Title: Four-dimensional-flow MRI and TSPO-PET as a predictive imaging modality for complications of aortic dissections

Rationale and Background. Aortic dissection (AD) is one of the most common catastrophic pathologies affecting the aorta leading to severe complications and death. ADs are classified based on the origin of the entry tear and its extension. Type A dissections originate in the ascending aorta, whereas the entry tear in Type B aortic dissections (TBAD) start distally to the left subclavian artery[1]. Although it has been generally accepted that initial management of uncomplicated TBAD is medical therapy, the outcomes of medical management for TBAD remain poor, with morbidity and mortality ranging from 10% to 25%[2,3] subsequently requiring surgical intervention in many patients[4,5,6]. Thus, the decision and timing of surgical intervention is of utmost importance to prevent potential future complications such as rupture or malperfusion, and delaying aneurysmal degeneration[7]. However, to date, we lack a reliable predictive tool to determine the risk of developing these complications and whether patients benefit from early surgical intervention. Computational tomography (CT) imaging has been utilized to predict the future outcome of patients with TBAD[8]. However, evidence is sparse, and only the relative and not the individual risk of rupture can be determined[9]. Hence, there is a critical need to understand the individual risk factors leading to progression and rupture of TBAD in patients on conservative medical therapy. Those patients at higher risk of rupture could be switched to surgical treatment.

To better predict TBAD outcomes, it is essential to investigate the disease beyond morphologic changes. AD was defined as the separation of the aortic wall layers[10]. In current pathologic perspectives, metabolic processes including chronic inflammation and proteolysis play a crucial role in the degeneration of the aortic wall, resulting in the formation, progression, and rupture of acute AD[11,12]. It has been shown 18F-FDG uptake is linked to active atherosclerotic inflammation within the aorta, carotid, iliac, femoral, and vertebral arteries[13,14,15]. Studies have also demonstrated abnormal 18F-FDG uptake in diseased thoracic aortas of patients with AD[16,17], and increased mortality and major adverse events at 3-year follow-up[18]. Although these studies demonstrated the potential utility of imaging marker for inflammation in TBAD, 18F-FDG suffers from the fundamental weakness that it is not specific to inflammation.

Translocator protein (TSPO) is an 18 kDa protein, composed of 5 transmembrane domains found on the outer mitochondrial membrane. TSPO is involved in the inflammation process. TSPO is a potentially specific diagnostic tool for vascular inflammation because of its high expression level in macrophages activated by cytokines. Studies have demonstrated that increased expression of TSPO is linked to the inflammatory responses in the cardiovascular system. In fact, a 2012 study using a TSPO tracer, 3H-PK11195, demonstrated its utility in imaging large vessel vasculitis. This study further demonstrated the lack of specific uptake in asymptomatic patients, confirming the selectivity of TSPO tracers. Our center has significant experience in a 2nd generation TSPO tracer – 18F-FEPPA, which will be used in this proposed study to investigate inflammation in TBAD patients. To our knowledge, there has been no study using TSPO PET for the management of medically controlled AAD patients.

Another additional diagnostic complement to TSPO tracer and CT Angiography is the modality of 4D flow MRI, which would greatly benefit the personalization of dissection characterization and risk stratification. 4D flow MRI enables the ability in a single scan to obtain flow data of the entire aortic volume in order to visualize complex temporal blood flow

patterns. Several studies have looked at its utility to better elucidate key pathologic processes of TBAD hemodynamic characteristics that are correlated with the rate of aortic expansion[19,20]. Furthermore, the ability to identify the hemodynamic behaviors of aortic dissections such as visualizations of fenestrations, helical flow patterns in false lumens, velocity, and stroke volume can have a major impact of not only triggering timing of intervention but playing a significant role in operative planning. Currently, there are no studies that combine 4D flow MRI and PET tracer 18F-FEPPA technology in the assessment of TBAD. Using these two modalities simultaneously we hope to develop a novel non-invasive prognostic imaging modality that will enable us to assess and manage TBAD patients.

