Application for Pre-Doctoral Student Support – T32 NRSA Award

Applicant: Carson Hoffman

Advisor: Oliver Wieben, Ph.D., Associate Professor, Depts. of Medical Physics and Radiology

About the Applicant

Carson Hoffman is a third year student in the Medical Physics program who joined the UW-Madison and the Wieben lab in the summer of 2014 with a B.Sc. in Physics from Fresno State University. He passed his Ph.D. qualifier after 3 semesters in January 2016. At this time, he has fulfilled all his class requirements for the Medical Physics Ph.D. program, including the minor requirements (as confirmed by Tomy Varghese in March 2016). He plans to take his preliminary exam in the Summer semester 2017.

His research so far has focused on the assessment of vascular anatomy and hemodynamics with novel imaging approaches, namely 4D DSA, 4D Flow MRI, and 7D DSA. His mentor is Oliver Wieben and he has been partially co-advised by Chuck Mistretta in work related to 4D DSA and 7D DSA. He is co-author on two peer reviewed publications[1,2], co-author on four conference abstracts[16-19] and first author on six conference abstracts[11-15,20]. He has conducted flow analysis in two major studies, a hypercadnia challenge[1] and assessing vascular health in the progression of Alzheimer's Disease[2]. He has also developed analysis and visualization schemes for the novel 4D Flow MRI[11,12,15] and 7D DSA approaches, specifically in the context of brain aneurysms and arteriovenous malformations (AVMs). He is currently conducting validation studies for velocity assessment via 4D DSA tracer analysis[16] and particle imaging velocimetry (PIV). In a pilot study, he investigated abdominal flow distributions in patients with kidney cancer[13,14]. In future work, he will extend these concepts to cancer applications by developing analysis and visualization tools and clinical pilot studies, particularly for (1) renal cell carcinoma, (2) the treatment planning of liver cancer, specifically assessment in the donor, and (3) by assessing tumor vascularization by combining perfusion based measurements with 4D Flow MRI and 4D DSA measures. He is currently funded by a NIH R01 on the development for 4D/7D DSA (PI Mistretta). He is passionate about his research and wants to pursue an academic career in diagnostic medical imaging.

T32 requirements

We confirm our agreement with the 5 requirements outlined in the application guidelines, specifically:

1) There is a direct link between the pre-doctoral candidate's research project and the goal of the training grant (see research plan below).
2) The trainee is a resident and has not received prior NRSA institutional training grants and/or individual NRSA fellowship awards.
3) I and Carson are aware that he is expected to submit at least one manuscript as first author based on research supported in whole or in part by the training grant and I will provide annual updates to the training grant Program Director. I fully expect Carson to submit at least 2, possibly more, first author manuscripts based on research supported in whole or in part by the training grant.
4) I will supply any additional funding required to maintain the current UW stipend level of $xx,xxx (post-dissertator status) and other additional costs that are not fully supported by the training grant award and might occur.

5) In regards to fulfilling training requirements, Carson:
    a. Has taken Medical Physics 701, "Ethics and Responsible Conduct of Research in Medical Physics" in Spring of 2015.
    b. Will take MP 410 (Radiobiology) at the next time it is offered, which is in the spring of 2018 (this course is only offered biannually).
    c. Will take Oncology 401 – Introduction to Experimental Oncology in fall of 2017, thereby fulfilling the requirement for a course in cancer biology
    d. Will attend the two ICTR workshops on grant writing and on manuscript writing

Proposed Research

Background:

4D DSA and 7D DSA

4D DSA is a method developed by Chuck Mistretta to provide time-resolved 3D-DSA vascular volumes with better spatial and temporal resolution than that which is available with CT or MR angiography[4]. The Mistretta lab is currently working on the adding functionality to 4D DSA to derive mean blood velocities from the tracer kinetics. While such measures have much less information compared to 4D MR Flow (vessel segment average velocity vs ECG gated velocity vector fields), this information could be available during interventional procedures for immediate feedback. **7D DSA** is a new method proposed by Chuck Mistretta as well. It combines 4D Flow MRI data with 4D DSA data through a constrained reconstruction process for a combined dataset with the benefits of improved spatial resolution, contrast dynamics, and velocity vector fields. In contrast to 4D DSA, this approach will not be able to update all velocity information during a procedure since simultaneous MRI and DSA imaging is currently not possible.

