A acute ischemic stroke is a leading cause of death and disability worldwide. Mechanical thrombectomy has recently become the cornerstone therapy in stroke caused by large-vessel occlusion (LVO) and rapid recanalization has been shown to be associated with improved clinical outcomes and decreased mortality.1 Although successful recanalization (Thrombosis in Cerebral Infarction [TICI] scale grade 2b, 2c, or 3) is routinely achieved in 80%--90% of cases, there is at least a 30% mismatch between radiographic success and clinical outcomes.2 In addition, despite improved aspiration catheters and stent retrievers and accumulating user experi-

**Failure modes and effects analysis of mechanical thrombectomy for stroke discovered in human brains**

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**OBJECTIVE** Despite advancement of thrombectomy technologies for large-vessel occlusion (LVO) stroke and increased user experience, complete recanalization rates linger around 50%, and one-third of patients who have undergone successful recanalization still experience poor neurological outcomes. To enhance the understanding of the biomechanics and failure modes, the authors conducted an experimental analysis of the interaction of emboli/artery/devices in the first human brain test platform for LVO stroke described to date.

**METHODS** In 12 fresh human brains, 105 LVOs were recreated by embolizing engineered emboli analogs and recanalization was attempted using aspiration catheters and/or stent retrievers. The complex mechanical interaction between diverse emboli (elastic, stiff, and fragment prone), arteries (anterior and posterior circulation), and thrombectomy devices were observed, analyzed, and categorized. The authors systematically evaluated the recanalization process through failure modes and effects analysis, and they identified where and how thrombectomy devices fail and the impact of device failure.

**RESULTS** The first-pass effect (34%), successful (71%), and complete (60%) recanalization rates in this model were consistent with those in the literature. Failure mode analysis of 184 passes with thrombectomy devices revealed the following. 1) Devices loaded the emboli with tensile forces leading to elongation and intravascular fragmentation. 2) In the presence of anterograde flow, small fragments embolize to the microcirculation and large fragments result in recurrent vessel occlusion. 3) Multiple passes are required due to recurrent (15%) and residual (73%) occlusions, or both (12%). 4) Residual emboli remained in small branching and perforating arteries in cases of alleged complete recanalization (28%). 5) Vacuum caused arterial collapse at physiological pressures (27%). 6) Device withdrawal caused arterial traction (41%), and severe traction provoked avulsion of perforating and small branching arteries.

**CONCLUSIONS** Biomechanically superior thrombectomy technologies should prevent unrestrained tensional load on emboli, minimize intraluminal embolus fragmentation and release, improve device/embolus integration, recanalize small branching and perforating arteries, prevent arterial collapse, and minimize traction.

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**KEYWORDS** thrombectomy; ischemic stroke; thrombus aspiration; stent; cadaveric model; vascular disorders
ence, complete recanalization (TICI grade 3) rate, which is associated with the best patient outcome, has lingered around 50%, and the first-pass effect (FPE) rate is only 25%. The biomechanics of mechanical thrombectomy in LVO stroke and the failure mechanisms leading to multiple passes, failed recanalization, poor neurological outcome despite successful recanalization, and pain during the intervention are poorly understood, both clinically and experimentally. On the clinical side, using current fluoroscopic techniques, physicians have no visualization of the interaction between the arteries, emboli, and endovascular devices to evaluate such complex dynamics within the human skull. On the experimental side, the bulk of knowledge and technological development is derived from benchtop testing in artificial phantoms or peripheral arteries of large-animal models that oversimplify the human cerebral angioarchitecture and do not appropriately represent the response of delicate arterial walls to mechanical forces from devices and vacuum.

To gain further understanding of the forces and responses driving the dynamic interaction of artery/embolus/device under physiological hemodynamic conditions within the unmodified complexity of the cerebral vasculature, our group recently developed and validated a test platform. This novel hybrid platform is constructed with fresh human brains with the arterial system complete and pressurized by a customized hydraulic system and enables replicating LVO with different mechanically representative emboli. In this study, employing failure modes and effects analysis (FMEA), we systematically review 184 revascularization passes for LVO due to elastic, stiff, and fragment-prone emboli, including both the anterior and posterior circulations. Then, we provide a discussion on the biomechanical forces driving these events during en bloc thrombectomy with direct aspiration and stent retrievers. We hope that this work sheds some light on understanding the biomechanics and failure modes of thrombectomy and highlights opportunities for technical and technological improvements in treating LVO stroke.

