual cortex, elicited by steady-state flickering at 8 Hz, is non-invasively probed by multi-speckle diffusing-wave spectroscopy (DWS). Parallel detection of the intensity fluctuations of statistically equivalent, but independent speckles allows to resolve stimulation-induced changes in the field autocorrelation of multiply scattered light of less than 2%. In a group of 9 healthy subjects we find a faster decay of the field autocorrelation function during the stimulation periods for data measured with a long-distance probe (30 mm source-receiver distance) at 2 positions over the occipital cortex (t-test: $t(8) = -2.672$, $p = 0.028 < 0.05$ for position 1, $t(8) = -2.874$, $p = 0.021 < 0.05$ for position 2). In contrast, no statistically significant change is seen when a short-distance probe (16mm source-receiver distance) is used (t-test: $t(8) = -2.043$, $p = 0.075 > 0.05$ for position 1, $t(8) = -2.146$, $p = 0.064 > 0.05$ for position 2). The enhanced dynamics observed with DWS is positively correlated with the functional increase of blood volume in the visual cortex, while the heartbeat rate is not affected by stimulation. Our results indicate that the DWS signal from the visual cortex is governed by the regional cerebral blood flow velocity.
- [83] Jun Li, Markus Ninck, Leonie Koban, Thomas Elbert, Johanna Kissler, and Thomas Gisler. Transient functional blood flow change in the human brain measured noninvasively by diffusing-wave spectroscopy. *Optics letters*, 33(19):2233–2235, 2008.
- ANNOTATION: fDCS
 ABSTRACT: Multispeckle diffusing-wave spectroscopy (DWS) is used to measure blood flow transients in the human visual cortex following stimulation by 7.5 Hz full-field and checkerboard flickering. The average decay time τ_d characterizing the decay of the DWS autocorrelation function shows a biphasic behavior; within about 2s after stimulation onset, τ_d increases rapidly to about 6% above the baseline value. At later times, τ_d slowly decreases and reaches a steady-state value about 5% below the baseline value after about 15s. The initial increase of the DWS signal suggests a transient reduction of the cortical blood flow velocity shortly after stimulation onset. Measurements of this transient response at different positions over the primary visual cortex show a spatial pattern different from the one measured by electroencephalography.
- [84] Turgut Durduran, Chao Zhou, Brian L Edlow, Guoqiang Yu, Regine Choe, Meeri N Kim, Brett L Cucchiara, Mary E Putt, Qaisar Shah, Scott E Kasner, Joel H Greenberg, Arjun G Yodh, and John A Detre. Transcranial optical monitoring of cerebrovascular hemodynamics in acute stroke patients. *Optics express*, 17(5):3884–3902, 2009.
- ANNOTATION: N=17, stroke, adult
 ABSTRACT:
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- ANNOTATION: N = 12, critically brain-injured adults
 ABSTRACT: Non-invasive assessment of micro-vascular physiology of deep tissue over long periods of time at the bedside has been a real clinical demand. In the neuro-intensive care unit (nICU) real-time physiological monitoring could lead to a more individualized and efficient treatment. Recent advances of diffuse optical techniques, such as frequency-domain diffuse optical spectroscopy (FD-DOS) and diffuse correlation spectroscopy (DCS), enabled the

continuous monitoring of patient hemodynamics at the bedside. Concurrent measurements of tissue oxygenation (from FD-DOS) and relative cerebral blood flow (from DCS) also allow continuous assessment of relative changes in cerebral metabolic rate of oxygen (rCMRO₂) in critical patients. This information could be used to better understand, and potentially guide, patient care during hospitalization. The goal of this work was to build a hybrid DCS/FD-DOS system for continuous real-time monitoring of rCMRO₂, and to fully integrate the system into the nICU. We then evaluated the systems performance as a bedside monitor of neurocritical patients during hospitalization. The hybrid system consists of a homemade DCS module that employs 16 photon counters (SPCM-AQ4C, Perkin Elmer), a long coherence laser (785 nm, CrystaLaser) and a correlator board (Correlator.com). The FD-DOS module employs a commercial system (Imagent, ISS) with 4 detectors and 32 sources emitting in 4 different wavelengths. A graphical interface was built based on similar nICU instrument interfaces so that clinicians can assess all patient's hemodynamic and metabolic information in real time. In the software, we used a semi-infinite approach for estimating the absolute optical properties from the FD-DOS data, and the blood flow index from the DCS data. For the patient monitoring, the optical sensor was designed to allow measurements with 4 different source-detector distances (1.5-3.0 cm) for both FD-DOS and DCS. The injured region was accurately located in real-time using the patients computerized tomography image in the InVesalius Navigator software (df.fclrp.usp.br/biomag) connected to a spatial tracker (FASTRAK, Polhemus). We monitored both the ipsi- and the contra-lesion hemispheres of all patients for periods ranging from 2 to 5 hours. Our preliminary results suggest that the system can aid patients care with real-time bedside monitoring by evidencing differences between different patients diagnosis. For instance, the blood flow index (BFI) in the ipsi-lesion hemisphere of a patient with a frontal lobe ischemic stroke was an order of magnitude lower than the BFI found for patients with cerebellar ischemic stroke. In addition, the technique can be used to longitudinally monitor the injured region by comparison with the contra-lesion regions. For example, in a patient diagnosed with sub- arachnoid hemorrhage that could not be monitored with transcranial Doppler (TCD) during the pre-vasospasm phase, the BFI on the ipsi-lesion hemisphere was approximately 200% higher than the BFI in the contra-lesion hemisphere. Overall, we presented the construction of a real-time hybrid optical system designed specifically to monitor patients in the critical state at the nICU. Although this is a pilot study, our preliminary results suggest that the real-time feature can help clinicians to identify worsening conditions of patients by continuously monitoring hemodynamic oscillations over time.