4D Flow MRI at UW

Over the last decade, the Wieben lab has developed **PC VIPR[5]**, a novel **4D Flow MRI** approach[6], into a widely used diagnostic tool for the analysis of vascular anatomy and hemodynamics. With the concept of radial undersampling, blood velocity vector fields can be recorded throughout the cardiac cycle with large volumetric coverage while also providing high spatial and temporal resolution in clinically feasible scan times of < 5 min for cranial scans and <10 min for respiratory gated scans in the chest and abdomen[5]. This technique has been ported to and is currently supported by the UW team at 11 external. At the UW, more than 4,000 subjects have been scanned with PC VIPR, mostly in the context of research studies but also about 200 patients for clinical referrals. There is a wide range of applications and UW collaborations on the use of PC VIPR including assessing (1) cranial vascular health in aging and dementia; (2) liver hemodynamics in patients with portal hypertension using meal challenge paradigms; (3) placental health; (4) severity of renal artery stenosis with non-invasive pressure gradients; and (5) congenital heart disease – diagnosis, patient monitoring, and surgical planning.

Flow Measures and Cancer Treatment

The clinical use of MRI to obtain functional vascular information in the context of cancer diagnosis and treatment planning is primarily based on perfusion MRI, specifically using dynamic contrast-enhanced MRI for the characterization of lesions. While not explored yet in larger studies or projects, 4D Flow MRI has potential to **improve the care of cancer patients through the provided comprehensive information of vascular anatomy and macroscopic flow by itself or in addition to perfusion MRI.**

We have received several clinical referrals for 4D Flow MRI for surgical planning including cases for tumor resection because of insufficient information from standard clinical exams. One such example is described in detail in Figure 1 which represents one of several clinical referrals from Dr. Matsamuras Division of Vascular Surgery, here for a **Whipple procedure** used for patients with pancreatic cancer.

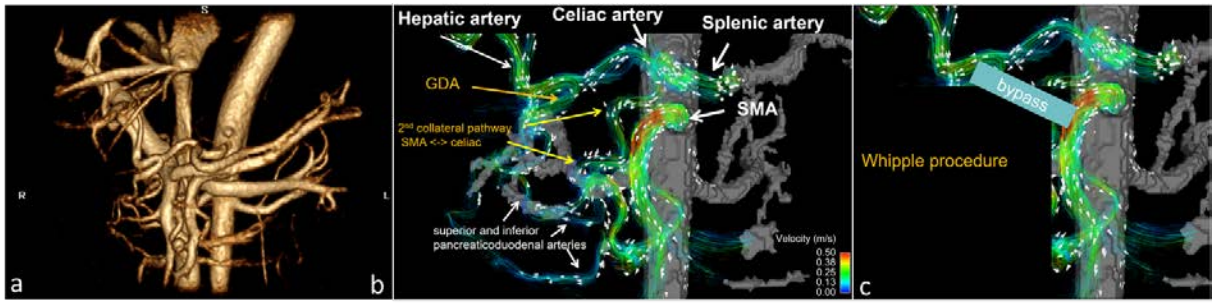

***Fig. 1**. 60y old female with a pancreatic mass, requiring the removal of the pancreas and duoduem with the Whipple procedure. The pre-surgical CT (a) indicates a celiac artery narrowing at the origin and several pancreaticoduodenal collateral, suggesting that blood flow to the liver was coming from the SMA. The important clinical question was which direction the flow was taking in the collateral vessels: anterograde or retrograde? The PC VIPR exam provided a high quality MR Angiogram (grayscale in b). One can see the normal collaterals between the SMA and GDA (point at superior and inferior pancreaticoduodenal arteries) and the abnormal 2nd collateral pathway between the SMA and celiac artery. This display also superimposes the flow direction onto the streamlines, showing that the flow through both, the GDA and the 2nd collateral pathway, is reversed: all blood entering the celiac artery is really supplied from the SMA. With a standard Whipple procedure, the pancreaticodudenal collaterals would be ligated and arterial blood flow to the liver would be cut off. Instead, the Whipple procedure was augmented using a bypass graft from the SMA to the proper hepatic artery in order to ensure adequate arterial blood supply to liver (c).*

