

A swine model of reproducible timed induction of peripheral arterial shunt failure: Developing warning signs of imminent shunt failure



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ABSTRACT

Temporary intravascular shunts are used to maintain perfusion in injured vessels, although failure can be unpredictable and lead to significant morbidity. The aim of the present study was to develop a dose- and timing-controlled swine model of intrinsic shunt failure to facilitate the development of a warning system for impending failure. Ten Yorkshire swine (weight, 56.6 ± 4.2 kg) underwent bilateral Argyle shunt (Cardinal Health, Dublin, OH) placement in the external iliac arteries, with proximal cannulation of the circumflex iliac arteries for infusion of thrombin. The thrombin infusion was randomized to the left or right side for 5000 vs 10,000 U/h. The 5000-U/h group required 2.1 times as long as the 10,000-U/h group to reach failure (mean, 21.8 minutes vs 46.4 minutes; $P < .0001$), as shown by a Kaplan-Meier survival analysis (log-rank $P < .0001$). However, the 5000-U/h group required the same total amount of thrombin (mean, 3752 ± 856 U; $P = .57$). Thus, time- and/or thrombin dose-controlled induction of shunt failure is technically feasible. Furthermore, in the final 15 minutes before failure, the flow was similar between the two groups ($P > .05$), and the slope of the flow curve became more negative the closer the model was to failure. Overall, this model could be used to develop an alert system to predict for impending shunt failure or the need for intervention. (*JVS—Vascular Science* 2022;3:285-91.)

Keywords: Argyle shunt; Arterial shunt; Combat vascular injury; Peripheral shunt; Swine model of vascular injury; Vascular trauma

Temporary intravascular shunts (TIVSs) are used by surgeons as a temporizing maneuver to maintain blood flow through an artery or vein.¹⁻⁴ Although these will generally be used for short periods (ie, minutes to hours) in highly monitored environments (eg, operating room or intensive care unit), this will not always be the case. Military vascular injuries could require shunting for hours to days because the patients will need to be transported to higher echelons of care. Civilian polytrauma and mass casualty victims could also require prolonged shunting because of resource constraints.

A critical need exists for TIVS monitoring during these periods,⁵⁻⁷ which, at present, is provided by clinical and Doppler ultrasound examinations. Such monitoring can be challenging for hypovolemic patients or those with vasospasm and requires a skilled provider to perform and interpret the findings. Furthermore, the mechanism of TIVS failure has not yet been clearly defined, and neither the duration nor the type of TIVS have been proved to be associated with the thrombosis rate or timing.^{6,8} Overall, TIVS failure has been thought to multifactorial and likely related to reduced runoff resulting from capillary bed thrombosis, which slows TIVS blood transit and thrombosis. To determine the factors leading to shunt failure and to develop an early warning system that could prompt intervention, such as an earlier return to the operating room or medical management (eg, heparin or blood pressure titration), and to avoid complete shunt failure, a reproducible and clinically relevant model of intrinsic TIVS failure is required.

The swine ileofemoral segment provides an ideal framework for modeling human peripheral arterial shunts. Yorkshire swine weighing 40 to 90 kg will have proximal external iliac to distal common femoral artery sizes in the range of 3 to 7 mm.⁹⁻¹¹ The reliability that the external iliac artery will be ≥ 6 mm if the pig weighs ≤ 50 kg has been shown to $>90\%$ ¹¹ and thus represents a model for human size brachial to superficial femoral arteries, common anatomic locations for TIVS placement.^{1,6-8,12}

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The aim of the present study was to develop a reproducible swine model of intrinsic peripheral arterial shunt failure that could be used to identify optimal TIVS management and develop a warning system for imminent shunt failure.

METHODS

Study overview. The institutional animal care and use committee approved the study, which conformed to the National Institutes of Health guidelines for ethical animal research (approval no. 0920007). The present study used castrated adolescent male Yorkshire swine (*Sus scrofa*) obtained from a local approved U.S. Department of Agriculture vendor (Animal BioTech Industries, Doylestown, PA). The sample size, subspecies choice, and sex composition were determined using a power calculation after a comprehensive literature review performed with the institutional animal care and use committee at our institution using a qualified librarian. Before the experiments, the swine were housed in communal pens under veterinary supervision with free access to food and water until 12 hours before proceduralization.