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ANNOTATION: DCS, N=18, adults

ABSTRACT: The critical closing pressure (CrCP) of the cerebral circulation depends on both tissue intracranial pressure and vasomotor tone. CrCP defines the arterial blood pressure (ABP) at which cerebral blood flow approaches zero, and their difference (ABP - CrCP) is often employed as a proxy for cerebral perfusion pressure. Here we demonstrate a novel non-invasive technique for continuous monitoring of CrCP at the bedside. The methodology combines optical diffuse correlation spectroscopy (DCS) measurements of pulsatile cerebral blood flow in arterioles with concurrent ABP data during the cardiac cycle. Together, the two waveforms permit calculation of CrCP via the Windkessel model for flow in the cerebral arterioles. Measurements of CrCP by optics (DCS) and transcranial Doppler ultrasound (TCD) were carried out in 18 healthy adults; they demonstrated good agreement ($R = 0.66$, slope = 1.14 ± 0.23) with means of 11.1 ± 5.0 and 13.0 ± 7.5 mmHg, respectively. Additionally, a potentially useful and rarely measured arteriole compliance parameter was derived from the phase difference between ABP and DCS arteriole blood flow waveforms. The measurements provide evidence that DCS signals originate predominantly from arteriole blood flow and are well suited for long-term continuous monitoring of CrCP and assessment of arteriole compliance in the clinic.

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ANNOTATION: Human, adult, brain, N=7

ABSTRACT: We investigate a scheme for noninvasive continuous monitoring of absolute cerebral blood flow (CBF) in adult human patients based on a combination of time-resolved dynamic contrast-enhanced near-infrared spectroscopy (DCE-NIRS) and diffuse correlation spectroscopy (DCS) with semi-infinite head model of photon propagation. Continuous CBF is obtained via calibration of the DCS blood flow index (BFI) with absolute CBF obtained by intermittent intravenous injections of the optical contrast agent indocyanine green. A calibration coefficient (γ) for the CBF is thus determined, permitting conversion of DCS BFI to absolute blood flow units at all other times. A study of patients with acute brain injury ($N=7$) is carried out to ascertain the stability of γ . The patient-averaged DCS calibration coefficient across multiple monitoring days and multiple patients was determined, and good agreement between the two calibration coefficients measured at different times during single monitoring days was found. The patient-averaged calibration coefficient of $1.24 \times 10^{-9} \text{ mL}/100\text{g}/\text{min}/(\text{cm}^2/\text{s})$ was applied to previously measured DCS BFI from similar brain-injured patients; in this case, absolute CBF was underestimated compared with XeCT, an effect we show is primarily due to use of semi-infinite homogeneous models of the head.