We have received clinical referrals to provide presurgical information on the curative management of renal cell carcinoma (RCC). Recent advances in preoperative staging through imaging, and improvements in surgical techniques have made nephron-sparing surgery (NSS) an attractive alternative to radical nephrectomy in select patients. Dr. Jason Abel from the Dept. of Urology has used PC VIPR anatomy and flow measurements of the kidneys for the planning of **partial nephrectomies**. For now, the analysis focused on identifying assessory renal arteries (occurring in about 25% of patients) and quantifying the distribution of blood flow through the feeding renal artery (arteries) in the kidneys to guide decisions on the size and locations of sections to be removed. In future work, we seek to further improve the surgical technique by incorporating more detailed knowledge on arterial supply and venous return on a segmental level. We hypothesize that this approach can improve surgical decision making, e.g. by guiding section sizes and identifying patients at risk for the development of hypertension.

Cancer treatment in the abdomen often involves major changes in the vascular tree, resistance, and circulation patterns. That includes surgeries with resections, e.g. Whipple procedure, partial and full nephrectomy, and liver resection but also embolization and ablation treatments that shunt blood supply to previously highly perfused areas. The reaction of the body to adjust to the modified flow resistive network can be complicated to predict. For example, patients and even donors can suffer from major systemic hypertension and liver hypertension after the resection, embolization, or ablation of kidney or liver tissue. This also includes procedures such as Transcatheter arterial chemoembolization (also called transarterial chemoembolization or TACE). Thus, a better characterization of the hemodynamics before, during, and after the procedure via 4D Flow MRI or 4D DSA and 7D DSA has the potential to improve patient management.

In the brain, neoplastic processes such as metastatic disease and meningioma frequently involve the dural sinuses. Surgical resection is often limited by incomplete understanding of the degree of venous sinus involvement. 4D Flow MRI is well suited to augment routine cross sectional imaging to pre operatively assess dural sinus flow by providing high quality venous angiograms and quantitative measures of velocity and volume flow. These would be valuable to determine the degree of compromise of venous outflow. In the case of complete venous occlusion, 4D Flow MRI can identify collateral flow facilitating tumor resection.

In thermal ablation (laser, microwave, or rf) of nodules and lesions in the lungs, liver, and kidneys, blood transport is an influencing factor on temperature development during ablation. It is currently known as the 'major unknown' as it causes perfusion-mediated tissue cooling similar to a heat sink effect. Vessel vicinity and flow should be taken into account during the planning and preparation of tumor treatment in order to achieve better dosing for ablation.

Research / Training Plan

Timeline for the research conducted using training grant funding

The previous section has discussed several areas where knowledge of vessel anatomy and blood velocities and flow via 4D DSA or 4D Flow MRI could improve the care of cancer patients. To date, we have assisted in the workup of several individual clinical cases, but no larger scale or prospective studies have been conducted. For this training grant, we propose that Carson will **develop hemodynamic analysis and visualization tools** that can provide the basis for a more intuitive and reproducible analysis and visualization of the hemodynamic analysis specific to cancer applications. The availability of improved analysis and visualization tools will facilitate the use of these unique approaches in the clinic and research applications. We have ongoing collaborations with Drs. Jason Abel (Urology) and Luis Fernandez (Section of Liver and Kidney Surgery, Division of Transplantation), Dr. Paul Laeseke (Section: Interventional Radiology), and Dr. Shane Wells (Section: Abdominal Imaging and Intervention). Through these projects, Carson will apply the developed methods in clinical pilot studies in **the renal and hepatic vasculature**. He will also continue his work on the **validation of 4D DSA flow measures** which would provide flow measures during interventional procedures.

