Title: **Patent foramen ovale, right-to-left shunts, and the association with perioperative ischemic stroke**

Sponsor Name: **Sundry**

PI Name: **Eikermann, Matthias** Protocol #: **2017P000260** Type: **New Protocol**

Date Received: **February 03, 2017**

Study Staff

Name	Role	Degree	Organization	Citi Certified
Eikermann, Matthias	Principal Investigator	MD, Ph.D	MGH > Anesthesia	2/18/2015
Yeung, Pui	Co-Investigator		MGH > Anesthesia	1/3/2017

Signatures

PI Name: Eikermann, Matthias, MD,Ph.D
Authenticated: February 03, 2017

Sponsor Funding: SUNDRY

Select the source of funding that will be used to support the proposed research:

- ○ Government / Foundation / Other Non-Profit
- ○ Corporate
- ○ Institutional Award
- ⊙ Department Funds
- ○ None

Enter department name:

10AA-MGH

Enter Peoplesoft fund # (if known):

222302

Is there a research fund, gift or sundry account supporting this study?

⊙ Yes ○ No

InfoEd proposal number (read-only field):

2013A050514

Enter Principal Investigator name (if different):

Medicare Coverage Analysis Requirement

Does the protocol for this study involve any items or services that will be billed to Medicare/private insurance, including study-specific procedures or those considered usual and customary care ("standard of care") outside the trial context?

○ Yes ⊙ No

NOTE: If you are unsure how to answer this question, please contact Sarah Bednar at Partners Clinical Trials Office at 617-954-9364, or for NWH investigators, please contact Jayita Sen at 617-243-6517 for more information.

Is this the primary source of funding?

○ Yes ⊙ No ○ Not applicable

Sponsor Funding: SUNDRY

Select the source of funding that will be used to support the proposed research:

○ Government / Foundation / Other Non-Profit

○ Corporate

○ Institutional Award

⊙ Department Funds

○ None

Enter department name:

10AA-MGH

Enter Peoplesoft fund # (if known):

220860

Is there a research fund, gift or sundry account supporting this study?

⊙ Yes ○ No

InfoEd proposal number (read-only field):

2012A051252

Enter Principal Investigator name (if different):

Medicare Coverage Analysis Requirement

Does the protocol for this study involve any items or services that will be billed to Medicare/private insurance, including study-specific procedures or those considered usual and customary care ("standard of care") outside the trial context?

○ Yes ⊙ No

NOTE: If you are unsure how to answer this question, please contact Sarah Bednar at Partners Clinical Trials Office at 617-954-9364, or for NWH investigators, please contact Jayita Sen at 617-243-6517 for more information.

Is this the primary source of funding?

⊙ Yes ○ No ○ Not applicable

Will the funding cover all subject study-related drugs, devices, procedures, tests, and visits?

○ Yes ○ No ⊙ Not applicable (no subject study-related costs)

Health / Medical Records

More detailed descriptions of specific questions/categories below can be found in the Research Navigator "Specialized Forms" section under the Apply for IRB Approval. See here.

1. Purpose

Briefly describe the purpose of the research:

Patent foramen ovale (PFO), the persistence of a flap-like opening in the embryonic atrial septum, is one of the commonest cardiac anomalies in the general population. The majority of PFOs remain undetected in healthy individuals, but studies have reported an incidence of 18-34.3% depending on age and diagnostic method.[1, 2] In usual circumstances, higher mean left atrial pressures create a functional closure of the PFO. The pathological significance of PFO lies in its potential transition to a right-to-left intracardiac shunt when there is reversal of the normal inter-atrial pressure gradient. Alongside other causes of right-to-left shunting, such as atrial septal defect (ASD) and ventricular septal defect (VSD), this group of structural cardiac anomalies poses the threat of paradoxical embolism and ischemic stroke.[3]

There has been a steadily increasing interest in the relationship between right-to-left shunts, in particular PFO, and stroke since 1990s. One of the earliest studies of this relationship found a significantly higher prevalence of PFO in a group of 60 patients with stroke than in patients without (40% vs 10%, P<0.001).[4] Further analyses showed an even higher prevalence of PFO in patients with cryptogenic stroke than those with an identified cause of stroke (48.8% vs 21%, P<0.05). These findings have been replicated in multiple observational studies.[5-7] A meta-analysis confirmed the increased prevalence of PFO in patients younger than 55 years with stroke (odds ratio 3.1, 95 percent confidence interval 2.29 to 4.21), and again, particularly with cryptogenic stroke (odds ratio 5.1, 95 percent confidence interval 3.24 to 7.75).[8] Despite these efforts, the controversy surrounding the association of right-to-left shunts and stroke continues, largely due to inconclusive evidence from small prospective trials[9-11] and lack of high quality observational studies that allow for adequate confounder control.