The study protocol for each pig consisted of three overall phases: (1) sedation and instrumentation; (2) baseline data collection, followed by initiation of thrombin and monitoring of the first shunt until failure; and (3) contralateral baseline data collection and initiation of thrombin and monitoring of the second shunt until failure (Fig 1).

Swine instrumentation and baseline monitoring. The pigs were sedated with 5 mg/kg of tiletamine and zolazepam (Telazol; Zoetis US, Parsippany-Troy Hills, NJ) and 2 mg/kg of xylazine via intramuscular injection and placed under general anesthesia with isoflurane via a facemask, followed by orotracheal intubation. The swine were mechanically ventilated with a targeted fraction of inspired oxygen of 40% and maintenance of an end-tidal carbon dioxide of 30 to 45 mm Hg. The pigs were placed on a warming blanket set to maintain the rectal temperature at 37°C.

The instrumentation for each pig involved percutaneous access using the Seldinger technique and cannulation of one brachial artery for placement of a solid-state aortic pressure catheter for continuous blood pressure monitoring (Transonic Corp, Ithaca, NY), external jugular cannulation for central venous gas monitoring, transfusion, and medication administration. Catheter and pressure monitor placement were confirmed via C-arm fluoroscopy (OEC 9800; General Electric, Boston, MA), as previously described.^{9,13-15} Open cystostomy was performed for urinary drainage, and electrocardiography, temperature probes, and pulse oximetry were used for monitoring.

A lower midline laparotomy was performed to expose the iliofemoral vasculature, and 3-mm vascular flow probes (Transonic Corp) were placed circumferentially

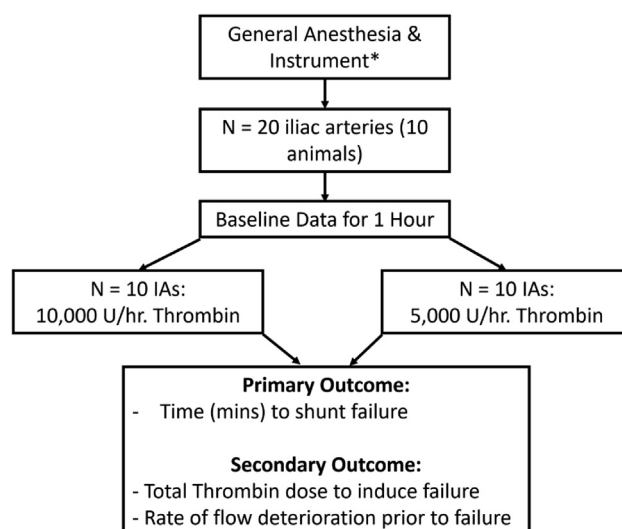


Fig 1. Study timeline. The swine were placed under general anesthesia and appropriate monitoring and other instruments placed. Each swine has one left and one right iliac artery, which were pairwise randomized to 5000 vs 10,000 U of thrombin/h. Baseline data were collected, and the time to failure was measured in minutes and repeated for the contralateral side. *Endotracheal tube, cystostomy, electrocardiographic leads, solid-state aortic pressure monitoring, pulse oximetry, bilateral iliac exposure, flow probe placement, iliac transection, temporary intravascular shunt placement, and cannulation for thrombin infusion. IAs, Iliac arteries.

around the artery (Fig 2, A and B). The circumflex iliac artery was cannulated for thrombin injection, which was delivered via a size 18 angiocatheter from the infusion tubing and an electronic digital pump (DigiPump SR31x; DigiCare Biomedical Technology, Boynton Beach, FL), with insertion of the TIVS (14F Argyle shunt; Cardinal Health, Dublin, OH) through the transected external iliac artery (Fig 2, A and B). Digital subtraction angiography was used to confirm placement and assess patency (Fig 2, C and D). The swine were randomized to a thrombin infusion of 5000 U/h vs 10,000 U/h as determined by prior experience with thrombin infusions and reported applications of thrombin in swine.^{7,8,11}

Once the instruments had been placed according to the stated strategy, the swine were given 50 mg of dextrose in 1 L of 0.9% normal saline and allowed to equilibrate for 1 hour with baseline flow data acquired before the thrombin infusion was begun.