**Methods**

**Setup of Hybrid Cadaveric Platform and Generation of LVO**

The development and testing conditions of the human brain platform were previously described and validated by our group (Fig. 1A). Briefly, after institutional approval, fresh adult cadaveric heads were harvested, and the vertebral arteries and the internal carotid arteries (ICAs) were cannulated and connected to a hydraulic system to infuse a 0.9% saline solution at physiological flow rates. To enable the visualization of the thrombectomy process, the superficial arachnoid layers of the cisterns and proximal sylvian fissures were sharply divided, with preservation of most arachnoid webs to maintain periarterial support. To recreate LVO in this human brain test platform, three types of embolus analogs (EAs) engineered to match the mechanical properties of patient emboli were fabricated using the methods previously described by our group.

**Mechanical Thrombectomy of LVO**

Revascularization was conducted by 1) the direct aspiration (DA) technique with an aspiration catheter (ACE 68, Penumbra) and 2) the stent retriever + aspiration (SR+A) technique with a stent retriever (Solitaire Platinum, Medtronic) and an aspiration catheter (ACE 68, Penumbra). Aspiration was generated by a vacuum pump (01–12–405, Allied Healthcare) with −650 mm Hg pressure. For the DA technique, the aspiration catheter was able to be pushed to the proximal face of the EA without

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**Figure 1.** Overview of the human brain test bed for thrombectomy. A: Schematic representation of intraarterial pressure measurement and the catheterization (1 to 4) of the main arteries of the circle of Willis, including the vertebral artery (VA), BA, the first and second segments of the posterior cerebral artery (P1 and P2), the posterior and anterior communicating arteries (PCOM and ACOM), and M1, A1, emerging from the ICA terminus. B: LVO of the M1 and A1. C: LVO of the BA. Copyright Yang Liu. Published with permission. Figure is available in color online only.
Statistical Analysis

The embolus sizes are presented as mean and SD. To compare embolus sizes among different groups, the Shapiro-Wilk test was carried out to check for normality, and then the t-test was used for normally distributed data, and the Mann-Whitney U-test was used for nonnormally distributed data. Statistical significance is indicated by p < 0.05.

Results

A total of 17 brains were harvested, and 5 brains were excluded from the study given the short ICAs precluding catheterization, damaged segments, and extensive atherosclerotic disease preventing cannulization of 8-Fr sheaths or transmural visualization. Within the remaining 12 brains, we were able to successfully visualize at high definition the revascularization process in 105 consecutive LVO cases: 51 in the anterior circulation (Fig. 1B) and 54 in the posterior circulation (Fig. 1C). The DA technique was used in 61 LVO cases with 102 device passes, and the SR+A technique was used in 44 LVO cases with 82 passes. The revascularization outcomes were as follows. 1) The FPE was 49% for the DA technique and 14% for the SR+A technique. 2) The rate of successful recanalization was 90% for the DA technique and 34% for the SR+A technique. 3) The rate of complete recanalization was 79% for the DA technique and 34% for the SR+A technique.

The main mechanism of recanalization failures identified in our study for SR+A was poor embolus/stent integration with an inability to mobilize the EA and/or downstream migration of the EA mass. For DA, failures were due to catheter clogging followed by device withdrawal, leading to intravascular embolus elongation and fragmentation resulting in iatrogenic embolization and/or residual occlusion. Residual occlusion in the main parent artery—inability to mobilize the embolus from the obstructed artery—was the most common reason for repeated attempts of recanalization. Residual occlusion in small branching arteries and perforating arteries was also common but not amenable for mechanical recanalization using the tested devices. In addition to unsuccessful recanalization, adverse events included arterial collapse and traction.

Poor Embolus/Stent Integration

Stent integration to the embolus was weaker at the branching point, especially when the stent was deployed in a smaller tributary and the arterial takeoff was in an angle. This phenomenon was frequently observed for an embolus lodged at the basilar apex and due to the high variation in size of the P1 segment and the proximity of the ostium of the superior cerebellar arteries (Video 1).

VIDEO 1. Failure modes of thrombectomy found in a whole human brain model. Copyright Yang Liu. Published with permission. Click here to view.