Our simultaneous PET/MRI scanner is being upgraded to a newer version VE11P from VB20P at the end of August 2021, this major software upgrade finally enables 4D flow MRI imaging on this scanner. Currently, Stony Brook's PET/MRI research has been focusing on neuroimaging, with some oncological applications, we believe this is the optimal time to expand Stony Brook's PET/MRI research into cardiovascular research.

Specific Aim 1: Determine the feasibility of TSPO tracer 18F-FEPPA imaging in the diagnostic evaluation of TBAD. Although TSPO tracer has been used to evaluate active inflammation within vessels such as the aorta and carotid arteries (**Figure 1**), it has not been utilized in assessing aortic dissection. This study seeks to determine the feasibility of using TSPO PET MRI to image TBAD in a pilot study that includes twenty patients. We anticipate that TSPO could be used to visualize and assess the level of inflammation in these patients.

Specific Aim 2: Determine TSPO PET and/or 4D flow MRI could be used as a predictive tool for long-term type B dissection complications. There is a crucial need to predict the course of Type B dissection complications to decide on whether and when surgical intervention is required. Based on previous studies, we anticipate that the increased expression of TSPO PET MRI correlates with the level of atherosclerotic and inflammation in the aorta and a high level of risk for rupture and imminent serious complications. In this Aim, in our twenty-patient pilot sample size, we will investigate this relationship, and examine the sensitivity and specificity of this metric.

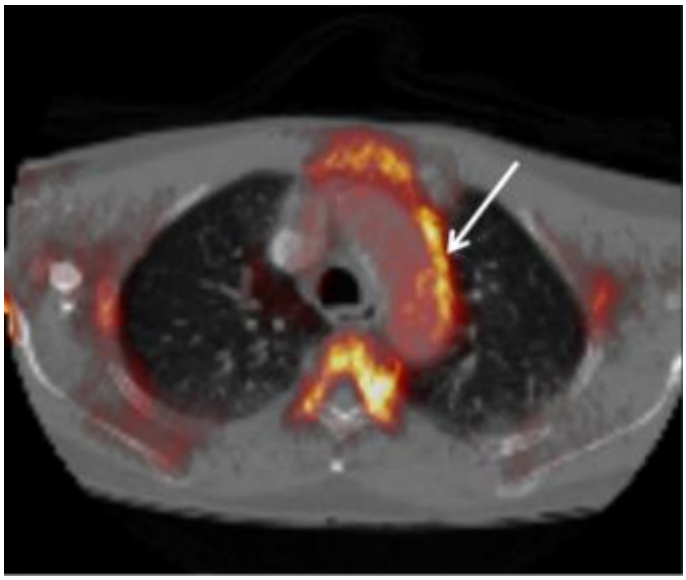

Figure 1. TSPO uptake in a patient with aortic inflammation due to vasculitis

Experimental Design & Preliminary Data. We propose a prospective study to recruit a total of twenty patients during two years who present to the Stony Brook emergency department with an acute uncomplicated TBAD. These selected patients will be followed over time with various imaging modalities in an attempt to elucidate key novel characteristics of aortic disease pathology that will be used to better able understand the necessity and/or timing of intervention. Initial CTA imaging will be acquired as the current standard of care at the initial time of presentation and subsequent days after. Once patients are medically stable and hemodynamically acceptable for discharge, patients will receive routine CTA for their one-month follow-up and in addition will also undergo 18F-FEPPA imaging using the simultaneously PET/MR scanner and 4D flow MRI.

Inclusion & exclusion criteria

Inclusion criteria: Acute uncomplicated type B aortic dissection. Over the age of 18 years old.

Exclusion criteria: No history of connective tissue disorder. Conversion to complicated aortic pathology prior to discharge or requiring intervention. MR contraindications. Participation in this study would lead to annual research radiation doses higher than the FDA limit.

Aortic dissections are one of the most pernicious disease pathologies of the vascular system that constitutes a true medical emergency. Although we have made extensive ground in regard to the diagnostic and treatments of aortic dissections, we have remained to stagnate in our current clinical abilities. Current and past clinical trials have focused on therapeutic devices for the treatment of aortic dissections, leaving a vacancy on potential developments to the diagnostic approach for the management of dissections. In addition, upon further literature review, there is a paucity of evidence on the diagnostic applicability of tracer PET MRI, in addition to 4D MRI flow.