Perioperative stroke is a devastating complication for the surgical patient, with implications on postoperative morbidity, mortality, and discharge disposition.[12] The incidence depends on the type and complexity of surgical procedure, ranging from 0.2-1% for general surgical patients[13] to 1.9-9.7% for patients undergoing cardiac surgery,[14] as well as the age and coexisting risk factors of the patients. The potential of right-to-left shunts in causing ischemic stroke is of particular concern in the perioperative period. Physiologic changes during surgery such as hemorrhage, mechanical ventilation, and the administration of anesthesia directly affect intra-atrial pressures and may modify the direction or increase the degree of shunting in patients with pre-existing intracardiac defects. Subsequently, patients undergoing surgery and anesthesia may be exposed to an excess risk of stroke from paradoxical embolism. With the advance of percutaneous closure devices[15] for repair of such lesions, studies are urgently needed to identify patients who may benefit from preventive treatment.

There is a lack of literature on the specific association between right-to-left shunt and perioperative stroke. Krasuski et al retrospectively reviewed the intraoperative transesophageal echocardiograms of 13092 patients undergoing cardiac surgery, and found no difference in incidence of in-hospital death and postoperative stroke between patients with and without incidental finding of PFO.[16] The major limitation of this study is that it excluded over 1000 patients with PFOs or ASDs diagnosed preoperatively (presumably larger and more physiologically significant) and considered only those detected incidentally during surgery by direct visualization or transesophageal echocardiography (likely much smaller with limited potential for right-to-left shunting).

Our group recently reported an increased risk of perioperative stroke in patients with migraine.[17] In post hoc exploratory analysis, the presence of a possible right-to-left shunt in migraineurs was found to be a potential independent predictor of perioperative stroke with a relative excess risk of 4.1. We therefore designed the current study to directly investigate the impact of PFO and other right-to-left shunts on perioperative stroke and other outcomes. The primary outcome is perioperative ischemic stroke within 30 days of surgery. The secondary outcomes are hospital length of stay, 30 day hospital readmission, and 30 day mortality.

References

1. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17-20.
2. Lynch JJ, Schuchard GH, Gross CM, Wann LS. Prevalence of right-to-left atrial shunting in a healthy population: detection by Valsalva maneuver contrast echocardiography. Am J Cardiol 1984;53:1478-80.
3. Srivastava TN, Payment MF. Images in clinical medicine. Paradoxical embolism--thrombus in transit through a patent foramen ovale. N Engl J Med 1997;337:681.
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9. Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001;345:1740-6.
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11. Meissner I, Khandheria BK, Heit JA, et al. Patent foramen ovale: innocent or guilty? Evidence from a prospective population-based study. J Am Coll Cardiol 2006;47:440-5.
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14. Bucerius J, Gummert JF, Borger MA, et al. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. Ann Thorac Surg 2003;75:472-8.
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16. Krasuski RA, Hart SA, Allen D, et al. Prevalence and repair of intraoperatively diagnosed patent foramen ovale and association with perioperative outcomes and long-term survival. JAMA 2009;302:290-7.
17. Timm FP, Houle TT, Grabitz SD, et al. Migraine and risk of perioperative ischemic stroke and hospital readmission: hospital based registry study. BMJ 2017;356:i6635.

Data resulting from this research will be used for the following. Check all that apply.

- ☑ Publication
- ☑ Oral Presentation

☐ Other

Will data resulting from this research ever be submitted to the FDA?

○ Yes ⊙ No

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2. Study Population

Describe the study population, e.g., age, gender, diagnosis. Note: Healthcare providers may be considered subjects if you are studying provider behavior or performance, or analyzing patient outcomes based on provider. In such cases, you must consider the privacy risks and privacy rights of providers.

Data from all patients who underwent surgery under general anesthesia between January 2007 and December 2015 (inclusively) at Massachusetts General Hospital and two affiliated community hospitals (Mass General West Waltham, and Mass General / North Shore Center for Outpatient Care) will be reviewed. This database of patients has been used for earlier projects approved by Partners IRB[17,18] (Partners IRB protocol numbers 2015P002660 and 2013P001954).

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3. Source of Health / Medical Information

Indicate:

☑ Partners Sites

Partners Sites - Check all that apply:

☐ BWH
☐ Faulkner
☑ MGH
☐ NWH
☑ NSMC
☐ PCHI
☐ SRH
☐ McLean
☑ Other

Enter the other sources of health / medical information and move to the box on the right.

