Modeling Endothelial Barrier Properties of Diseased Cerebral Vasculature
(Technical project)

The Effect of the Alexis ® O Retractor on the Health of Economically Disadvantaged Patients Receiving C-Sections
(STS project)

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Biomedical Engineering

By
Elise Carey

October 27, 2022

Madison Myott, Maia Jenckes

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

ADVISORS

Dr. MC Forelle, Department of Engineering and Society

Dr. Brian Helmke, Department of Biomedical Engineering

Introduction:

Cesarean sections, planned or unplanned, are major surgeries that almost always cause at least one complication, whereas the risk of at least one complication occurring in vaginal deliveries is cut in half (Taffel & Placek, 1983). One major risk in c-sections is infection that occurs at the incision site during the operation. The Alexis O ® protector-retractor is a relatively new device used during some cesareans that is a single-use, cylindrical polymer membrane attached to "semi-rigid polymer rings" at each end (Greenberg, 2008). One of these rings is inserted into the abdomen after an incision has been made and the other remains outside. Once in place, the soft polymer membrane covers the incision to protect it and increases the surface area of the surgical field while limiting the need for a relatively large incision. Compared to the traditionally used, reusable metal retractors, there is a statistically significant decrease in surgical site infection, blood loss, interference from the bowel, and less pain at the incision site both at discharge and 6-weeks after the operation with the Alexis O ® device. Furthermore, physicians generally agreed that using the metal retractor was more difficult and offered worse visualization of the operating field than the Alexis O ® (Hinkson et al., 2016).

A cost effectiveness analysis of the O-Rings suggests that the benefits that come from using the device is worth the cost (Lauricella et al., 2021). On the other hand, the overall cost of each $75 disposable retractor in thousands of cesareans performed by almost all hospitals each year builds up to be a notable expense (Greenberg, 2008). For this reason, only some people will have the ability to afford the use of the device while more economically disadvantaged individuals will be forced to undergo c-sections with the metal retractors. If physicians don't continue practicing medical procedures over a period of time, they are prone to loss of skills (Klec et al., 2020). Physicians who routinely use the Alexis O ® retractor in c-sections for

patients who can afford it are more likely to lose skill when operating without the device on more economically disadvantaged people, which would likely lead to even more complications.

Cerebral cavernous malformations (CCM) is a genetic disease that results in leaky, malformed blood vessels (lesions) in the brain. Compared to normal blood vessels, the ones in the lesions are thinner and less elastic (*Cavernous Malformations*, 2019). These lesions are characterized by impaired blood-brain barrier function, which can lead to major neurological problems and cerebral hemorrhage (Awad & Polster, 2019). CCM affects only 0.5% of the population (Choquet et al., 2016) and are usually diagnosed after symptoms have begun (Healthwise Staff, 2019). Currently the only treatment available is an invasive surgery and there is no preventative therapy available (*Cerebral Cavernous Malformation | National Institute of Neurological Disorders and Stroke*, n.d.). Further research is needed to develop better treatments and preventative medicine, but there is currently limited research into the mechanics and signaling mechanisms involved in this disease.

In my STS project, I will be focusing on economically disadvantaged people who undergo cesareans and are given different care than others who can afford other options, such as the use of the Alexis O ® retraction device. In my technical project, I will be focusing on another overlooked group: people who have uncommon diseases, specifically those with CCMs, which still is not well studied and has limited treatment options. These two groups represent people who are overlooked in the medical community for various reasons.

Technical Topic:

CCM is caused by mutations in specific genes, and is often genetically linked. KRIT-1 (or CCM-1) is one of three genes responsible for the disease, with the phenotype usually caused by a “two-hit” mechanism: a mutation of one gene from birth and a spontaneous mutation of the

second, coupled gene to produce a loss-of-function mutation due to the change of both of the coupled genes (Pagenstecher et al., 2009). While KRIT-1 has been confidently linked to CCM, its role in the cell signaling pathways that regulate endothelial (cells that line blood vessels) behavior and morphology (how the cell changes shape) is not well understood. The established involvement of KRIT-1 in shear stress regulated cell communication and the area at which CCM lesions develop to mostly low shear stress blood vessels provokes the hypothesis that lesion formation may be a result of abnormal shear stress response of the endothelial layer (Li et al., 2019). By using the method of silencing RNA (siRNA) to force the cell to stop (knock down) KRIT-1 protein expression and exposing the knockdown cells to shear stress, we can start to establish the possible role of KRIT-1 in endothelial shear stress adaptation.

We plan to simulate the conditions of CCM lesion formation with a parallel-plate flow chamber, which allows us to subject cells to a set amount of shear stress over a period of at least 24 hours. From this, we can measure the effects of the simulated KRIT-1 gene mutation on cell-cell junctions by staining certain relevant proteins and comparing images of cells under a microscope. If the results indicate compromised junctions, it means the KRIT-1 gene could contribute to blood-brain barrier leakiness.