Please describe how obtaining this award will allow you to compete for extramural funding; type of proposal, funding agency, and expected date of submission. Once feasibility is shown for TSPO tracer in the diagnostic evaluation of aortic dissections, we will pursue further funding options in order to advance this much-desired diagnostic tool and its application to fully complement therapy for aortic dissections. Such as pursuing grant funding from the NIH R01 application.

Study team: Prior to joining Stony Brook, Dr. Chuan Huang published some of the first PET/MRI studies on MR-assisted cardiac motion correction for PET imaging[21,22]. Similar to the heart, PET imaging of the aorta also suffers from cardiac motion blurring. Dr. Huang's expertise in PET cardiac motion correction is perfectly suited for this project.

References:

1. Chiesa R, Melissano G, Civilini E, de Moura MLR, Carozzo A, Zangrillo A. Ten years experience of thoracic and thoracoabdominal aortic aneurysm surgical repair: lessons learned. *Ann Vasc Surg*. 2004;18(5):514-520. doi:10.1007/s10016-004-0072-z

2. Nienaber CA, Eagle KA. Aortic Dissection: New Frontiers in Diagnosis and Management. *Circulation*. 2003;108(5):628-635. doi:10.1161/01.cir.0000087009.16755.e4

3. Suzuki T, Mehta RH, Ince H, et al. Clinical profiles and outcomes of acute type B aortic dissection in the current era: lessons from the International Registry of Aortic Dissection (IRAD). *Circulation*. 2003;108 Suppl 1:II312-II317. doi:10.1161/01.cir.0000087386.07204.09

4. Estrera AL, Miller CC, Goodrick J, et al. Update on outcomes of acute type B aortic dissection. *Ann Thorac Surg*. 2007;83(2):S842-S845; discussion S846-S850. doi:10.1016/j.athoracsur.2006.10.081

5. Tefera G, Acher CW, Hoch JR, Mell M, Turnipseed WD. Effectiveness of intensive medical therapy in type B aortic dissection: a single-center experience. *J Vasc Surg*. 2007;45(6):1114-1118; discussion 1118-1119. doi:10.1016/j.jvs.2007.01.065

6. Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA*. 2000;283(7):897-903. doi:10.1001/jama.283.7.897

7. Tintoiu IC, Elefteriades JA, Ursulescu A, Underwood MJ, Droc I. *New Approaches to Aortic Diseases from Valve to Abdominal Bifurcation*. Academic Press; 2017. https://play.google.com/store/books/details?id=fYyZDgAAQBAJ.

8. van Bogerijen GHW, Tolenaar JL, Rampoldi V, et al. Predictors of aortic growth in uncomplicated type B aortic dissection. *J Vasc Surg*. 2014;59(4):1134-1143. doi:10.1016/j.jvs.2014.01.042

9. Reeps C, Essler M, Pelisek J, Seidl S, Eckstein H-H, Krause B-J. Increased 18F-fluorodeoxyglucose uptake in abdominal aortic aneurysms in positron emission/computed tomography is associated with inflammation, aortic wall instability, and acute symptoms. *Journal of Vascular Surgery*. 2008;48(2):417-423. doi:10.1016/j.jvs.2008.03.059

10. Olsson C, Thelin S, Stahle E. Thoracic aortic aneurysm and dissection: Increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Journal of Vascular Surgery*. 2007;46(3):609. doi:10.1016/j.jvs.2007.07.017

11. Barbour JR, Spinale FG, Ikonomidis JS. Proteinase systems and thoracic aortic aneurysm progression. *J Surg Res*. 2007;139(2):292-307. doi:10.1016/j.jss.2006.09.020

12. Guo D-C, Papke CL, He R, Milewicz DM. Pathogenesis of thoracic and abdominal aortic aneurysms. *Ann N Y Acad Sci*. 2006;1085:339-352. doi:10.1196/annals.1383.013