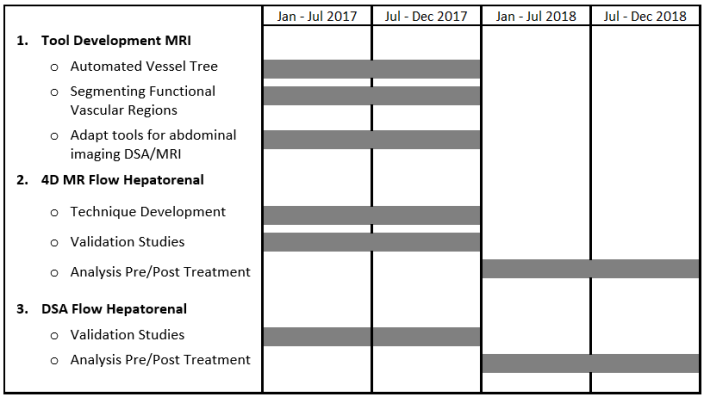

***Fig. 2**. Timeline of research conducted suing training grant funding*

Automated Vessel Tree Analysis

The Wieben group developed a sophisticated flow analysis tool for the automated analysis of cranial 4D Flow MRI data[7]. The tool supports an automated workflow that includes the generation of a vessel skeleton including labeling of all branches, subsequent placement of analysis planes for every voxel orthogonal to the vessel path, segmentation of the vessel boundaries of each plan using local parameters, and the export of various parameters for every plane including area, mean velocity, flow, forward flow, peak velocity, pulsatility index, resistive index, and more. It dramatically minimizes user interaction over

prior workflows, thereby (1) reducing processing time, (2) improving reproducibility, and (3) reducing data storage burdens by eliminating intermittent storage between programs. This tool has facilitated the analysis of large datasets such as Alzheimer's Disease[2, 8] and in MS patients[8].

The tool is well adapted for cranial imaging. However, it currently fails in applications below the neck where vessel pulsatility causes area changes and vessel displacement throughout the cardiac cycle. **Carson will implement extensions to the current automated vessel tree analysis tool by implementing a time-resolved skeleton and segmentation process.** He will investigate a constrained segmentation approach that incorporates knowledge from adjacent time frames to overcome the challenges of compromised SNR.

Segmenting Functional Vascular Regions

We will investigate a new concept that segments organs (brain, liver, kidney) into functional vascular regions based on the arterial tree. The starting point will be the skeleton generated with the Vessel Tree Analysis Tool. From that, a region growing algorithm with additional information (normal atlas, distance from branching points, …) will automatically derive vascular regions that are identified by their main supplying arterial branch. This is somewhat similar to work done in the lungs using the bronchopulmonary segmental anatomy of the lung (Fig. 3), which is easier because of fairly consistent anatomy among subjects and detectable image contrast changes between functional regions in CT images. This work will lay the foundation for **merging information from flow and perfusion data**. It will also help **to analyze the impact of embolizations, ablations, and resections in a more systematic fashion**.

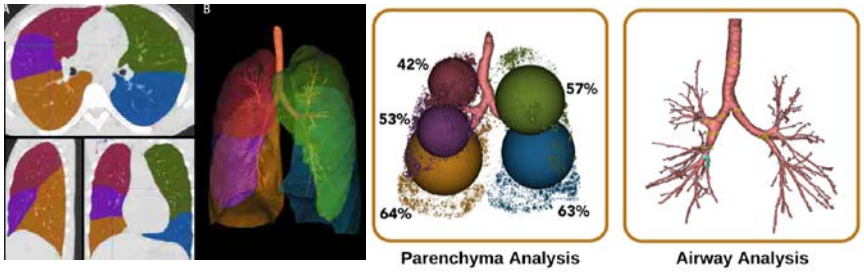

***Fig. 3**. Lung segmentation into functional units based on the bronchial tree (from Vida Diagnostics: https://vidadiagnostics.com). A similar scheme will be implemented for vascular tree segmentation, which will also allow for the fusion of perfusion and flow data.*