It was also identified at the middle cerebral artery (MCA) bifurcation when the stent was deployed in the nondominant trunk. In these cases, final stent deployment was confined by a smaller arterial lumen, leaving a significant amount of embolus substance outside the stent tines in the parent artery and resulting in poor integration. Moreover, poor embolus/stent integration was also due to the insufficient radial force of the stent to expand into the emboli and the insufficient stent cell size to enable the emboli to enter the stent lumen. These problems, which were mostly observed with stiff EAs, resulted in embolus “rolling” outside the tines of the stent during device withdrawal (Video 1).

Catheter Clogging

EAs entered the aspiration catheters and were progressively ingested until the aspiration catheter was clogged. The stiff EAs had a higher propensity to clog the distal end of the catheter, making the withdrawal of devices from the vasculature necessary and unleashing the failure modes described below.

EmboloL Elongation and Fragmentation With Residual and Recurrent Occlusion

During device withdrawal, the EAs were observed to elongate, decrease in diameter, and undergo multistage fracture leading to embolization into the same vascular territory and/or other arterial branches (Fig. 2A and Video 1). This mechanism was the principal cause of failed recanalization both by the residual embolus (i.e., embolus that remains impacted at the target artery) and/or recurrent embolization (i.e., embolus that is mobilized from the arterial wall but migrates downstream to reocclude the same arterial tree).

In LVO of the MCA, the need for further passes was due to residual emboli for 73% of the time, iatrogenic embolization for 15% of the time, and both residual emboli and iatrogenic embolization for 12% of the time. In LVO of the basilar artery (BA), the need for further passes was due to residual emboli for 53% of the time, iatrogenic embolization for 19% of the time, and both residual emboli and iatrogenic embolization for 28% of the time.
Iatrogenic Embolization

Iatrogenic embolization, or fragments released during the manipulation of the thrombus, was observed during advancement of the microwire, microcatheter, aspiration catheter, and stent deployment through the EAs, during thrombus withdrawal and due to embolus shearing at the entry of the aspiration catheter and/or at the entry of the delivery sheath/catheter. Most of the iatrogenic embolization was observed during pulling of the emboli by the thrombectomy devices in a two-stage process. On initial mobilization of the embolus, we observed partial flow reconstitution with a showering of small fragments downstream into the microvasculature (Video 1). Further embolus pulling leads to elongation, fracture, and release of fragments large enough to reobstruct the same artery (generally in a more distal location) or embolize into a new vascular territory (Fig. 2B). Table 1 and Fig. 3 summarize the embolization result, including the number and size of emboli. The stiff EAs were associated with the lowest number of emboli (0.40 per case). The DA technique generated fewer emboli (0.59 per case) than the SR+A technique (1.05 per case). LVO in the BA was associated with more emboli (1.07 per case) than LVO in the MCA (0.47 per case). Most of the emboli (57/82) were generated in the first pass. The differences in embolus size across different thrombectomy techniques and EA types were not statistically significant. However, emboli from LVOs in the BA were larger (p = 0.02) than those in the MCA.

Residual Occlusion of Small Branching and Perforating Arteries

Complete recanalization of the parent artery with residual embolic material obstructing small branching and perforating arteries corresponded to a RELVO grade of 2c (Fig. 2C). Employing the DA technique, RELVO grade 2c was identified at the conclusion of the revascularization to be 14% for the elastic, 14% for the stiff, and 71% for the fragment-prone EAs. Employing the SR+A technique, RELVO grade 2c recanalization was identified at the conclusion of the revascularization to be 50% for the elastic, 0% for the stiff, and 55% for the fragment-prone EAs.

Arterial Collapse

Arterial collapse (Fig. 2D and Video 1) was observed in 27% of the recanalization attempts. For the DA technique, arterial collapse happens when the vacuum is activated while the aspiration catheter tip is parked a few millimeters away from the emboli or after the emboli are ingested. For the SR+A technique, the expansion of stent tines and integration with emboli prevent the emboli from corking into the aspiration catheter tip, leaving the intraluminal space between the catheter tip and emboli exposed to aspiration. This results in a decrease in the intraluminal pressure and eventual arterial collapse and explains the higher frequency of arterial collapse associated with the SR+A technique (50%) compared with the DA technique (9%).

Arterial Traction

Arterial traction (Fig. 2E and Video 1) was consistently observed in our experiments and considered severe when the entire vascular territory, including the cortical arteries, was pulled by the device.