13. Tahara N, Kai H, Yamagishi S-I, et al. Vascular Inflammation Evaluated by [18F]-Fluorodeoxyglucose Positron Emission Tomography Is Associated With the Metabolic Syndrome. *Journal of the American College of Cardiology*. 2007;49(14):1533-1539. doi:10.1016/j.jacc.2006.11.046

14. Rudd JHF, Warburton EA, Fryer TD, et al. Imaging Atherosclerotic Plaque Inflammation With [18F]-Fluorodeoxyglucose Positron Emission Tomography. *Circulation*. 2002;105(23):2708-2711. doi:10.1161/01.CIR.0000020548.60110.76

15. Dunphy MPS, Freiman A, Larson SM, Strauss HW. Association of vascular 18F-FDG uptake with vascular calcification. *J Nucl Med*. 2005;46(8):1278-1284. https://www.ncbi.nlm.nih.gov/pubmed/16085583.

16. Kuehl H, Eggebrecht H, Boes T, et al. Detection of inflammation in patients with acute aortic syndrome: comparison of FDG-PET/CT imaging and serological markers of inflammation. *Heart*. 2008;94(11):1472-1477. doi:10.1136/hrt.2007.127282

17. Ryan A, McCook B, Sholosh B, et al. Acute intramural hematoma of the aorta as a cause of positive fluorodeoxyglucose positron emission tomography/computed tomography. *J Thorac Cardiovasc Surg*. 2007;134(2):520-521. doi:10.1016/j.jtcvs.2007.02.049

18. Gorla R, Erbel R, Kuehl H, et al. Prognostic value of (18)F-fluorodeoxyglucose PET-CT imaging in acute aortic syndromes: comparison with serological biomarkers of inflammation. *Int J Cardiovasc Imaging*. 2015;31(8):1677-1685. doi:10.1007/s10554-015-0725-8

19. Clough RE, Waltham M, Giese D, Taylor PR, Schaeffter T. A new imaging method for assessment of aortic dissection using four-dimensional phase contrast magnetic resonance imaging. *J Vasc Surg*. 2012;55(4):914-923.

doi:10.1016/j.jvs.2011.11.005

20. François CJ, Markl M, Schiebler ML, et al. Four-dimensional, flow-sensitive magnetic resonance imaging of blood flow patterns in thoracic aortic dissections. *J Thorac Cardiovasc Surg*. 2013;145(5):1359-1366. doi:10.1016/j.jtcvs.2012.07.019

21. Huang C, Petibon Y, Ouyang J, et al. Accelerated acquisition of tagged MRI for cardiac motion correction in simultaneous PET-MR: Phantom and patient studies. *Medical Physics*. 2015;42(2):1087-1097. doi:10.1118/1.4906247

22. Petibon Y, Ouyang J, Zhu X, et al. Cardiac motion compensation and resolution modeling in simultaneous PET-MR: a cardiac lesion detection study. *Phys Med Biol*. 2013;58(7):2085-2102. doi:10.1088/0031-9155/58/7/2085

TRO Budget

FUSION AWARD – BUDGET (2021-2022)

Graduate Student - 100% effort, 12 person-months per year. Direct salary
This graduate student will assist in protocol development, data collection, and data analysis under supervision of Drs. Bannazadeh and Huang. She/he will assist with publications (abstracts, journal publications, grant reporting). $32000 per year will cover tuition cost as mandated by the institution.

Publication fee. $2000 per year

Scan fee. $6000

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES**.

NAME: Bannazadeh, Mohsen

eRA COMMONS USER NAME (credential, e.g., agency login): MOHSENBANNAZADEH

POSITION TITLE: Clinical Assistant Professor of Surgery

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Shahid Beheshti University of Medical Sciences (Tehran,Iran)	M.D.	01/2003	Medicine
Cleveland Clinic, (OH, USA)	Postdoctoral	06/2009	Vascular and Endovascular Surgery
Oakland University William Beaumont School of Medicine (MI, USA)	Residency	06/2015	General Surgery
Icahn School of Medicine at Mount Sinai (NY, USA)	Fellowship	06/2017	Vascular and Endovascular Surgery