Hepatorenal Vascular Assessment

Renal Cell Carcinoma

As mentioned above, we have acquired PC VIPR datasets in 13 clinical referrals to provide presurgical information on the management of renal cell carcinoma (RCC). An analysis on seven of the subjects were completed measuring flow rates in eight locations in the arterial and venous systems. One of the most significant findings was a clear asymmetry of flow seen in all cases between the renal arteries not correlated with tumor location, which differs from the symmetric flow distribution seen in healthy volunteers. A study to compare pre and post surgery renal hemodynamics utilizing PC VIPR has been initiated to investigate (1) if the symmetric flow distribution is recovered post treatment (2) and if hemodynamic analysis (including flow asymmetry) is correlated with outcomes. Comprehensive analysis of lumen and hemodynamics can possibly detect damage from the necessary renal artery clamping during the procedure. Also, the effect of surgical procedures such as reconstruction or removal of the Inferior Vena Cava (IVC) due to cancer invasion are thought to result in hemodynamic changes but are currently not well understood. Our collaborator Dr. Jason Abel from the Dept. of Urology has great interest in all the mentioned areas.

Liver Transplants

We have extensive experience in the hemodynamic analysis of the liver, specifically in the context of portal hypertension[9, 10]. We have recently formed a new research initiative with Dr. Luis Fernandez (Section of Liver and Kidney Surgery, Division of Transplantation), Dr. Scott Reeder (Radiology), and Dr. Alejandro Roldan (Mechanical Engineering) to investigate the use of 4D Flow MRI in the planning of liver transplants for improved outcome for donors and recipients. Among tumors, hepatoblastoma (in children) and hepatocelllular carcinoma (in adults) are the most common forms that necessitate a liver transplant and the UW is revamping its liver transplant program. Fig. 4 shows an example PC VIPR imaging before and after a right lobe hepatectomy.

It is currently not possible to predict the effects of changes in mesenteric and portal hemodynamics in response to partial hepatectomy in vivo. We hypothesize that donors with a low hemodynamic response to a meal challenge will be at higher risk of developing complications related to portal hypertension such as thrombocytopenia, splenomegaly and ascites.