Data management, outcomes, and statistical analysis.

Physiologic data, including oxygen saturation, end-tidal carbon dioxide, core body temperature (in degrees Celsius), electrocardiography, aortic arch pressure, central venous pressure, and heart rate (HR), were monitored continuously and recorded using PowerLab and LabChart software (ADInstruments, Sydney, NSW, Australia).

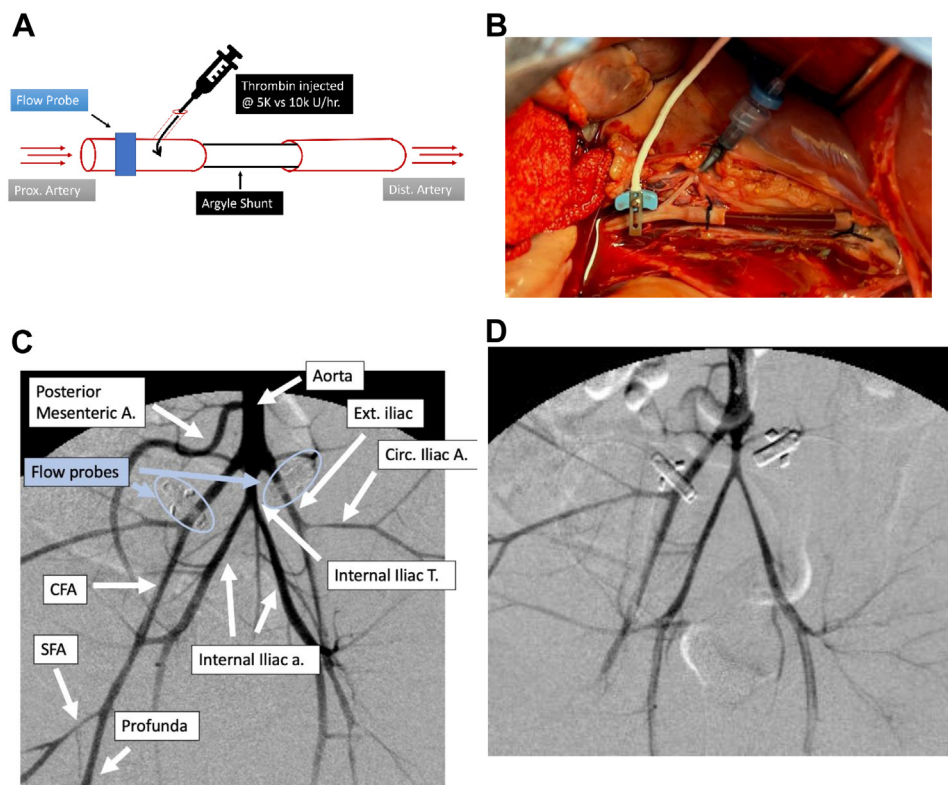


Fig 2. Experimental setup and preparation. **A**, Schematic representation of the experimental setup showing left-to-right blood flow, with a proximal flow probe, a cannulated circumflex iliac artery with a size 18 angio-catheter for thrombin infusion, and Argyle shunt placement through the external (*Ext.*) iliac artery transection. **B**, Intraoperative photograph of the same setup. **C**, Angiogram of the experimental setup. **D**, Angiogram of the same pig at failure of the left shunt. *A.*, Artery; *a.*, artery; *CFA*, common femoral artery; *Circ.*, circumflex; *Dist.*, distal; *Prox.*, proximal; *SFA*, superior femoral artery; *T.*, trunk.

The flow data were measured and monitored continuously during the study, recorded in microseconds, and exported in 1-second increments and averaged for 60-second periods, which was determined to be a clinically reasonable time for a noticeable change in the flow.

The time to failure (primary outcome) was monitored at the bedside using a remote-controlled wall clock timed by monitoring the arterial flow. Confirmation was obtained using Doppler ultrasound and/or angiography via percutaneous brachial artery access using a 5F to 6F sheath, placement of a distal aortic, 65-cm, 4F OmniFlush catheter (Angiodynamics, Latham, NY), and a 2.5-mL/s infusion for 2 to 10 seconds of iohexol. The median time to failure was compared using Kaplan-Meier survival analysis and the log-rank test. The flow and mean time to failure were then compared statistically using paired *t* tests, because each pig had undergone one left-sided procedure and one right-sided procedure. Thus, the flow across the samples was paired and initially dependent (given the baseline variability in animal weight and artery caliber and, thus, the baseline flow).