Mass General West – Waltham

☐ Non-Partners Sites
☐ Network Sites

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4. Data To Be Collected / Obtained

Check all that apply.

Administrative:

- ☑ Billing data
- ☑ Coded encounter data (diagnoses, procedures, dates)
- ☑ Demographic data (age, gender, vital status)
- ☑ Personal data (name, address, PCP)

Health / Medical:

- ☐ Allergies
- ☑ Discharge Summary
- ☐ Doctors Orders
- ☑ History / Physical
- ☐ Immunizations
- ☑ Medication List
- ☑ Office / Clinic Notes
- ☑ Operative / Procedure Notes (e.g. endoscopy)
- ☑ Pharmacy
- ☑ Problem List

Health/Medical Reports/Results:

- ☑ Blood Bank
- ☑ Laboratory
- ☑ Pathology reports (reports only). Complete the Excess Human Material form for use of tissue/slides instead of this form.
- ☑ Radiology

Sensitive/Personal Information:

- ☑ HIV Status
- ☑ Mental Health
- ☐ Reproductive History (e.g., abortions)
- ☐ Sexual Behavior/Sexually Transmitted Diseases
- ☑ Substance Abuse (e.g., drug or alcohol abuse)
- ☐ Other potentially stigmatizing behaviors

Will any Sensitive/Personal Information listed above be collected?

- ⊙ Yes
- ○ No

Explain why the sensitive/personal data checked above is needed to achieve the goals of the study:

The HIV status and mental health information are necessary in order to compute the Charlson comorbidity index (CCI), one of the potential confounders in our study of the association between PFO or right-to-left shunts and perioperative ischemic stroke. Alcohol abuse is another confounder that needs to be adjusted for during our regression analysis.

Other Health/Medical Information:

☑ Other

Specify:

Data are obtained from the MetaVision Anesthesia Information Management System (AIMS) (iMDsoft, Dedham, MA), the Research Patient Data Registry (RPDR), and Enterprise Performance Systems Inc (EPSi) (Allscripts Healthcare). The AIMS prospectively collects intraoperative data including physiological parameters such as blood pressure, ventilator and respiratory indices, administered drug doses, and fluid volumes. This is matched to the patients demographic data and pre-/post-procedural condition using RPDR, a centralized clinical data warehouse that compiles health records and billing data from various Partners hospital systems specifically for research purposes. Information on hospital length of stay and costs will be collected through EPSi. Work relative value units (work RVU), a marker of operation procedural complexity, will be recorded.

Have you created a data collection form or other tool for data collection?

⊙ Yes ○ No

NOTE: If Yes, attach a data collection form in the Attachments section of this application using the Attachment type "Data Collection Form."

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5. Data To Be Requested From The Following Time Period (Encounter Dates)

Indicate the time period of interest for your study, e.g. 01/01/2000 - 01/01/2005. Prospective reviews may be allowed, usually limited to 5-7 years in the future. The end date can be extended by amendment.

From (mm/yyyy):

01/2007

To (mm/yyyy):
For future data, use anticipated project end date.

12/2015

NOTE: This information is needed for the IRB to determine whether the research use of the health/medical information meets the criteria for an exemption from the requirement for IRB review. For more information about HUMAN SUBJECTS RESEARCH or EXEMPT RESEARCH, see the policy 'Exempt Human-Subjects Research.'

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6. Protected (Identifiable) Health Information

PHI refers to health/medical information that is accompanied by any of the listed 18 HIPAA identifiers or by a code where the key to the code that links to the identifiers is accessible to investigators. DE-IDENTIFIED DATA (without any identifiers or codes that link back to individuals) are not considered PHI, and are not subject to HIPAA regulations.

Will you be recording any of the identifiers listed above with the data or using a code to link the data to any of the identifiers? If yes, than under the HIPAA Privacy Rule provisons the data cannot be considered de-identified and authorization from the subject or a waiver of authorization must be granted by the IRB. When answering this question, consider the need for recording dates or retaining direct identifiers, such as name and/or medical record number, to link data from multiple sources, to avoid duplicating records, or for QA purposes. NOTE: If you are recording medical record number or other identifiers, even if temporarily for QA purposes or to avoid duplicating records, then answer "Yes".

◉ Yes ○ No

Check the identifiers that will be recorded with or linked by code to the data.