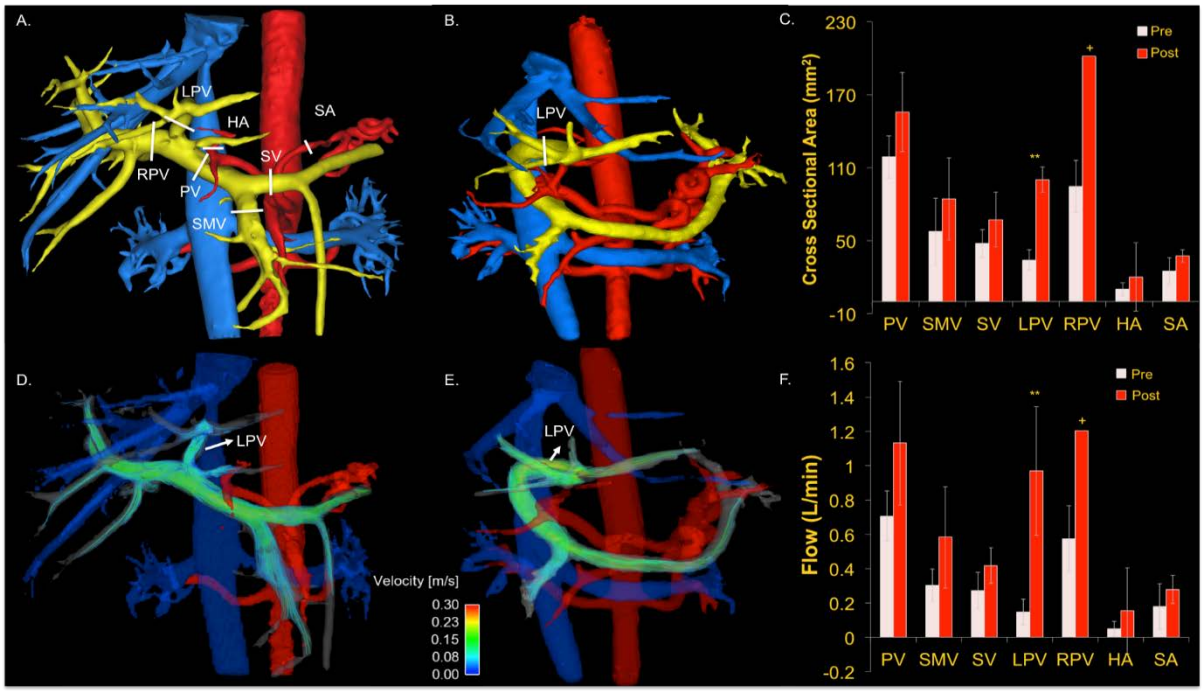

Fig. 4. *Visualization and quantification of hepatic blood flow and anatomy in a 33 year-old female (right-lobe hepatectomy).* ***A, B.*** *3D volume rendered images from complex difference dataset of 4D Flow MRI acquisition pre (A) and 2 weeks post surgery (B), respectively. White lines show the location of the measurement planes.* ***C.*** *Change in cross sectional vessel area.* ***D, E.*** *Streamlines with velocity distribution in the portal venous system.* ***F.*** *Blood flow changes in response to liver resection*.

Summary

Carson has been involved in the development, validation, and visualization of novel non-invasive angiography methods developed here at the UW, that convey detailed information on hemodynamics: 4D MR Flow, 4D DSA, and 7D DSA. These methods are currently mostly used in assessing vascular disease, but have the potential for high impact on the planning of surgery, ablation, and embolization of cancer patients. Projects with clinical collaborators that want to adopt DSA and MRI flow measures related to hepatorenal cancers have been initiated. If awarded funding, Carson could focus the remainder of his

predoctoral work on optimizing and applying advanced flow measurements to these applications. Through the training grant mechanism, Carson would acquire unique skills sets as well as a thorough background in cancer research so that he could continue to contribute as a cancer researcher in his future career.

Publications and References

1. Kellawan JM, Harrell JW, Schrauben EM, **Hoffman CA**, Roldan-Alzate A, Schrage WG, Wieben O. Quantitative cerebrovascular 4D flow MRI at rest and during hypercapnia challenge. *Magn Reson Imaging.* 2015.
2. Rivera-Rivera LA, Turski P, Johnson KM, **Hoffman C**, Berman SE, Kilgas P, Rowley HA, Carlsson CM, Johnson SC, Wieben O. 4D flow MRI for intracranial hemodynamics assessment in Alzheimer's disease. *J Cereb Blood Flow Metab.* 2015.
3. Rivera-Rivera LA, Turski P, Schrauben EM, Kilgas P, Johnson KM, Loecher M, Illingworth C, Johnson SC, Wieben O. 4D Flow MRI for intracranial hemodynamic assessment in Alzheimer's Disease. Paper presented at: International Society for Magnetic Resonance in Medicine, ISMRM 23rd Scientific Meeting and Exhibition, 2015; Toronto, Canada.
4. Davis B, Royalty K, Kowarschik M, Rohkohl C, Oberstar E, Aagaard-Kienitz B, Niemann D, Ozkan O, Strother C, Mistretta C. 4D digital subtraction angiography: implementation and demonstration of feasibility. *AJNR Am J Neuroradiol.* 2013;34(10):1914-1921.
5. Johnson KM, Lum DP, Turski PA, Block WF, Mistretta CA, Wieben O. Improved 3D phase contrast MRI with off-resonance corrected dual echo VIPR. *Magn Reson Med.* 2008;60(6):1329-1336.
6. Markl M, Frydrychowicz A, Kozerke S, Hope M, Wieben O. 4D flow MRI. *J Magn Reson Imaging.* 2012;36(5):1015-1036.
7. Schrauben E, Wahlin A, Ambarki K, Spaak E, Malm J, Wieben O, Eklund A. Fast 4D flow MRI intracranial segmentation and quantification in tortuous arteries. *J Magn Reson Imaging.* 2015;42(5):1458-1464.
8. Berman SE, Rivera-Rivera LA, Clark LR, Racine AM, Keevil JG, Bratzke LC, Carlsson CM, Bendlin BB, Rowley HA, Blennow K, Zetterberg H, Asthana S, Turski P, Johnson SC, Wieben O. Intracranial Arterial 4D-Flow is Associated with Metrics of Brain Health and Alzheimer's Disease. *Alzheimers Dement (Amst).* 2015;1(4):420-428.
9. Frydrychowicz A, Landgraf BR, Niespodzany E, Verma RW, Roldan-Alzate A, Johnson KM, Wieben O, Reeder SB. Four-dimensional velocity mapping of the hepatic and splanchnic vasculature with radial sampling at 3 tesla: a feasibility study in portal hypertension. *J Magn Reson Imaging.* 2011;34(3):577-584.
10. Roldan-Alzate A, Frydrychowicz A, Said A, Johnson KM, Francois CJ, Wieben O, Reeder SB. Impaired regulation of portal venous flow in response to a meal challenge as quantified by 4D flow MRI. *J Magn Reson Imaging.* 2015;42(4):1009-1017.
11. **Carson Hoffman**, Eric Schrauben, Oliver Wieben. MRI vessel slice tool visualization with an interactive 3-D display. *Accepted for presentation at ISMRM Annual Scientific Meeting Honolulu*. 2017;4759
12. **Carson Hoffman**, Gabe Shaughnessy, Oliver Wieben. Automated 4D Flow Conservation Utilizing Adjacency Matrices. *Accepted for presentation at ISMRM Annual Scientific Meeting Honolulu*.2017;4758
13. **Carson A. Hoffman**, Sylvana García-Rodríguez, Alejandro Roldán-Alzate, E. Jason Abel,Oliver Wieben, and Christopher J. Francois. 4D Flow Analysis of Renal Flow Changes due to Kidney Cancer. *Society of Magnetic Resonance Angiography,Chicago*.2016