As a sensitivity analysis to further examine the deterioration and final shunt failure, the final 15 minutes before

shunt failure were examined more closely. The average flow per minute for each minute of the final 15 minutes before failure was compared using a scatter plot with linear splines, with error bars representing standard deviation. The mean flow per minute was compared using paired *t* tests. The slopes of each of these splines were then computed and interpolated with simple linear regression testing for significance for a nonzero slope. *P* < .05 was considered statistically significant. After data extraction, some data were saved in Excel 2019 (Microsoft Corp, Redmond, WA), and postprocessed for figure creation using Prism, version 9.2.0 (GraphPad Software, San Diego, CA). An iPhone 13 (Apple Inc, Cupertino, CA) was used to create the intraoperative photograph. Some images were altered, although only by labeling and cropping.

RESULTS

Ten adolescent male Yorkshire swine (56.6 ± 4.2 kg) had successfully undergone instrumentation without complications. Baseline data were collected before thrombin infusion. No baseline differences were found in the external iliac artery systolic flow between the two groups

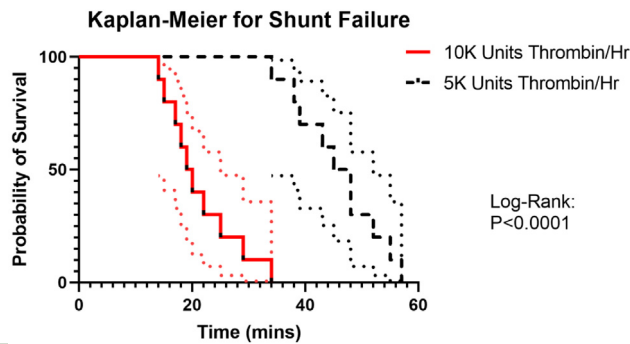


Fig 3. Kaplan-Meier survival analysis comparing median time to failure, with 95% confidence bands, using the log-rank test.

(10,000 U/h: 420.1 mL/s; vs 5000 U/h: 409.2 mL/s; $P = .69$). No differences were present between the two groups in the baseline hemodynamics, including the mean arterial pressure and HR (5000 U/h vs 10,000 U/h: mean, 82.3 ± 4.1 mm Hg vs 84.2 ± 3.5 mm Hg; and mean, 96 ± 5 bpm vs 94 ± 4 bpm, respectively; $P > .05$ for both). The hemodynamic data were also compared before thrombin infusion to 10 minutes after thrombin infusion, which was before the first shunt had failed. No differences were found in the mean arterial pressure (10 minutes after thrombin started, 5000 U/h vs 10,000 U/h: mean, 80.1 ± 5.0 mm Hg vs 82.6 ± 3.9 mm Hg) or HR (10 minutes after thrombin started, 5000 U/h vs 10,000 U/h: mean, 94 ± 4 bpm vs 93 ± 4 bpm) for either group ($P > .05$ for all).

A Kaplan-Meier survival analysis comparing the median shunt survival between groups was performed (Fig 3). Log-rank statistics revealed an association between shunt failure and thrombin regimen (10,000-U/h group: median 19.5 minutes; 5000-U/h group: median, 46.5 minutes; $P < .001$). The 5000-U/h group had required ~2.1 times than the 10,000-U/h group to reach failure (10,000-U/h group: mean, 21.8 ± 6.3 minutes; vs 5000-U/h group: mean, 46.4 ± 7.7 minutes; $P < .001$). Because the thrombin infusion dose of 5000 U/h was one half that of the higher dose but had required 2.1 times as long to reach failure, the mean total thrombin dose (time to failure [minutes] \times infusion rate [dose/min]) required to cause shunt failure was the same for both groups, regardless of the infusion rate (10,000 U/h: mean, 3640.0 ± 1052.3 U of thrombin; vs 5000 U/h: mean, 3865.8 ± 642.3 U of thrombin; $P = .57$). For all 20 shunt failures, the mean dose of thrombin required was 3752 ± 856 U to cause failure. Angiography was used to confirm the flow tracings and confirm shunt failure. The [Supplementary Video](#) shows an angiogram completed immediately before complete shunt failure of the left iliofemoral system, demonstrating application of this confirmatory technique. The [Supplementary Fig](#) shows a more distal angiogram timed immediately