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- ANNOTATION: sleep, apnea, sleep apnea, OSA, obstructive, adult
 ABSTRACT: The objective of this study was to adapt a novel near-infrared diffuse correlation spectroscopy (DCS) flow-oximeter for simultaneous and continuous monitoring of relative changes in cerebral blood flow (rCBF) and cerebral oxygenation (i.e. oxygenated/deoxygenated/total hemoglobin concentration: $\Delta [\text{HbO}_2] / \Delta [\text{Hb}] / \Delta \text{THC}$) during overnight nocturnal polysomnography (NPSG) diagnostic test for obstructive sleep apnea-hypopnea (OSAH). A fiber-optic probe was fixed on subjects frontal head and connected to the DCS flow-oximeter through a custom-designed fiber-optic connector, which allowed us to easily connect/detach the optical probe from the device when the subject went to bathroom. To minimize the disturbance to the subject, the DCS flow-oximeter was remotely operated by a desktop located in the control room. The results showed that apneic events caused significant variations in rCBF and ΔTHC . Moreover, the degrees of variations in all measured cerebral variables were significantly correlated with the severity of OSAH as determined by the apnea-hypopnea index (AHI), demonstrating the OSAH influence on both CBF and cerebral oxygenation. Large variations in arterial blood oxygen saturation (SaO_2) were also found during OSAH. Since frequent variations/disturbances in cerebral hemodynamics may adversely impact brain function, future study will investigate the correlations between these cerebral variations and functional impairments for better understanding of OSAH pathophysiology.
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- [96] David R. Busch, Jennifer M. Lynch, Madeline E. Winters, Ann L. McCarthy, John J. Newland, Mary Ann Cornaglia, Jerilyn Radcliffe, Joseph McDonough, John Samuel, Edward Matthews, Rui Xiao, Arjun G. Yodh, Carole L. Marcus, Daniel J. Licht, and Ignacio E. Tapia. Cerebral blood flow response to hypercapnia in children with obstructive sleep apnea syndrome. *Sleep*, 2016.
- ANNOTATION: N=30, pediatric apnea/controls/snorers
 ABSTRACT: Children with obstructive sleep apnea syndrome (OSAS) often experience periods of hypercapnia during sleep, a potent stimulator of cerebral blood flow (CBF). Considering this hypercapnia exposure during sleep, it is possible that children with OSAS have abnormal CBF responses to hypercapnia even during wakefulness. Therefore, we hypothesized that children with OSAS have blunted CBF response to hypercapnia during wakefulness, compared to snorers and controls. CBF changes during hypercapnic ventilatory response (HCVR) were tested in children with OSAS, snorers, and healthy controls using diffuse correlation spectroscopy (DCS). Peak CBF changes with respect to pre-hypercapnic baseline were measured for each group. Academic pediatric sleep center. Twelve children with OSAS (aged 10.12.5 [mean+standard deviation] y, obstructive apnea hypopnea index [AHI] = 9.4 [5.1-15.4] [median, interquartile range] events/hour), eight snorers (11.3 y, 0.5 [0-1.3] events/hour), and 10 controls (11.4.2.6 y, 0.3 [0.2-0.4] events/hour) were studied. The fractional CBF change during hypercapnia, normalized to the change in end-tidal carbon dioxide, was significantly higher in controls (9.1.8 %/mmHg) compared to OSAS (7.1.1.5, p=0.023) and snorers (6.7.1.9, P = 0.025). Children with OSAS and snorers have blunted CBF response to hypercapnia during wakefulness compared to controls. Noninvasive DCS blood flow measurements of hypercapnic reactivity offer insights into physiopathology of OSAS in children, which could lead to further understanding about the central nervous system complications of OSAS.
- [97] Yu Shang, Ran Cheng, Lixin Dong, Stephen J Ryan, Sibup P Saha, and Guoqiang Yu. Cerebral monitoring during carotid endarterectomy using near-infrared diffuse optical spectroscopies and electroencephalogram. *Physics in medicine and biology*, 56(10):3015, 2011.
- ANNOTATION: Intraoperative monitoring of cerebral hemodynamics during carotid endarterectomy (CEA) provides essential information for detecting cerebral hypoperfusion induced by temporary internal carotid artery (ICA) clamping and post-CEA hyperperfusion syndrome. This study tests the feasibility and sensitivity of a novel dual-wavelength near-infrared diffuse correlation spectroscopy technique in detecting cerebral blood flow (CBF) and cerebral oxygenation in patients undergoing CEA. Two fiber-optic probes were taped on both sides of the forehead for cerebral hemodynamic measurements, and the instantaneous decreases in CBF and electroencephalogram (EEG) alpha-band power during ICA clamping were compared to test the measurement sensitivities of the two techniques. The ICA clamps resulted in significant CBF decreases (24.7.7.3%) accompanied with cerebral deoxygenation at the surgical sides (n = 12). The post-CEA CBF were significantly higher (+43.2.16.9%) than the

pre-CEA CBF. The CBF responses to ICA clamping were significantly faster, larger and more sensitive than EEG responses. Simultaneous monitoring of CBF, cerebral oxygenation and EEG power provides a comprehensive evaluation of cerebral physiological status, thus showing potential for the adoption of acute interventions (e.g., shunting, medications) during CEA to reduce the risks of severe cerebral ischemia and cerebral hyperperfusion syndrome.