Of the 102 passes using the DA technique, arterial traction was observed in 0% of the elastic, 11% of the stiff, and 0% of the fragment-prone EAs in the BA and in 25% of the elastic, 50% of the stiff, and 43% of the fragment-prone EAs in the MCA. Of the 82 passes using the SR+A technique, arterial traction was observed in 31% of the elastic, 73% of the stiff, and 100% of the fragment-prone EAs in the BA and in 71% of the elastic, 71% of the stiff, and 100% of the fragment-prone EAs in the MCA.
Discussion

Aspiration catheters and stent retrievers are based on the classic paradigm of en bloc removal of the embolus by applying tensile forces via vacuum and withdrawal of the devices (Fig. 4). To remove an embolus wedged in the artery, thrombectomy devices integrate with the embolus by vacuum aspiration or stent engagement to apply tensile forces on the embolus to overcome the resistance forces, including static friction and adhesion of the embolus to the vascular surface, the pressure gradient across the embolus (proximal pressure–distal pressure), and the preload inside the deformed embolus that protrudes into branches of the main artery of evacuation (Fig. 4A). If the embolus is not strong enough to withstand such tension, the embolus will undergo complex multifocal fractures leading to material weakening and eventual fragmentation (Fig. 4B). Therefore, emboli with weak multiple spots (i.e., heterogeneous) may lead to residual obstruction that requires multiple passes. In addition, mobilization of a previously wedged embolus will reconstitute blood flow, giving rise to embolicogenic forces that include the dynamic friction of the embolus to the vascular surface and the hemodynamic forces of the blood flow. These embolicogenic forces, which favor downstream showering of free fragments (Fig. 4B), are concurrent to the uncontrolled intravascular fragmentation due to tensile load of emboli. These events, as consistently observed in our experiments, result in the release of emboli that reobstruct the same artery, migrate deeply into smaller distal arteries and the microvasculature, or embolize into a new vascular territory.

Iatrogenic embolization is of major clinical significance due to the potential of disrupting the collateral blood supply to the penumbra or obstructing previously opened microvascular beds and, therefore, deteriorates the neurological status and clinical outcome despite “successful” radiographic recanalization. As demonstrated in this study, fragmentation of emboli at the ostium of small branches and/or perforating arteries with residual occlusion (RELVO grade 2c) despite complete recanalization of the parent artery was up to 40%. This suggests that residual occlusion of small branches and/or perforating arteries may be more common than previously acknowledged and likely underdiagnosed since they are easily overlooked on angiography. Future research is necessary to better define the frequency and clinical relevance of persistent occlusion of small and perforating arteries, and potentially redefine “complete” recanalization to include these arteries in the scoring system. Although many territories irrigated by perforating arteries such as the basal ganglia are considered to have high ischemic vulnerability, it is possible that persistent occlusions of these vessels are responsible for the secondary stroke advancement despite apparent successful recanalization and therefore are potentially preventable.

Stent integration was weak at branching points, especially when the stent was deployed in the nondominant trunk or in a tributary emerging at an angle such as the basilar apex and in an unbalanced MCA bifurcation. In these cases, the stents had limited ability to load the emboli with tensile forces to overcome impaction forces, leading to frequent residual occlusions. In addition, the embolus substance that did integrate with the stents had to withstand a high concentrated stress at the tines causing EA fracture during device withdrawal. As demonstrated here, the main driver for persistent arterial occlusion and low rates of FPE is the inability of the thrombectomy device to mobilize/detach an embolus from the arterial wall. This finding suggests that, in addition to reducing iatrogenic embolization by flow stagnation or reversal with the...
use of balloon guide catheters and having a significant increased FPE rate, new technologies should minimize the amount of residual embolic material on each pass through improved stent/embolus integration or in situ embolus ingestion.14

Poor embolus/stent integration was also due to the insufficient radial force of the stent to expand into the emboli or insufficient cell size, preventing the embolus to fall inside the tines, causing emboli to “roll” (Fig. 4B), and was the main mechanism leading to the diminished efficacy of the SR+A technique in our model. Next-generation stent retrievers with higher radial force or designed with open baskets may mitigate this problem.