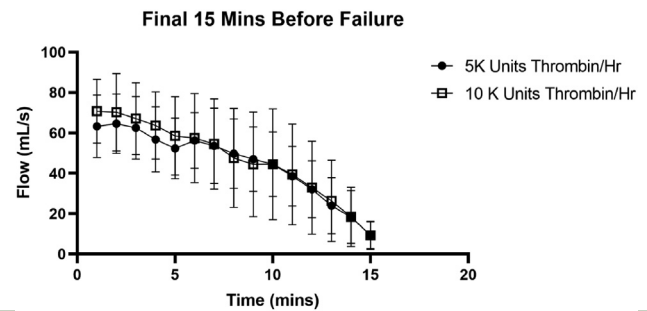


Fig 4. Flow through the proximal flow probe (mL/s) vs time (minutes), where time at 0 represents the 15-minute mark before shunt failure and time at 15 minutes represents the time at which the shunt had failed. Mean \pm standard deviation flow values provided for each minute for both groups.

before and after administration of thrombin, which demonstrated good runoff through the ankle before thrombin administration, followed by generally poor run off beyond the knee, and no runoff at all into the foot.

As a sensitivity analysis, the flow through the shunt was reanalyzed for the final 15 minutes before shunt failure (Fig 4), with no differences between the two groups observed at any point or on the regression analysis ($P > .05$ for all). Because the initial comparisons were not significantly different statistically, adjustments for multiple comparisons were not pursued. The slope of these linear splines was computed for each minute of the final 15 minutes of patency (Fig 5). When the reduction in the mean flow (ie, the slope of the mean flow curve from Fig 4) was greater in magnitude than -2.5 mL/s in the last minute (ie, the flow had not decreased by >2.5 mL/s/min), no shunt had failed within the next 5 minutes. However, an increasingly negative slope of the mean flow curves was associated with an increased likelihood of shunt failure (linear regression: 10,000 U/h slope, -0.60 mL/s/min; $P = .0016$; 5000 U/h slope, -0.50 ; $P = .0019$). A cutoff value for a high likelihood of failure was observed at -6 mL/s/min (Fig 5).

DISCUSSION

In the present study, we used 10 swine to conduct 20 shunt failures, with the time to failure monitored across two study arms (10,000 U/h of thrombin vs 5000 U/h of thrombin). We generated a reproducible model of intrinsic shunt failure. The 5000-U/h group required ~2.1 times as long to reach failure. However, because the dose was one half as high as the 10,000-U/h group, the former group had required the same total dose of thrombin. Furthermore, once the shunts had begun to fail, they had ultimately failed in a predictable pattern in both groups (ie, the slope and timing of flow during the last 15 minutes of patency was the same for both groups). The main difference was the deterioration

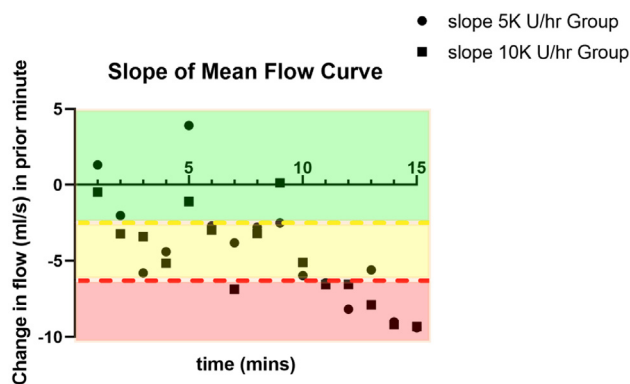


Fig 5. Slope of mean flow (mL/s) over time (minutes) for last 15 minutes of failure per group. Preliminary failure shown at possible cutoffs of a -2.5 -mL/s reduction in flow per minute, indicating a moderate risk of failure within the next 5 minutes (yellow bar), and a -6 -mL/s reduction in flow per minute, indicating a high risk of shunt failure within the next 5 minutes (red bar). Yellow and red dashed lines added for effect.