ABSTRACT: intraoperative

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- ANNOTATION: N=1, neonate cardiac surgery with deep hypothermic circulatory arrest
ABSTRACT: While survival of children with complex congenital heart defects has improved in recent years, roughly half suffer neurological deficits suspected to be related to cerebral ischemia. Here we report the first demonstration of optical diffuse correlation spectroscopy (DCS) for continuous and non-invasive monitoring of cerebral microvascular blood flow during complex human neonatal or cardiac surgery. Comparison between DCS and Doppler ultrasound flow measurements during deep hypothermia, circulatory arrest, and rewarming were in good agreement. Looking forward, DCS instrumentation, alone and with NIRS, could provide access to flow and metabolic biomarkers needed by clinicians to adjust neuroprotective therapy during surgery.
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- [100] Erin M Buckley, Benjamin F Miller, Julianne M Golinski, Homa Sadeghian, Lauren M McAllister, Mark Vangel, Cenk Ayata, William P Meehan, Maria Angela Franceschini, and Michael J Whalen. Decreased microvascular cerebral blood flow assessed by diffuse correlation spectroscopy after repetitive concussions in mice. *Journal of Cerebral Blood Flow & Metabolism*, 35(12):1995–2000, 2015.
- ANNOTATION: N=118 C57 adult mice, concussion
ABSTRACT: Repetitive concussions are associated with long-term cognitive dysfunction that can be attenuated by increasing the time intervals between concussions; however, biomarkers of the safest rest interval between injuries remain undefined. We hypothesize that deranged cerebral blood flow (CBF) is a candidate biomarker for vulnerability to repetitive concussions. Using a mouse model of human concussion, we examined the effect of single and repetitive concussions on cognition and on an index of CBF (CBFi) measured with diffuse correlation spectroscopy. After a single mild concussion, CBFi was reduced by 35+4% at 4 hours (P <0.01 versus baseline) and returned to preinjury levels by 24 hours. After five concussions spaced 1 day apart, CBFi was also reduced from preinjury levels 4 hours after each concussion but had returned to preinjury levels by 72 hours after the final concussion. Interestingly, in this repetitive concussion model, lower CBFi values measured both preinjury and 4 hours after the third concussion were associated with worse performance on the Morris water maze assessed 72 hours after the final concussion. We conclude that low CBFi measured either before or early on in the evolution of injury caused by repetitive concussions could be a useful predictor of cognitive outcome.
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- [105] Ajay Rajaram, Gemma Bale, Matthew Kewin, Laura B. Morrison, Ilias Tachtsidis, Keith St. Lawrence, and Mamadou Diop. Simultaneous monitoring of cerebral perfusion and cytochrome c oxidase by combining broadband near-infrared spectroscopy and diffuse correlation spectroscopy. *Biomed. Opt. Express*, 9(6):2588–2603, Jun 2018.

ANNOTATION:

ABSTRACT: Preterm infants born with very low birth weights are at a high risk of brain injury, in part because the premature brain is believed to be prone to periods of low cerebral blood flow (CBF). Tissue damage is likely to occur if reduction in CBF is sufficient to impair cerebral energy metabolism for extended periods. Therefore, a neuromonitoring method that can detect reductions in CBF, large enough to affect metabolism, could alert the neonatal intensive care team before injury occurs. In this report, we present the development of an optical system that combines diffuse correlation spectroscopy (DCS) for monitoring CBF and broadband near-infrared spectroscopy (B-NIRS) for monitoring the oxidation state of cytochrome c oxidase (oxCCO) – a key biomarker of oxidative metabolism. The hybrid instrument includes a multiplexing system to enable concomitant DCS and B-NIRS measurements while avoiding crosstalk between the two subsystems. The ability of the instrument to monitor dynamic changes in CBF and oxCCO was demonstrated in a piglet model of neonatal hypoxia-ischemia (HI). Experiments conducted in eight animals, including two controls, showed that oxCCO exhibited a delayed response to ischemia while CBF and tissue oxygenation (StO₂) responses were instantaneous. These findings suggest that simultaneous neuromonitoring of perfusion and metabolism could provide critical information regarding clinically significant hemodynamic events prior to the onset of brain injury.