Additionally, in order to study the 3D morphology of CCM lesions as they occur in blood vessels, a perfusable hydrogel (gel-like solid block that allows fluid to flow through it) model of the affected blood vessels can be designed. Some of the possible methods of designing the 3D hydrogel are through 3D printing and poking holes of approximately the size of a small blood vessel through an existing hydrogel. This 3D model will help identify how the dimensional aspects of cerebral blood vessels play into lesion formation and characteristic leakiness. The parallel-plate flow chamber will help us study the role of shear stress in the development of

CCMs. Creating a 3D hydrogel model lets us study these same factors within the specific architecture of cerebral microvasculature (small blood vessels).

Understanding the abnormalities in endothelial barrier properties and shear stress adaptation as a result of KRIT-1 mutations will provide insight into the signaling pathways involved in CCM lesion formation. Mapping these cell communication pathways is a step towards the development of non-surgical treatments that target or compensate for faulty cell signaling pathways and treat CCM at its source. Research like this project is the only way of finding less invasive treatments or preventions for people with this rare disease. In doing this research, we are able to explore the limited current research that has been done for CCM and understand what it takes to take steps towards a solution for this overlooked community.

STS Topic:

Studies indicate that more economically disadvantaged patients, as well as those in marginalized racial groups, are more likely to undergo c-sections involuntarily (Roth & Henley, 2012). In our current society, more affluent people are more able to afford superior technology. Instead of determining a more cost efficient method of reducing complications during c-sections or finding a way of allowing everyone to afford equal treatment, this class divide is carried into medical technologies. Unlike other technologies in which there is minimal risk when using them, medical technologies more frequently have the ability to either reduce or contribute to morbidity and mortality.

The STS framework that I will be employing in this research project is diffusion of innovation (DOI). In this theory, people adopt technology at different rates, which appears as

approximately a normal distribution. In chronological order, people fall into the categories of innovators, early adopters, early majority, late majority, and laggards (Singer, 2016).

I propose that in the healthcare system, both historically and presently, there is an altered DOI occurring for different groups of people. In the altered model of diffusion of innovation I am proposing, there are two separate DOI events based on socioeconomic status. The diffusion curve for economically disadvantaged people appears to be a normal distribution skewed left, while that of economically advantageous people looks more like an S-curve. Sociologists and health science scholars Hurst and Summey explain that "technology is introduced on poorer patients where it is tested, and where physicians learn to use the new methods, devices, or medications; if accepted, it is then passed on to the private sector and becomes the preferred 'modern' style of practice" (Hurst & Summey, 1984, p. 629). In other words, technology is at first forced onto economically disadvantaged people before being commonly used among more economically advantaged people.

At the beginning of my proposed alteration in DOI, many economically disadvantaged patients undergo operations with the Alexis O ® as physicians are still testing it out, while it hasn't yet been used on economically advantaged patients. As physicians became more familiar with it, the technology shifted to be used increasingly among more affluent patients. Once this shift occurs, the cost of the device prevents economically disadvantaged people from accessing the technology. Given that the Alexis O ® retractor was approved by the FDA in 2006 (Komiyama, 2017), I predict that it is currently being used primarily by more economically advantageous people as the price increases. At this point, it would already have been tested on a large number of patients and physicians who employ it are skilled at using it.

Studies implementing the diffusion of innovation theory into healthcare identify an especially difficult attempt to initially persuade physicians to use new technology, but after some time the technology becomes more widespread (Cain & Mittman, 2002). Since the risk of using faulty technology or not having enough skill to use new technology can be fatal, physicians are wary to deviate from the norm. The model from public health expert (*Speakers – HERO Forum*, 2018) Cain and science strategist (*Robert Mittman*, 2016) Mittman's seems to be missing the instances in which the technology becomes too expensive for the innovators to afford. When the number of physicians using this technology peaks, a loss of some skill for the older method can be expected due to fewer abilities to practice it (Klec et al., 2020). In the instance of technology like the Alexis O ®, the altered diffusion of innovation model could have broader implications, such as explaining the role of technology in the high maternal mortality rates among economically disadvantaged people in the United States (Jeong et al., 2020).

Research question and methods:

The question I will set out to answer is: How did the introduction of the Alexis O ® C-Section Protector-Retractor create challenges for physicians who need to also remain skilled at older techniques for the sake of economically disadvantaged patients? To answer this question, I will interview physicians at the Labor and Delivery Department at the University of Virginia Hospital. In doing this, I hope to learn more about their experience using the Alexis O ® and in what situations they choose to use it. Following up on this, I would like to inquire how much they take someone's socioeconomic status into consideration when making decisions based on their health. I also think it will be helpful to ask them questions about the methods they teach to their residents and the reasons behind them. Finally, I plan to inquire what they believe the best course of action is either in personal practice, biomedical innovation, and/or healthcare policy

making. These interviews will be semi-structured so I can better explore their reasonings for decisions they make during cesareans. I hope to interview at least three physicians for my research. Along with the interviews, I plan to continue my literature review of benefits and drawbacks of using the Alexis O ® as well as maternal health statistics in order to draw firmer connections between socioeconomic status, use of the Alexis ® retraction device, and morbidity and mortality rates following cesareans.