required longer to start in the low-dose group. Thus, this predictable and reproducible model can be used to develop a warning system of shunt failure or to test various medical therapies or surgical strategies to prolong patency within a valid model. Preliminary data from a sensitivity analysis of the flow before failure indicated that the slope of the flow curve could serve as a possible signal for deriving a “warning” (moderate probability) and “watch” (high probability) system for shunt failure within the next 5 minutes, or, if other alert parameters (eg, high sensitivity, high specificity) are desired, could provide a strategy to derive such signals.

The first result was that developing a model of intrinsic shunt failure (ie, the shunt had failed because of an intravascular complication instead of because the vessel had been compressed or clamped) is feasible, reproducible, and even fully controllable from a dosing (using thrombin) or timing standpoint—depending on which is desired. Although the use of TIVS in animal models is not novel, to the best of our knowledge, controlled induction of intrinsic shunt failure has not been previously reported.^{5,6,16-20} Our model has the added benefit of the ability to be controlled from a timing and/or dosing standpoint. This will allow for future research to determine this variable and test novel therapeutic agents or management strategies without confounding resulting from the timing. An important question is whether euvoolemia vs hypovolemia would augment shunt failure timing. Now that we have a model for controlled shunt failure, we can alter these other variables as we explore these hypotheses.

A sensitivity analysis of the shunt failure also revealed interesting findings. The shunts had deteriorated in the final 15 minutes in a predictable manner (ie, the shape

of the 10,000-U/h and 5000-U/h flow deterioration curves were the same). The only difference was that it required about twice the long for deterioration to begin in the 5000-U/h group (and, thus, the same dose of thrombin). We hypothesized that a threshold would be found at which once the flow had decreased below a certain cutoff, the shunt would invariably fail, similar to the conventional thinking for venous bypass for chronic vascular disease.²¹⁻²⁴ However, in our continuous monitoring scenario for acute shunt failure, a larger signal arose in the slope of the minute-to-minute linear splines. This finding provided preliminary evidence of a second signal (slope of the flow curve), in addition to the flow itself, that might prove useful in future feature selection or time series analyses to develop an analytic strategy to predict imminent shunt failure.²⁵⁻³⁰ In the present study, we identified possible cutoffs for an impending shunt “warning” at -2.5 mL/s deterioration in flow per minute and a “watch” at -6 mL/s deterioration in flow per minute. These cutoffs can be increased or decreased to adjust for the desired sensitivity or specificity.³¹

The present study had important limitations. We used 10 castrated male swine to approximate a young, relatively healthy cohort to recapitulate the most common target of intervention using TIVS after trauma: young, healthy men. The study design also focused on the most common size arteries that will undergo shunting after military and civilian trauma. This strategy, however, neglected other groups for whom TIVS could be applied, such as young women, those who have sustained other mechanisms of injury such as iatrogenic injury, and those with chronic vascular pathology. Furthermore, shunts can be placed in humans using arteries of other sizes or veins. Although our model could be adapted to suit studies of those situations, the model has not yet been validated. It has also not yet been validated for other types of shunts, such as luminal coated or TIVSs made of other materials. The sample size was justified by a power calculation and the parameters did reach statistical significance. However, with our small sample size, we saw limited baseline biophysiologic variability. Our study might require repetition in a more diverse animal model or with the use of other specific cohorts to draw conclusions about management in other scenarios, most especially when arterial injury is combined with hemorrhagic shock, hemodilution, or hypothermia, each of which might augment the pattern of shunt failure created in our model. However, our model might be useful for randomizing animals to groups with these systemic physiologic perturbations to investigate their role in shunt failure (eg, whether intermittent or sustained hypotension portends shunt failure, and, if so, how). This model might provide a foundation to test these and other hypotheses or to devise new TIVS management strategies or therapies to delay or warn of shunt failure.