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ANNOTATION: RMD,

ABSTRACT: Repair of soft tissue defects of the lips as seen in complex maxillofacial injuries, requires pre-vascularized multi-tissue composite grafts. Protocols for fabrication of human ex-vivo produced oral mucosal equivalents (EVPOME) composed of epithelial cells and a dermal equivalent are available to create prelaminated flaps for grafting in patients. However, invivo assessment of neovascularization of the buried prelaminated flaps remains clinically challenging. Here, we use diffuse reflectance spectroscopy (DRS) and diffuse correlation spectroscopy (DCS) to non-invasively quantify longitudinal changes in the vessel density and blood-flow within EVPOME grafts implanted in the backs of SCID mice and subsequently to determine the utility of these optical techniques for assessing vascularization of implanted grafts. 20 animals were implanted with EVPOME grafts (1x1x0.05 cm³) in their backs. DRS and DCS measurements were obtained from each animal both atop the graft site and far away from the graft site, at one week post-implantation, each week, for four consecutive weeks. DRS spectra were analyzed using an inverse Monte Carlo model to extract tissue absorption and scattering coefficients, which were then used to extract blood flow information by fitting the experimental DCS traces. There were clear differences in the mean optical parameters (averaged across all mice) at the graft site vs. the off-site measurements. Both the total hemoglobin concentration (from DRS) and the relative blood flow (from DCS) peaked at week 3 at the graft site and declined to the off-site values by week 4. The optical parameters remained relatively constant throughout 4 weeks for the off-site measurements.

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ANNOTATION: N=6, human

ABSTRACT: Photodynamic therapy (PDT) using topical 5-aminolevulinic acid (ALA) is currently used as a clinical treatment for nonmelanoma skin cancers. In order to optimize PDT treatment, vascular disruption early in treatment must be identified and prevented. We present blood flow responses to topical ALA-PDT in a preclinical model and basal cell carcinoma patients assessed by diffuse correlation spectroscopy (DCS). Our results show that ALA-PDT induced early blood flow changes and these changes were irradiance dependent. It is clear that there exists considerable variation in the blood flow responses in patients from lesion to lesion. Monitoring blood flow parameter may be useful for assessing ALA-PDT response and planning.

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ANNOTATION: N=15, human breast

ABSTRACT: Rationale and objectives: This study measures hemodynamic properties such as blood flow and hemoglobin concentration and oxygenation in the healthy human breast under a wide range of compressive loads. Because many breast-imaging technologies derive contrast from the deformed breast, these load-dependent vascular responses affect contrast agent-enhanced and hemoglobin-based breast imaging. Methods: Diffuse optical and diffuse correlation spectroscopies were used to measure the concentrations of oxygenated and deoxygenated hemoglobin, lipid, water, and microvascular blood flow during axial breast compression in the parallel-plate transmission geometry. Results: Significant reductions ($P < .01$) in total hemoglobin concentration (app. 30%), blood oxygenation (app. 20%), and blood flow (app. 87%) were observed under applied pressures (forces) of up to 30 kPa (120 N) in 15 subjects. Lipid and water concentrations changed $\leq 10\%$. Conclusions: Imaging protocols based on injected contrast agents should account for variation in tissue blood flow due to mammographic compression. Similarly, imaging techniques that depend on endogenous blood contrasts will be affected by breast compression during imaging. Key Words: Mammographic compression; breast cancer; blood flow; breast imaging; diffuse optics.

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- [115] Daniel J Rohrbach, Nestor Rigual, Hassan Arshad, Erin C Tracy, Michelle T Cooper, Gal Shafirstein, Gregory Wilding, Mihai Merzianu, Heinz Baumann, Barbara W Henderson, et al. Intraoperative optical assessment of photodynamic therapy response of superficial oral squamous cell carcinoma. *Journal of biomedical optics*, 21(1):018002–018002, 2016.

ANNOTATION: N=3

ABSTRACT: This study investigated whether diffuse optical spectroscopy (DOS) measurements could assess clinical response to photodynamic therapy (PDT) in patients with head and neck squamous cell carcinoma (HNSCC). In addition, the correlation between parameters measured with DOS and the crosslinking of signal transducer and activator of transcription 3 (STAT3), a molecular marker for PDT-induced photoreaction, was investigated. Thirteen patients with early stage HNSCC received the photosensitizer 2-(1-hexyloxyethyl)-2-devinylpyropheophorbide-a (HPPH) and DOS measurements were performed before and after PDT in the operating room (OR). In addition, biopsies were acquired after PDT to assess the STAT3 crosslinking. Parameters measured with DOS, including blood volume fraction, blood oxygen saturation (StO₂StO₂), HPPH concentration (cHPPH), HPPH fluorescence, and blood flow index (BFI), were compared to the pathologic response and the STAT3 crosslinking. The best individual predictor of pathological response was a change in cHPPH (sensitivity=60%, specificity=60%, sensitivity=100%, specificity=100%), while discrimination analysis using a two-parameter classifier (change in cHPPH and change in StO₂StO₂) classified pathological response with 100% sensitivity and 100% specificity. BFI showed the best correlation with the crosslinking of STAT3. These results indicate that DOS-derived parameters can assess the clinical response in the OR, allowing for earlier reintervention if needed.