The recanalization rate and distal embolization are different among the three EA types. The fragment-prone EAs had a propensity to clog the catheters and fracture during catheter withdrawal due to the poor cohesion, leading to piecemeal removal by multiple passes and the lowest recanalization rates. The stiff EAs had higher resistance force to deform into the catheter lumen, resulting in early clogging, and also higher friction to the arterial surface because of its higher fibrin concentration,15 leading to residual occlusions. These results are aligned with clinical evidence that it is more challenging to remove fibrotic emboli, although they are less likely to cause iatrogenic embolization.16,17

Arterial collapse happens if there is insufficient inflow to prevent the pressure from dropping below a collapsibility threshold. During recanalization, there is diminished anterograde blood flow within the obstructed artery, which drops further after the introduction of a large-bore aspiration catheter. On vacuum activation, the brisk outflow of blood into the large-bore catheter drops intraarterial blood pressure and induces vessel collapse. In this paradigm, the larger the catheter, the lower the anterograde blood flow and the higher the aspiration flow, and arterial collapse is more likely.

Arterial collapse diminishes embolus evacuation and is potentially harmful to the vessel integrity. Collapse followed by withdrawal of the device increases the barotrauma by exposing the endothelium to high tensile and shear forces, leading to potential damages. This mechanism could explain the higher rate of intimal and medial layer edema caused by aspiration catheters compared with other thrombectomy devices observed in vivo.18 In our experiments, we observed arterial collapse when the aspiration catheter was parked a few millimeters proximal to the obstructing embolus (Video 1). This phenomenon is likely underdiagnosed, as optimal roadmaps are not standard during emergency stroke revascularizations, and the absent outflow in the collection canister due to arterial collapse can be misinterpreted by embolus engagement. Our experiments support the importance of advancing the aspiration catheter into the embolus before connecting the

FIG. 4. Biomechanics of removal of emboli in LVO stroke with the aspiration catheter and the stent retriever. A: At the impaction stage, the embolus is engaged by vacuum and the tines of the stent. Resistance forces include static friction and adhesion of embolus to vascular surface, the pressure gradient across the embolus (proximal pressure–distal pressure), and the preload inside the deformed embolus that protrudes into branches of the parent artery. B: At the disimpaction stage, the device withdrawal exerts tension forces on the embolus to overcome resistance forces. In this process, traction on the embolus accords the arterial wall and drags perforating and branching arteries (B1–B4). The loaded embolus elongates (L1 vs L2) and undergoes multifocal fractures, releasing embolus fragments (B3–B4). This downstream migration can occur in a new or the same arterial territory causing a recurrent occlusion (B4). In addition, embolus fracture can occur at the level of perforating arteries and small branches where embolus surface/mass ratio is the highest (higher adhesion and friction with lower coherence strength), leading to residual occlusion (B4). Copyright Yang Liu. Published with permission. Figure is available in color online only.
catheter to the vacuum source and suggest that a larger aspiration catheter may not be better. Future aspiration-based technology should be developed to enable more efficient clot removal at equal or lower vacuum.

Interestingly, arterial collapse was also observed in thrombectomy performed with the SR+A technique, especially in the setting of poor collateral flow, suggesting that the vacuum can be strong enough to overcome radial forces of stent retrievers that support the arterial lumen. In the SR+A cases, EA removal was generally successful but incomplete (Video 1) and was likely associated with endothelial damage due to high friction between the stent tines with propensity to expand and the arterial wall with propensity to collapse under vacuum. This damage will be further signified during vessel traction. This is a critical finding, as at least 3 passes of the stents are currently needed to achieve successful recanalization. Multiple recanalization attempts may result in local vessel wall injury with focal denudation of the endothelium that exposes a highly thrombogenic surface that facilitates local thrombus formation. This can lead to formation of distal emboli or promote vessel reclosure. This observation is supported by the histopathological results of animal studies, where extensive endothelial damage was observed following the use of stent retrievers and aspiration catheters.

The abovementioned observations pose a question to the current trend in aspiration catheter development. Aspiration force is proportional to the square of the diameter of the catheter, and therefore small changes in catheter size (or target artery) can have major effects in the efficacy and safety of our interventions. Newer catheters under development have larger inner diameters and claim to have stronger vacuums. However, based on our findings, arterial collapse may be an undiagnosed event, and it could become a more serious event with the upcoming introduction of larger aspiration catheters.