Conclusion:

In my technical project, I will be creating a hydrogel model of leaky blood vessels in the brains of people with CCM, so that future research on treatments and preventative methods can be more easily, efficiently, and accurately tested. In the STS deliverable, I will be investigating how the Alexis O ® Retractor device is being used for people who are more economically advantaged, which might lead to physicians being less skilled at performing c-sections without the device, putting less economically advantaged people at higher risk of complications. By understanding the ways in which these two groups have been overlooked in medicine, we can create and find solutions that will towards more equal attention that society gives to larger, more mainstream groups.

Citations:

Awad, I. A., & Polster, S. P. (2019). Cavernous angiomas: Deconstructing a neurosurgical disease. *Journal of Neurosurgery*, *131*(1), 1–13. https://doi.org/10.3171/2019.3.JNS181724

Cain, M., & Mittman, R. (2002). *Diffusion of Innovation in Health Care* (p. 29). Institute for the Future.

Cavernous Malformations. (2019, May 13). https://www.hopkinsmedicine.org/health/conditions-and-diseases/cavernous-malformations

Cerebral Cavernous Malformation | National Institute of Neurological Disorders and Stroke. (n.d.). Retrieved October 27, 2022, from https://www.ninds.nih.gov/health-information/disorders/cerebral-cavernous-malformation

Choquet, H., Pawlikowska, L., Lawton, M. T., & Kim, H. (2016). Genetics of Cerebral Cavernous Malformations: Current Status and Future Prospects. *Journal of Neurosurgical Sciences*, *59*(3), 211–220.

Greenberg, J. A. (2008). Alexis® O™ C-Section Retractor. *Reviews in Obstetrics and Gynecology*, *1*(3), 142–143.

Healthwise Staff. (2019, June 9). *COPD's Effect on the Lungs | Michigan Medicine*. https://www.uofmhealth.org/health-library/ug1539abc

Hinkson, L., Siedentopf, J.-P., Weichert, A., & Henrich, W. (2016). Surgical site infection in cesarean sections with the use of a plastic sheath wound retractor compared to the traditional self-retaining metal retractor. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *203*, 232–238. https://doi.org/10.1016/j.ejogrb.2016.06.003

Hurst, M., & Summey, P. S. (1984). Childbirth and social class: The case of cesarean delivery. *Social Science & Medicine*, *18*(8), 621–631. https://doi.org/10.1016/0277-9536(84)90290-9

Jeong, W., Jang, S.-I., Park, E.-C., & Nam, J. Y. (2020). The Effect of Socioeconomic Status on All-Cause Maternal Mortality: A Nationwide Population-Based Cohort Study. *International Journal of Environmental Research and Public Health*, *17*(12), 4606. https://doi.org/10.3390/ijerph17124606

Klec, R., Vogrin, M., & Klec, J. (2020). Cognitive training for the prevention of skill decay in temporarily non-performing orthopedic surgeons. *Acta Orthop.*, 523–526.

Komiyama, A. (2017, March 27). *Med Device Monday: C-Section Retractor*. RQM+. https://www.rqmplus.com/blog/med-device-monday-c-section-retractor

Lauricella, S., Caricato, M., Mascianà, G., Ciccozzi, M., Angeletti, S., & Capolupo, G. T. (2021). Cost-effectiveness analysis of O-Ring wound retractor in elective laparoscopic colorectal surgery. *Annali Italiani Di Chirurgia*, *92*, 460–464.

Li, J., Zhao, Y., Coleman, P., Chen, J., Ting, K. K., Choi, J. P., Zheng, X., Vadas, M. A., & Gamble, J. R. (2019). Low fluid shear stress conditions contribute to activation of cerebral cavernous malformation signalling pathways. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1865*(11), 165519. https://doi.org/10.1016/j.bbadis.2019.07.013

Pagenstecher, A., Stahl, S., Sure, U., & Felbor, U. (2009). A two-hit mechanism causes cerebral cavernous malformations: Complete inactivation of CCM1, CCM2 or CCM3 in affected endothelial cells. *Human Molecular Genetics*, *18*(5), 911–918.

Robert Mittman. (2016, August 31). Concordia. https://www.concordia.net/community/robert-mittman/

Roth, L. M., & Henley, M. M. (2012). Unequal Motherhood: Racial-Ethnic and Socioeconomic Disparities in Cesarean Sections in the United States. *Social Problems*, *59*(2), 207–227. https://doi.org/10.1525/sp.2012.59.2.207

Singer, L. (2016, December 30). *On the Diffusion of Innovations: How New Ideas Spread*. Dr. Leif Singer. https://leif.me/on-the-diffusion-of-innovations-how-new-ideas-spread/

Speakers – HERO Forum. (2018). https://forum18.hero-health.org/speakers/

Taffel, S. M., & Placek, P. J. (1983). Complications in cesarean and non-cesarean deliveries: United States, 1980. *American Journal of Public Health*, *73*(8), 843–922. https://doi.org/10.2105/AJPH.73.8.856