A. Personal Statement

My medical training and extensive research experience in vascular diseases uniquely qualify me to complete the proposed project. At the national level, I have expertise in vascular and endovascular techniques to treat patients with vascular disorders. In my post-doctoral vascular fellowship at Cleveland Clinic, I accomplished multiple clinical and basic science research projects with local, national, and international presentation. I won prestigious Guthrie Award from Midwestern Vascular Society for my work in biodegradable stents. During my time at Stony Brook University, I cared for many patients with aortic dissection and their ominous complications from aneurysm to rupture, and ultimately death. I was deeply concerned by the suffering of these patients, but I also sought the opportunities to better understand the management of these critically ill patients. Lack of effective treatment for these patients deeply motivated me to find a feasible treatment modality.

I have extensive basic science research experience. During my vascular fellowship training, I won extramural funding to research vessel wall cell proliferation in response to endovascular balloon therapy. Since starting as an attending vascular surgeon at Stony Brook University Hospital, I also received a grant for clot geometry and its three dimensional properties. I am therefore uniquely positioned to complete the proposed experiments.

B. Positions and Honors

Positions and Employment

2007-2009 Postdoctoral Research Fellow, Cleveland Clinic, Cleveland, OH
2009-2015 Resident in General Surgery, Oakland University William Beaumont School of Medicine, MI
2012-2013 Postdoctoral Research Fellow, Oakland University William Beaumont School of Medicine, MI
2015-2017 Fellowship in Vascular Surgery, Mount Sinai, NY
2917-present Clinical Assistant Professor of Surgery, Stony Brook University, Stony Brook, NY

Other Experience and Professional Memberships

- Society of Vascular Surgery (SVS), Candidate Member
- American College of Surgeon (ACS), Candidate Member
- New York Society of Vascular Surgery (NYSVS)
- Midwestern Vascular Surgical Society (MVSS), Resident Member (2009-2015)
- Detroit Surgical Association, Resident Member (2009-2015)
- General Medical Council, London, UK, Member (2006)

Honors

- Stony Brook University Small Grant Prize, 2018
- New York Society for Vascular Surgery (NYSVS) Research Grant Prize 2017
- Veith Symposium Fellowluminaries Case Competition, Nov 2016 Finalist, New York, NY
- EVS Annual Meeting Travel/Mock Oral Scholarship, Sep 2016, Philadelphia, PA
- The New York Society for Vascular Surgery (NYSVS) 2016 Research Scholarship Award, New York, NY
- SCVS Annual Meeting Fellows Program Travel Scholarship, March 2016, Las Vegas, Nevada
- SCVS Annual Meeting Incoming Fellows Program Travel Scholarship, March 2015, Miami, Florida
- Outstanding Resident Research, 2014 Michigan Thoracic and Cardiovascular Surgeons Annual Meeting, Mackinac Island, Michigan
- D. Emericl Szilagy Michigan Vascular Prize, 2014 Michigan Chapter of the American College of Surgeons, Petosky, Michigan
- Alexander J. Walt Award , 2014 Michigan Chapter of the American College of Surgeons Annual Meeting and Resident Research Competition, Petosky, Michigan
- Society of Vascular Surgery Travel Scholarship, 2013 Vascular Annual Meeting, San Francisco, California
- Charles C. Gutherie Aware for Basic Science Research, 33rd Annual Meeting of the Midwestern Society of Vascular Surgery, Chicago, Illinois
- Cleveland Vascular Society Research Competition Award Finalist 2009, Cleveland, Ohio
- Cleveland Vascular Society Research Competition Award Finalist 2008, Cleveland, Ohio

GRANTS

- SUNY COVID-19 Seed grant , 2020
- Spatial and temporal characterization of fibrin as it pertains to Deep Vein Thrombosis and its resolution 2018 Research Committee

  Department of Surgery, Stony Brook University, Stony Brook, NY
- The In Vitro Effect of Antimyoprolifratives on smooth muscle cell proliferation and migration based on patient phenotype

  The New York Society for Vascular Surgery (NYSVS) Research Grant 2017, New York, NY

C. Contribution to Science

1. **Bannazadeh M**, Beckerman B, McKinsey JF. Comparison of Fenestrated Endografts And the Snorkel Technique., 2020 JVS-D-18-01287.