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ANNOTATION: N=1

ABSTRACT: We present initial results obtained during the course of a Phase I clinical trial of 2-(1-hexyloxyethyl)-2-devinylpyropheophorbide-a (HPPH)-mediated photodynamic therapy (PDT) in a head and neck cancer patient. We quantified blood flow, oxygenation and HPPH drug photobleaching before and after therapeutic light treatment by utilizing fast, non-invasive diffuse optical methods. Our results showed that HPPH-PDT induced significant drug photobleaching, and reduction in blood flow and oxygenation suggesting significant vascular and cellular reaction. These changes were accompanied by cross-linking of the signal transducer and activator of transcription 3 (STAT3), a molecular measure for the oxidative photoreaction. These preliminary results suggest diffuse optical spectroscopies permit non-invasive monitoring of PDT in clinical settings of head and neck cancer patients.

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ANNOTATION: N=2

ABSTRACT: Photodynamic therapy (PDT) efficacy depends on the local dose deposited in the lesion as well as oxygen availability in the lesion. We report significant interlesion differences between two patients with oral lesions treated with the same drug dose and similar light dose of 2-

hexyloxyethyl

-2-devinylpyropheophorbide-a (HPPH)-mediated photodynamic therapy (PDT). Pre-PDT and PDT-induced changes in hemodynamic parameters and HPPH photosensitizer content, quantified by diffuse optical methods, demonstrated substantial differences between the two lesions. The differences in PDT action determined by the oxidative cross-linking of signal transducer and activator of transcription 3 (STAT3), a molecular measure of

accumulated local PDT photoreaction, also showed $<$, 100-fold difference between the lesions, greatly exceeding what would be expected from the slight difference in light dose. Our results suggest diffuse optical spectroscopies can provide in vivo metrics that are indicative of local PDT dose in oral lesions.

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- ANNOTATION: N=11, healthy
 ABSTRACT: We present a technique for measuring transient microscopic dynamics within deep tissue with sub-second temporal resolution, using diffusing-wave spectroscopy with gated single-photon avalanche photodiodes (APDs) combined with standard ungated multi-tau correlators. Using the temporal autocorrelation function of a reference signal allows to correct the temporal intensity autocorrelation function of the sample signal for the distortions induced by the non-constant average photon count rate. We apply this technique to pulsation-synchronized measurements of tissue dynamics in humans. Measurements on the forearm show no dependence on the pulsation phase. In contrast, the decay rate of the DWS signal measured on the wrist over the radial artery shows a pulsation-induced modulation of 60–90% consistent with pulsatile variations of arterial erythrocyte flow velocity. This might make time-resolved DWS interesting as a sensitive and fast method for investigating deep tissue perfusion, e.g. in intensive care.
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- ANNOTATION:
 ABSTRACT: Noninvasive, direct measurement of local muscle blood flow in humans remains limited. Diffuse correlation spectroscopy (DCS) is an emerging technique to measure regional blood flow at the microvascular level. In order to better understand the strengths and limitations of this novel technique, we performed a validation study by comparing muscle blood flow changes measured with DCS and Doppler ultrasound during exercise. Nine subjects were measured (all males, 27.4 \pm 2.9 years of age) for a rhythmic handgrip exercise at 20% and 50% of individual maximum voluntary contraction (MVC), followed by a post-exercise recovery. The results from DCS and Doppler ultrasound were highly correlated ($R = 0.99 \pm 0.02$). DCS was more reliable and less susceptible to motion artifact.
- [124] Parisa Farzam, Claus Lindner, Udo M Weigel, Maria Suarez, Alvaro Urbano-Ispizua, and Turgut Durduran. Noninvasive characterization of the healthy human manubrium using diffuse optical spectroscopies. *Physiological measurement*, 35(7):1469, 2014.
- ANNOTATION: N=32, healthy
 ABSTRACT: The abnormal, uncontrolled production of blood cells in the bone marrow causes hematological malignancies which are common and tend to have a poor prognosis. These types of cancers may alter the hemodynamics of bone marrow. Therefore, noninvasive methods that measure the hemodynamics in the bone marrow have a potential impact on the earlier diagnosis, more accurate prognosis, and in treatment monitoring. In adults, the manubrium is one of the few sites of bone marrow that is rich in hematopoietic tissue and is also relatively superficial and accessible. To this end we have combined time resolved spectroscopy and diffuse correlation spectroscopy to evaluate the feasibility of the noninvasive measurement of the hemodynamics properties of the healthy manubrium in 32 subjects. The distribution of the optical properties (absorption and scattering) and physiological properties (hemoglobin concentration, oxygen saturation and blood flow index) of this tissue are presented as the first step toward investigating its pathology.
- [125] Songfeng Han, Michael D Hoffman, Ashley R Proctor, Joseph B Vella, Emmanuel A Mannoh, Nathaniel E Barber, Hyun Jin Kim, Ki Won Jung, Danielle SW Benoit, and Regine Choe. Non-invasive monitoring of temporal and spatial blood flow during bone graft healing using diffuse correlation spectroscopy. *PloS one*, 10(12), 2015.