14. **Carson A. Hoffman**, Sylvana García-Rodríguez, Alejandro Roldán-Alzate, E. Jason Abel,Oliver Wieben, and Christopher J. Francois. 4D Flow Analysis of Renal Flow Changes due to Kidney Cancer. *Gordon Research Conference: In Vivo Magnetic Resonance, Andover*.2016
15. **Carson Hoffman**, Eric Schrauben, Oliver Wieben. MRI vessel scalar data profile visualization with an interactive 3-D display. *ISMRM Workshop – Quantitative MR Flow: Innovation & Implementation for Clinical & Physiological Insights, San Francisco*.2016
16. Gabe Shaughnessy,Jimmy Xu, **Carson Hoffman**, Sebastian Schafer, Charles A. Mistretta,Charles M. Strother. Quantitative Flow and Velocity Measurements with 4D-DSA Using Fourier Analysis. *Radiological Society of North America, Chicago.*2016; NR364-SD-MOB4
17. Dahan Kim, **Carson Hoffman**, Oliver Wieben, and Kevin M. Johnson. Flow and Structure with Simultaneous Visualization of Registered 4D Flow and Black Blood MRI. *ISMRM Annual Scientific Meeting, Singapore.*2016; 2701
18. Benjamin P Aleckson, Mikhail Kellawan, John W. Harrell, Eric M. Schrauben, **Carson A. Hoffman**, Alejandro Roldan-Alzate, Oliver Wieben and William G. Schrage. Differential wall shear stress patterns in cerebral circulation of prediabetic adults: Possible evidence for increased stroke risk?. *American Physiological Society - Experimental Biology, San Diego.*2016; 1203.9
19. Leonardo A Rivera-Rivera, Patrick Turski, Eric M Schrauben, Phillip Kilgas, **Carson Hoffman**, Kevin M Johnson, Michael Loecher, Chuck Illingworth, Sterling C Johnson, and Oliver Wieben. 4D Flow MRI for intracranial hemodynamic assessment in Alzheimer's Disease. *ISMRM Annual Scientific Meeting, Toronto.*2015; PMID26661239
20. **Carson Hoffman**, David D. Lent. Analysis of Visual Characteristics related to Control of Travel Direction in Navigation of Ants. *Plenary Speaker 35th ANNUAL CENTRAL CALIFORNIA RESEARCH SYMPOSIUM, Fresno.*2014