2. **Bannazadeh M**, Tadros RO, McKinsey JF, Chander R, Marin ML, Faries PL. Contemporary Management of Type B Aortic Dissection in the Endovascular Era. Journal of surgical technology. 2016 Apr; 28:214-21.
3. Jenkins C, **Bannazadeh M**, Adeyemo A, Altshuler J, Brown OW, Sakwa M. Non-Operative Management of Atypical Type A Aortic Dissection Has High Mortality. In preparation for submission to JVS.

4. **Bannazadeh M**, Jenkins C Forsyth A, Kramer J, Aggarwal A, Long G. Outcomes for Concomitant Common Iliac Artery Aneurysms after EVAR. Journal of Vascular Surgery. J Vasc Surg. 2017 Jul 8. pii: S0741-5214(17)31109-6.

5. **Bannazadeh M**, Jenkins C, Adeyemo A, Altshuler J, Brown OW, Sakwa M. Aneurysmal degeneration in patients with Type B Aortic Dissection. Annals of Vascular Surgery. 2016 Oct;36:121-126.

6. 8.Adeyemo A, **Bannazadeh M**, Bednarz P, Shellnut J, Barkel D, Wasvary H, Riggs T. Does Sedation Type Affect Colonoscopy Perforation Rate? The Disease of Coloon and Rectum. 56(4). 2014 Jan;57(1):110-4.

7. Sarac TP, **Bannazadeh M**, Rowan AF, Bena J, Srivastava S, Eagleton M, Lyden S, Clair DG, Kashyap V. Comparative predictors of mortality for endovascular and open repair of ruptured infrarenal abdominal aortic aneurysms. Annals of Vascular Surgery. 2011 May;25(4):461-8.

8. Arthurs ZM, Titus J, **Bannazadeh M**, Eagleton MJ, Srivastava S, Sarac TP, Clair DG. A comparison of endovascular revascularization with traditional therapy for the treatment of acute mesenteric ischemia. Journal of Vascular Surgery. 2011 Mar;53(3):698-704; discussion 704-5.

9. Kashyap VS, Gilani R, Bena JF, **Bannazadeh M**, Sarac TP. Endovascular therapy for acute limb ischemia. Journal of Vascular Surgery. 2011 Feb;53(2):340-6.

10. **Bannazadeh M**, Altinel O, Kashyap VS, Clair DG, Sarac TP. Patterns of radiation exposure in the endovascular era: Impetus for further innovation. Journal of Vascular Surgery. 2009, 49 (6): 1520-1524

11. **Bannazadeh M**, Sarac T, Srivastava S, Ouriel K, Clair D. Reoperative Lower Extremity Revascularization With Cadaver Vein for Limb Salvage. Annals of Vascular Surgery. 2009, 23(1): 24-31.

12. **Bannazadeh M**, Sarac T. Renal Artery Stenting: Efficacy and Complications. Current Hypertension Reviews. 2009, 5(1): 7-12.

13. Sarac T, Kashyap V, **Bannazadeh M**, Lyden S, Ouriel K, Clair D. Midterm Outcome Predictors of Lower
14. Extremity Atherectomy Procedures. Journal of Vascular Surgery. 2008, 48(4): 885-890.

15. Kramer A, Galvagni P, Mertens R, Valdes F, Marine L, **Veith F**, Zarins C, **Bannazadeh M**, Clair D, Sarac T. Early clinical results of a tissue (peritoneal) lined stent grafts for superficial femoral artery occlusive disease. American journal of cardiology. 2007 Oct; 100(8): 120L.

16. Silveira PG , Kramer A, **Veith F**, **Bannazadeh M**, Clair D, Sarac T. Technical Details and Early Clinical Results of a Tissue Lined Self Expanding Stent for Superficial Femoral Artery Occlusions. Journal of Vascular and Interventional Radiology. 2007 Dec; 18(12): 1416.

Complete List of Published Work in MyBibliography:

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https://scholar.google.com/citations?view_op=list_works&hl=en&hl=en&user=9DVFk3AAAAAJ&sortby=pubdate