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- ANNOTATION: RMD,
ABSTRACT: Accident victims and victims of explosive devices often suffer from complex maxillofacial injuries. The lips are one of the most difficult areas of the face to reconstruct after an avulsion. Lip avulsion results in compromised facial esthetics and functions of speech and mastication. The process of reconstruction requires assessment of the vascularization of grafted ex vivo engineered tissue while it is buried underneath the skin. We describe the design and animal testing of a hand-held surgical probe based upon diffuse correlation spectroscopy to assess vascularization.
- [128] Chong Huang, Jeffrey P Radabaugh, Rony K Aouad, Yu Lin, Thomas J Gal, Amit B Patel, Joseph Valentino, Yu Shang, and Guoqiang Yu. Noncontact diffuse optical assessment of blood flow changes in head and neck free tissue transfer flaps. *Journal of biomedical optics*, 20(7):075008–075008, 2015.
- [129] Rickson C Mesquita, Angela DSouza, Thomas V Bilfinger, Robert M Galler, Asher Emanuel, Steven S Schenkel, Arjun G Yodh, and Thomas F Floyd. Optical monitoring and detection of spinal cord ischemia. *PLoS one*, 8(12):e83370, 2013.
- ANNOTATION: 10 adult sheep
ABSTRACT: Spinal cord ischemia can lead to paralysis or paraparesis, but if detected early it may be amenable to treatment. Current methods use evoked potentials for detection of spinal cord ischemia, a decades old technology whose warning signs are indirect and significantly delayed from the onset of ischemia. Here we introduce and demonstrate a prototype fiber optic device that directly measures spinal cord blood flow and oxygenation. This technical advance in neurological monitoring promises a new standard of care for detection of spinal cord ischemia and the opportunity for early intervention. We demonstrate the probe in an adult Dorset sheep model. Both open and percutaneous approaches were evaluated during pharmacologic, physiological, and mechanical interventions designed to induce variations in spinal cord blood flow and oxygenation. The induced variations were rapidly and reproducibly detected, demonstrating direct measurement of spinal cord ischemia in real-time. In the future, this form of hemodynamic spinal cord diagnosis could significantly improve monitoring and management in a broad range of patients, including those undergoing thoracic and abdominal aortic revascularization, spine stabilization procedures for scoliosis and trauma, spinal cord tumor resection, and those requiring management of spinal cord injury in intensive care settings.
- [130] Angela S Kogler, Thomas V Bilfinger, Robert M Galler, Rickson C Mesquita, Michael Cutrone, Steven S Schenkel, Arjun G Yodh, and Thomas F Floyd. Fiber-optic monitoring of spinal cord hemodynamics in experimental aortic occlusion. *The Journal of the American Society of Anesthesiologists*, 123(6):1362–1373, 2015.
- [131] Rajan S Gurjar, Suzannah L Riccardi, Blair D Johnson, Christopher P Johnson, Norman A Paradis, Michael J Joyner, and David E Wolf. Point-of-care optical tool to detect early stage of hemorrhage and shock. In *SPIE BiOS*, pages 89510K–89510K. International Society for Optics and Photonics, 2014.
- ANNOTATION: RMD,
ABSTRACT: There is a critical unmet clinical need for a device that can monitor and predict the onset of shock: hemorrhagic shock or bleeding to death, septic shock or systemic infection, and cardiogenic shock or blood flow and tissue oxygenation impairment due to heart attack. Together these represent 141 M patients per year. We have developed a monitor for shock based on measuring blood flow in peripheral (skin) capillary beds using diffuse correlation spectroscopy, a form of dynamic light scattering, and have demonstrated proof-of-principle both in pigs and humans. Our results show that skin blood flow measurement, either alone or in conjunction with other hemodynamic properties such as heart rate variability, pulse pressure variability, and tissue oxygenation, can meet this unmet need in a small self-contained patch-like device in conjunction with a hand-held processing unit. In this paper we describe and discuss the experimental work and the multivariate statistical analysis performed to demonstrate proof-of-principle of the concept.
- [132] *Twenty kHz ultrasound assisted treatment of chronic wounds with concurrent optic monitoring*, volume 9467, 2015.
- ANNOTATION: Number of subjects is not clear; wound area is primary outcome.
ABSTRACT: This paper describes a novel, wearable, battery powered ultrasound applicator that was evaluated as a therapeutic tool for healing of chronic wounds, such as venous ulcers. The low frequency and low intensity (100mW/cm²) applicator works by generating ultrasound waves with peak-to-peak pressure amplitudes of 55 kPa at 20 kHz. The device was used in a pilot human study (n=25) concurrently with remote optical (diffuse correlation spectroscopy - DCS) monitoring to assess the healing outcome. More specifically, the ulcers' healing status was determined by measuring tissue oxygenation and blood flow in the capillary network. This procedure facilitated an early prognosis of the treatment outcome and once verified - may eventually enable customization of wound management. The outcome of the study shows that the healing patients of the ultrasound treated group had a statistically improved (p<0.05) average rate of wound healing (20.6%/week) compared to the control group (5.3%/week). In addition, the calculated blood flow index (BFI) decreased more rapidly in wounds that decreased