☐ Name

☐ Social Security Number

☑ Medical record number

☐ Address by street location

☐ Address by town / city / zipcode

☑ Dates (except year), e.g., date of birth; admission / discharge date; date of procedure; date of death

☐ Telephone number

☐ Fax number

☐ Electronic email address

☐ Web URLs

☐ Internet protocol (IP) address

☐ Health plan beneficiary number

☐ Account number

☐ Certificate / license number

☐ Vehicle identification number and serial number, including license plate number

☐ Medical device identifiers and serial numbers

☐ Biometric identifiers (finger and voice prints)

☐ Full face photographic image

☐ Any other identifier; or combination of identifiers likely to identify the subject (e.g., Pathology Accession #)

Explain why it would be impossible to conduct the research without access to and use of identifiable health / medical information. For example, the data cannot be obtained from electronic health / medical records or databases without access to identifiers or identifiers are needed for prospective data collection.

The medical records number are necessary to link patient data among the MetaVision Anesthesia Information Management System (AIMS), the Research Patient Data Registry (RPDR), and Enterprise Performance Systems Inc (EPSi). Dates such as date of surgical procedure and date of discharge are necessary to calculate the hospital length of stay after surgery.

Will identifiers be removed from the data and destroyed after all of the data has been collected, the study has been completed, or all regulatory and sponsor obligations have been met, consistent with regulatory and institutional research record keeping requirements?

For guidance, see the PHRC Recordkeeping and Record Retention Requirements document.

◉ Yes ○ No

NOTE: Federal regulations mandate that, under a Waiver of Consent / Authorization, identifiers be destroyed as early as possible. De-identified datasets may be retained indefinitely.

6A. Waiver of Informed Consent / Authorization

Explain why the risk to subjects, specifically the risk to privacy, is no more than minimal risk. When addressing this question, describe the measures you have put in place to protect the privacy of subjects and confidentiality of the data; for example: (1) identifiable health information will be stored on a computer on the Partners network with password protections enabled and anti-virus software or an encrypted laptop, with access to data limited to study staff; (2) name and/or medical record number will be replaced with a study ID or code and the key to the code stored in a password protected file; (3) direct identifiers, such as name and medical record number, will be removed once all of the data is collected and analysis performed on de-identified data.

The risk to subjects and their privacy is no more than minimal risk. Identifiable health information will be stored on a computer on the Partners network with password protections enabled and anti-virus software or on an encrypted laptop, with access only limited to study staff. Once data collection is completed, patient identifiers such as name and medical record number will be removed, and subsequent analysis will be performed on de-identified data.

Explain why the research could not practicably be carried out without the waiver of consent / authorization. When addressing this question, consider the difficulty in locating individuals who may have moved, the number of subjects and cost and use of limited resources of locating individuals and sending letters and consent forms, and the impact on the scientific validity of the study if you could use only data of individuals from whom you were able to obtain informed consent.

We will be analyzing a large historical surgical cohort consisting more than 100,000 patients. It will cost prohibitive and a potentially poor use of limited resources to obtain consent from each subject. There will also be difficulty in

locating individuals who may have moved. If only data of individuals from whom we are able to obtain informed consent could be used, our sample size will be greatly decreased and the scientific validity will be impaired.

NOTE: "Only in a few research studies would it be impossible to obtain informed consent; however in many studies the financial cost would be prohibitive and a potentially poor use of limited research resources." Ensuring Voluntary Informed Consent and Protecting Privacy and Confidentiality, National Bioethics Advisory Commission.

Explain why the rights and welfare of the subjects will not be adversely affected by the waiver of consent / authorization. When addressing this question, consider the individual's right to privacy and the measures you have put in place to protect the privacy of subjects and confidentiality of any data and any health/medical implications for subjects; for example: (1) identifiable data will be stored securely with access limited to study staff; (2) information resulting from this study will not have any important health/medical implications for subjects.

The rights and welfare of the subjects will not be adversely affected by the waiver of consent. All identifiable health information will be stored on a computer on the Partners network with password protections enabled and anti-virus software or on an encrypted laptop, with access only limited to study staff. Moreover, information resulting from this study will not have any important health / medical implications for the subjects.

NOTE: If the research uncovers information about the subjects that has important health / medical implications for them, contact the PHRC to discuss the appropriate process for providing subjects with additional pertinent information.

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7. Research Data

How will research data be recorded and stored?

☑ Electronically

Electronic Research Data

What type of device will the research data be accessed and stored on? Check all that apply.