Along with arterial collapse, significant arterial traction was identified and is another major adverse event. It is generally believed that first-generation thrombectomy devices (e.g., Merci) were considered inferior to current stents and aspiration catheters on the basis of a vector force applied while pulling the embolus downward along the long axis of the cervical carotid artery and not horizontally along the axis of the MCA. This caused considerable torquing, stretching, and distortion of the parent vessel and presented a mechanical disadvantage to embolus removal. It has been proposed that aspiration and aspiration/stent thrombectomy minimize traction since the force vectors are parallel in orientation from the aperture of the catheter to the M segment. To challenge this hypothesis, in our experiments, although the delivery sheaths were aligned to the main axis of the MCA and the BA, arterial traction was still consistently observed during device pullback. Traction was particularly significant in cases of stiff clots and with the use of stent retrievers, likely due to higher fibrin amounts with higher adhesion to the vascular walls and the increased compaction force due to vessel collapse. In some cases, arterial traction was severe enough to displace the entire vascular territory, accoring the parent artery, and avulse perforating and cortical arteries (Video 1). We hypothesize that arterial traction and avulsion of cortical arteries are responsible for the high rates of subarachnoid hemorrhage observed during recanalization of the M arteries, which has been reported to be as high as 24.7%.

Traction on the cerebral vasculature is likely the culprit of the significant pain and discomfort of patients during the withdrawal of thrombectomy devices. As awake revascularizations are routinely performed with minimal conscious sedation, painless thrombectomy is, to date, an unmet clinical need. Arterial traction could be minimized by technologies capable of challenging the classic paradigm of en bloc removal by controlled embolus fragmentation and removal. Ideally, clot removal should be done proximally to distally without the need of loading the embolus with linear tensile forces, which would also minimize the risk of pushing the embolus material further into the vasculature or perforating arteries during the initial pass of the wire, microcatheter, or clogged aspiration catheters by the embolus.

Although this study provides mechanistic explanations for failure modes likely occurring in LVO recanalization procedures, there are limitations to consider. First, the reproducibility of the results has to be interpreted in the light of the entire range of cerebral angioarchitecture diversity, especially for arterial collapse under vacuum as variation in the circle of Willis and the different degrees in arterial lumen can have a significant impact in local hemodynamics. Further research should be conducted to better evaluate the pressure threshold that leads to collapse, how different variables interact (especially the ratio of arterial lumen/catheter lumen, vacuum power, and cerebral perfusion pressure), and the induced histological damage. Second, despite the use of fresh whole human brains with physiological flow conditions, the platform described here is ex vivo. Therefore, the influence of the cerebrovascular tone is not captured, and it is unclear how that would affect arterial behavior to device manipulation, traction, and collapse. The absent tone and weakened perivascular support resulting from the arachnoid dissections could possibly magnify the degree of arterial traction and collapse observed in this model compared to clinical practice. Third, we elected to use saline solution instead of blood to pressurize the arteries to maintain a transparent intraluminal embolus. Ideally, biomechanically superior thrombectomy technologies capable of challenging the classic paradigm of en bloc removal and the BA reveals that to have significant gains in efficacy and safety, biomechanically superior thrombectomy technologies should prevent unrestrained tensile load on emboli, minimize intraluminal embolus fragmentation and release, improve device/embolus integration to decrease.
residual occlusions, recanalize small branching and perforating arteries, prevent arterial collapse, and minimize traction.

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References

Disclosures
Dr. Savastano is the founder and a stake owner of Endovascular Engineering, Inc., which develops thrombectomy technologies. Dr. Liu serves on the Scientific Advisory Board of Endovascular Engineering, Inc. Drs. Liu, Zheng, Shih, and Savastano are inventors on international patent application no. WO2019199931A1, which was licensed to Endovascular Engineering, Inc., and they could benefit from royalties in the future.

Author Contributions
Conception and design: Savastano, Liu. Acquisition of data: Savastano, Liu, Gebrezgiabhier, Reddy, Davis, Arturo Larco. Analysis and interpretation of data: Savastano, Liu, Gebrezgiabhier. Drafting the article: Savastano, Liu, Gebrezgiabhier. Critically revising the article: Savastano, Liu, Gebrezgiabhier. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Savastano. Statistical analysis: Liu. Administrative/technical/material support: Savastano, Zheng, Shih, Pandey. Study supervision: Savastano, Shih, Pandey.

Supplemental Information
Videos

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