in size, indicating a correlation between BFI and wound healing prediction. Overall, the results presented support the notion that active low frequency ultrasound treatment of chronic venous ulcers accelerates healing when combined with the current standard clinical care. The ultrasound applicator described here provides a user-friendly, fully wearable system that has the potential for becoming the first device suitable for treatment of chronic wounds in patient's homes, which - in turn - would increase patients' compliance and improve quality of life.

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- [134] David R Busch, Genevieve Du Pont-Thibodeau, Constantine Mavroudis, Ann McCarthy, Tiffany Ko, Madeline Winters, John Newland, Kobina Mensah-Brown, Kaitlin R Griffith, Jennifer Lynch, et al. Cerebral autoregulation during pediatric extracorporeal membrane oxygenation therapy. In *Clinical and Translational Biophotonics*, pages JTU3A–49. Optical Society of America, 2016.
- ANNOTATION: Neonatal ECMO
ABSTRACT: Extracorporeal membrane oxygenation therapy mechanically circulates externally oxygenated blood. We assess cerebral blood flow during perturbation of ECMO parameters using diffuse optical and correlation spectroscopies. We observe both regulated and passive pressure dependent flow.
- [135] David R Busch, Clara Gregori-Pla, Igor Blanco, Martina Giovannella, Christopher Favilla, Jennifer Lynch, Madeline Winters, Kobina Mensah-Brown, Tiffany Ko, Ann McCarthy, et al. Blood flow response to orthostatic challenges in health and diseased populations. In *Clinical and Translational Biophotonics*, pages TTh4B–5. Optical Society of America, 2016.
- ANNOTATION: Stroke, head-of-bed, pediatric through adult
ABSTRACT: Supine postures are utilized to increase cerebral blood flow following ischemic stroke. We find supine cerebral blood flow is lower than sitting flow in ~25% of subjects and that postural changes increase supine blood flow.
- [136] Madeline E Winters, Ann L McCarthy, Jennifer M Lynch, Tiffany Ko, Elizabeth Bixler, Kaitlin Griffith, David R Busch, Rui Xiao, William Gaynor, Susan Nicholson, et al. Abstract t mp63: Cardiac diagnosis is the major risk for stroke in neonates with complex congenital heart defects. *Stroke*, 46(Suppl 1):ATMP63–ATMP63, 2015.
- ANNOTATION: Neonate
ABSTRACT:
- [137] Jennifer M Lynch, John J Newland, Madeline Winters, David R Busch, Ann L McCarthy, Rui Xiao, Susan C Nicolson, Lisa M Montenegro, Stephanie Fuller, JW Gaynor, et al. Pre-operative cerebral hemodynamics from birth until surgery in neonates with critical congenital heart disease. *Circulation*, 132(Suppl 3):A19890–A19890, 2015.
- ANNOTATION: Neonate
ABSTRACT:
- [138] David R. Busch, Constantine D. Mavroudis, Jennifer M. Lynch, Tiffany S. Ko, Genevieve Du Pont-Thibodeau, Madeline E. Winters, Ann L. McCarthy, John J. Newland, Kobina G. Mensah-Brown, Kaitlin R. Griffith, Peter J. Schwab, Erin M. Buckley, Todd J. Kilbaugh, Arjun G. Yodh, and Daniel J. Licht. Continuous monitoring of cerebral hemodynamics during extracorporeal membrane oxygenation therapy. BiOS, San Francisco, CA USA, Feb. 2017. SPIE, SPIE.