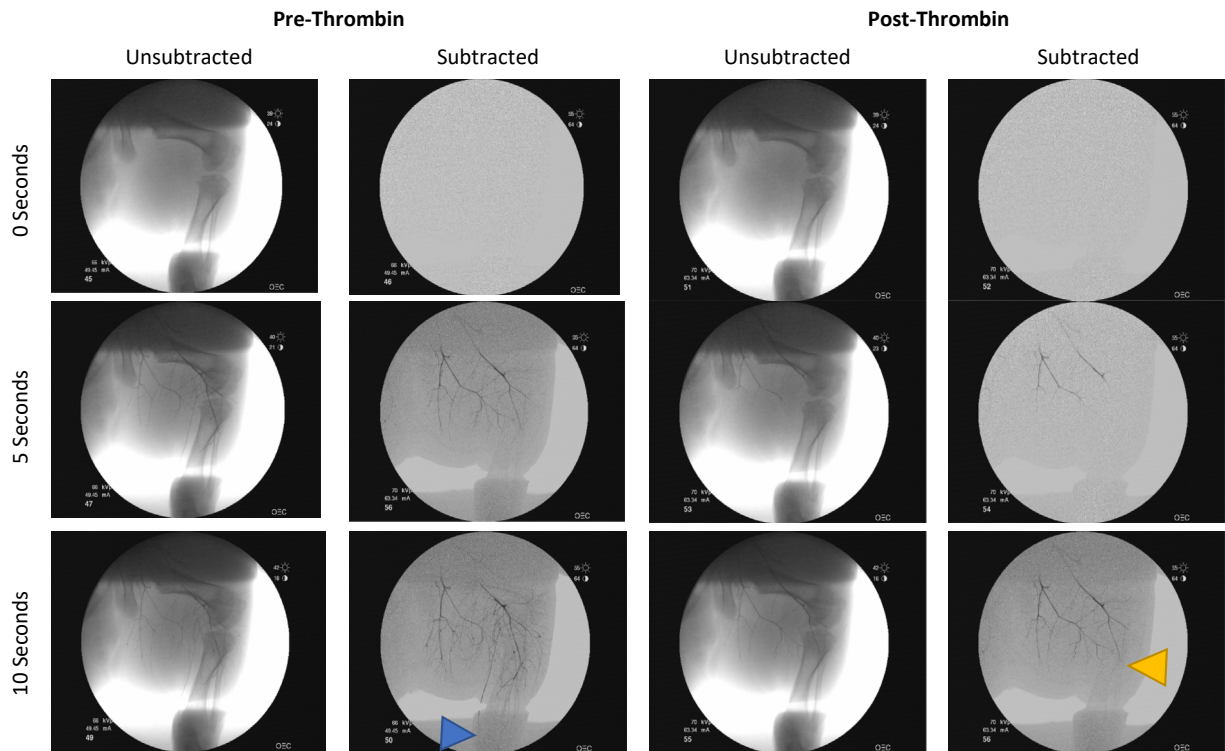
CONCLUSIONS

We have shown that time- and/or thrombin dose-controlled induction of shunt failure is technically feasible and continuous shunt flow can be used to reliably predict the timing of shunt failure if no intervention is pursued. We could control the timing of failure predictably by modifying the infusion rate of thrombin in our intrinsic shunt failure model. Furthermore, once the flow had begun to deteriorate, it did so within a predictable period regardless of which dose of thrombin was used. This swine model of TIVS failure could be used to develop an alert system by which impending shunt failure or the need for intervention could be predicted or used to test surgical or medical strategies to prolong shunt patency.

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Supplementary Fig 1. Unsubtracted and subtracted angiograms (both with external iliac selection) from before and after thrombin administration of right lower extremity of 45-kg male Yorkshire swine. The subtracted angiogram was performed immediately before complete runoff failure. These images were acquired using an identical contrast dose and timing (10 mL of iodixanol [Visipaque; GE Healthcare, Chicago, IL] over 2 seconds) and fluoroscopy settings and position, with the same hemodynamic parameters (heart rate [HR] and mean arterial pressure). The prethrombin angiogram shows runoff past the ankle at 10 seconds after the start of the injection (*blue triangle*). The post-thrombin 10-second angiogram shows no runoff beyond the mid-calf at 10 seconds and, in general, poor runoff throughout the thigh (*yellow triangle*).