☐ Desktop computer

☑ Portable device i.e., Laptop, Netbook, Tablet, iPod computer, Cell/Smart phone

☐ USB Flash/Thumb, External Hard Drive

☐ Other device

Portable devices can include cell phone/smart phones, laptops, iPad/tablet computers, iPods or any other electronic device that can communicate wirelessly. For information on portable device security, refer to the Partners Portable Device Security Handbook (PHS Internal only link)

Where is the primary storage location of the device(s)? For example, the laptop is stored in office 123 on White 1 and is secured to a desk with a laptop lock or the hard drive is stored in a locked cabinet in office 123 on White 1 and access is limited to study staff only.

The laptop is stored in a locked cabinet in office 533 on White 5, and access is limited to study staff with card and key access only.

Who will have access to the electronic research data?

Electronic research data will be password protected and only accessible by study staff.

NOTE: All computers and portable devices must have password protections enabled; All computers must have active anti-virus software; Laptops, tablet, netbook computers, and USB Flash/Thumb drives must be full disk encrypted; If data will be transmitted outside the Partners firewall, data must be encrypted during transit with the use of SSL/https.

Will data be uploaded to a website/server?

◉ Yes ○ No

Will the data be uploaded wirelessly?

◉ Yes ○ No

Will the data be uploaded outside of the Partners Firewall/computer network?

○ Yes ◉ No

Will the website/server be located in a Partners facility and maintained by Partners IS?

◉ Yes ○ No

☐ Paper

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8. Sending Health / Medical Information to Collaborators Outside Partners

Will any health / medical information be sent to collaborators outside Partners?

○ Yes ◉ No

HIPAA And Tracking Disclosures Of Identifiable Health Information (PHI)

1. Disclosures of PHI to persons or entities outside Partners without the written authorization of the subject must be tracked in accordance with Partners policy "Accounting of Disclosures" (PHS Intranet link). NOTE: A code derived from the subject's name is considered identifiable, for example, a code that contains subject initials.

2. Tracking is NOT required for disclosure of LIMITED DATA SETS under a DATA USE AGREEMENT. For more information about LIMITED DATA SETS and DATA USE AGREEMENTS, refer to Partners policy "Limited Data Sets Policy/Data Use Agreements" (PHS Intranet link).

NOTE: Partners (PHS) is the HIPAA covered entity. PHS includes BWH, Faulkner, MGH, McLean, PCHI, SRH, NSMC, and NWH, among others. PHS does not include other Harvard affiliated hospitals, such as BIDMC, DFCI, HSPH, CHB, or MEEI.

Attachments

Name	Mode
Data Collection Form	Electronic

Patent foramen ovale, right-to-left shunts, and the association with perioperative ischemic stroke

Data Collection Form

We will be using the same database built for earlier IRB-approved projects in our lab (Partners IRB protocol numbers 2015P002660 and 2013P001954).

The following data will be obtained from the MetaVision Anesthesia Information Management System (AIMS) (iMDsoft, Dedham, MA), the Research Patient Data Registry (RPDR), and Enterprise Performance Systems Inc (EPSi) (Allscripts Healthcare) at Massachusetts General Hospital.

Patient baseline demographics

- Age
- Gender
- Height
- Weight
- ASA physical status classification

Intraoperative data

- Duration of anesthesia (from intubation to extubation)
- Surgical procedure
- Surgical service
- Anesthesia techniques
- Type of access (e.g. peripheral I.V., arterial access)
- Vital signs and other physiological data
    - Blood pressure (mean arterial pressure)
    - Heart rate
    - Respiratory rate
    - Body temperature
    - Oxygen saturation (SpO2)
    - Bispectral index (BIS) values
    - Monitoring of neuromuscular blockade (e.g. train-of-four ratio)
- Laboratory values
    - Blood gases

        - Electrolytes
        - Others
- Medication
    - Intravenous anesthetics
    - Inhalational anesthetics
    - Neuromuscular blocking agents and reversal agents
    - Inotropes and vasopressors
    - Anti-arrhythmics
    - Analgesics
    - Others
- Fluid balance
    - Crystalloids
    - Colloids
    - Transfusion
    - Blood loss
    - Others

Pre-/post-procedural condition

- Billing data
- Diagnoses and comorbidities (ICD-9 codes)
- Smoking status
- Alcohol abuse
- Charlson comorbidity index
- Medication history
- Patient notes
    - Office and clinic notes
    - Problem lists
    - Operative and procedural notes
    - Laboratory values
    - Echocardiography reports
    - Radiology reports
    - Pathology reports
    - Medication and pharmacy notes
    - Discharge summary

Cost data

- Work relative value units
- Date of admission, discharge, or death
- ICU length of stay